

TRANSACTIONS
of the
McINTYRE-SARANAC CONFERENCE
on
OCCUPATIONAL CHEST DISEASE

Edited by G. W. H. Schepers, M.D., D.Sc.

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G. W. H. SCHEPERS, M.D., D.Sc., Editor

FOREWORD

For many years the Saranac Laboratory, of Saranac Lake, N. Y., and the McIntyre Research Foundation, of Toronto, Canada, have been conducting research along somewhat parallel lines. For the past five years the McIntyre Research Foundation has held its Annual Meeting on Silicosis and Aluminum Therapy in various cities in the United States and Canada, while The Saranac Laboratory, since 1934, has sponsored a series of Symposia on Industrial Pulmonary Diseases at Saranac Lake. These two organizations pooled their knowledge and resources for this conference, and the proceedings are documented in this volume.

Saranac Lake, for many years a center for the study and treatment of pulmonary tuberculosis and other chronic chest diseases and, moreover, a world-renowned recreational resort, provided a unique and attractive setting for the conference. The sessions, which were very well attended, attracted more than 250 persons, including visitors from the United States, Canada, South America, France, England, Scotland, Wales, India, and the Union of South Africa.

The pronouncements in respect of occupational chest diseases, which have been emanating from The Saranac Laboratory and more recently from the McIntyre Research Foundation, have in the past influenced medical, engineering, and legal thinking in terms of these diseases. The views expressed at the preceding conferences have guided management, labor, compensation courts, physicians, engineers, lawyers, and educators not only in the United States and Canada but in many other countries. It is hoped that the record of this most recent conference will in equal measure also prove of benefit to those who seek firsthand information and guidance concerning the problem of occupational chest diseases. The prediction that this will be so is strong, because practically every paper presented at the conference was based on original research.

ANTHONY J. LANZA, M.D.,
Conference Chairman
Emeritus Professor of Industrial Medicine
New York University-Bellevue Medical Center

MCINTYRE-SARANAC CONFERENCE
PROGRAM COMMITTEE

1955

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Conference Program

Sessions

1. General

Chairman: *Corey P. McCord, M.D.*, Consultant in Industrial Medicine, Institute of Industrial Health, University of Michigan, Ann Arbor, Mich.

2. Aluminum in Control of Silicosis

Moderator: *William A. Sawyer, M.D.*, Medical Consultant, International Association of Machinists, Rochester, N. Y.

Discussant: *Paul G. Bevard, M.D.*, Consulting Roentgenologist, Tarentum, Pa.

3. Epidemiology of Silicosis and Occupational Chest Disease

Moderator: *Thomas L. Shipman, M.D.*, Health Division Leader, Los Alamos Scientific Laboratory, Los Alamos, New Mexico

Discussant: *Philip Drinker, Sc.D.*, Professor of Industrial Hygiene, Harvard University School of Public Health, Boston, Mass.

4. The Evaluation of Experimental Research on Dust Diseases

Moderator: *Dudley A. Irwin, M.D.*, Medical Director, Aluminum Company of America, Pittsburgh, Pa.

Discussant: *Norton Nelson, Ph.D.*, Chairman, Institute of Industrial Medicine, New York University-Bellevue Medical Center, New York, N. Y.

5. Medico-Legal and Clinical Aspects of Pulmonary Disability

Moderator: *Ivan Sabourin, Q.C.*, Counsel to Quebec Asbestos Producers Association, Montreal, Quebec

Discussant: *Warren A. Cook, B.A.*, Associate Professor, Industrial Health and Hygiene, University of Michigan School of Public Health, Ann Arbor, Mich.

6. Experimental and Engineering Aspects of Occupational Chest Diseases

Moderator: *Angus D. Campbell*, Manager, McIntyre Research Foundation, Schumacher, Ontario

Epilogue: *Corey P. McCord, M.D.*

7. Conference Banquet

Master of Ceremonies: *Manfred Bowditch*, Director of Health and Safety, Lead Industries Association, New York, N. Y.

Leroy U. Gardner Memorial Address: *Paul S. Richards, M.D.*, Senior Consultant, Memorial Medical Center, Salt Lake City, Utah

Personal Impressions of Edward Livingston Trudeau and Edward R. Baldwin: *Hugh M. Kinghorn, M.D.*, Saranac Lake, N. Y.

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Prologue

CAREY P. McCORD, M.D., Ann Arbor, Mich.

For the first time the McIntyre Research Foundation and The Saranac Laboratory unite in a shared enterprise: the McIntyre-Saranac Conference on Occupational Chest Disease. These two facilities are bound together in the common and high-minded dedication to acquire and disseminate precise information on occupational diseases of the chest and notably the dusty lung diseases. Essentially these two organizations are devoted to research in their single field of coverage. The much that already has been achieved chiefly reveals the inadequacy of full understanding of the pulmonary occupational diseases and thus piques the realization that the days of such research are not numbered.

Recorded for publication April 4, 1955.

Acting Conference Chairman, Consultant in Industrial Medicine, Institute of Industrial Health, University of Michigan.

Read at the McIntyre-Saranac Conference on Occupational Chest Disease held at Saranac Lake, N. Y., Feb. 7-9, 1955, under the joint sponsorship of the McIntyre Research Foundation, of Toronto, and The Saranac Laboratory, of Saranac Lake.

The scientific programs that eventuate in this publication have been scheduled and contrived to emphasize current contributions of high order. The key word of the Conference has been "newness." Newness in science always implies an obligation to banish the old when clearly it becomes demonstrated that the old holds no values save as markers along the way to the fully acceptable ultimate.

The scientific status of both organizations sponsoring this Conference is such that enormous responsibility rests upon all participants. What has been said in the many sessions unfailingly will touch industry, management, labor unions, compensation courts, physicians, educators throughout America and, even more, many other portions of the world. This has imposed an earnest, zealous, cautious, and even prayerful approach to the tasks in hand.

Not lightly stated, the purpose of this Conference and its subsequent publications comes to be the determination to add to the sum total of scientific attainments that eventually will bring all occupational diseases of the chest to praiseworthy control.

The Objectives and Achievements of the McIntyre Research Foundation

FRANCIS B. TRUDEAU, M.D., Saranac Lake, N. Y.

McIntyre Research Foundation is a non-profit corporation formed to carry on research and investigation in connection with the prevention, mitigation, and eradication of industrial diseases. As a primary concern, however, it has for many years actively pursued a program seeking to prevent silicosis resulting from exposure to silica dust in occupations where men may be exposed to the hazard. The Foundation has pursued the latter objective, firstly, by encouraging the use of aluminum prophylaxis and therapy and, secondly, by sponsoring programs of intensified medical engineering control of dust and health hazards in industry.

To understand more thoroughly the organization as it operates today, a brief sketch of the historical background and the aims of the founders may be pertinent.

The name McIntyre Research, Limited, was chosen when the first company for the licensing of the aluminum patent was formed on Nov. 22, 1939, to identify the effort with its sponsors, McIntyre Porcupine Mines, Limited. The co-inventors of the patents covering aluminum therapy were Dr. W. D. Robson and the late J. J. Denny, who were, respectively, plant physician and engineer to this mining company.

In December, 1946, the shareholders of McIntyre Research, Limited, turned over its interest to McIntyre Research Foundation. This change was one in legal form only and in no way altered the work and objectives of its founders.

Thus the Foundation was formed with a charter membership of 10, and the interest of each member in the corporation was made nontransferable.

The Directors of the Foundation, who constituted the Committee of Management, were the surviving co-inventor of the patent, Dr. W. D. Robson, and those gentlemen who contributed to the success of the work accomplished up until the formation of the Foundation, namely, Messrs. J. P. Bickell, Balmer Neilly, R. J. Ennis, N. F. Parkinson, and Drs. D. A. Irwin and J. W. G. Hannon.

Messrs. Bickell and Ennis passed away in 1951, and Mr. Balmer Neilly, although still a Member of the Foundation, has retired from active duty in it. The present officers and directors are as follows:

E. D. Fox, President and Director—Director and Secretary, McIntyre Porcupine Mines, Limited, and President and Director, Belleterre Quebec Mines, Limited.

W. B. Dix, Secretary-Treasurer and Director—Director and Treasurer, McIntyre Porcupine Mines, Limited; Director and President, Castle-Trethewey Mines, Limited, and Director, Belleterre Quebec Mines, Limited.

A. D. Campbell, Manager and Director—Manager, Castle-Trethewey Mines, Limited.

Dr. J. W. G. Hannon, Medical Director and Director—of Washington, Pa.

Dr. D. A. Irwin, Director—Chief Medical Officer, Aluminum Company of America.

Dr. W. D. Robson, Medical Consultant and Director—of White Rock, B. C., Canada.

Dr. F. Rohde, Medical Director for Mexico—of Mexico, D. F., Mexico.

N. F. Parkinson, Director—Executive Director, Ontario Mining Association.

M. L. Urquhart, Director—Manager, McIntyre Porcupine Mines, Limited.

Recorded for publication April 4, 1955.

OBJECTIVES OF McINTYRE RESEARCH FOUNDATION

The Foundation's research work initially was concerned with those chemical and physical processes which determine the incidence and rate of development of silicosis. Many researches were carried out on these problems and included the effect of mine gases on the development of silicosis and studies of antidotal rocks, chemical and physical characteristics of air-borne mine dusts, and the modifying effect of admixtures of dust in an atmosphere that was primarily contaminated by silica. The experimental studies included an examination of not only the antidotal, or neutralizing, effect of admixed dust on the toxic properties of silica but also the opposite influence, i. e., a study of dusts that are capable of accelerating the action of silica.

Next followed clinical studies on the use of aluminum as a therapeutic means in silicotics with known disability. This necessitated an investigation of lung function in persons with advanced silicosis who were treated by aluminum therapy in order to gauge accurately the effects of the aluminum.

Later the scope of activities in the clinical research field was expanded to include the development of a field unit for the study of pulmonary function. The object of this study was to develop an instrument which could be placed in the hands of the average plant physician and which would measure with reasonably scientific accuracy the pulmonary

function of applicants for employment in an industry where atmospheric contaminants affect the lung function.

In order to standardize methods of aluminum therapy, a study of controlled production and dispersal of fine particulate dusts and aluminum powder was embarked on. The chemical and physical characteristics of air-borne dusts also required study, and some attention was given to the quantitative mineral retention of air-borne minerals in the lungs of miners.

Side-issues in the program sponsored by the Foundation included observations on the relationship between sterno-vertebral diameter of the chest and pathological conditions in the chest. More recently the Foundation has promoted pathological studies of the lungs by means of large lung sections according to Gough's technique and the effects of temperature, air flow, air velocity and humidity upon the production of dusts and powder.

The results of the Foundation's own research and those of important international research in connection with silicosis and other pneumoconioses have been presented by the Foundation to licensees and others interested at its yearly Conferences. These scientific contributions are published and distributed as separates and as complete yearly Proceedings.

The Contribution of the Saranac Laboratory to Research on Chest Diseases

E. D. FOX, M.E., Toronto, Canada

The Saranac Laboratory originated as a small unit which Dr. Edward Livingston Trudeau established in his homestead in 1885. In his autobiography Dr. Trudeau mentions that it was "the room opening from my little office, which was really the beginning of The Saranac Laboratory for the Study of Tuberculosis." A few years later, in December, 1893, at a time when he was ill in a New York hotel, Dr. Trudeau's home and laboratory were destroyed by fire. The Laboratory was continued, through the generosity of Mrs. Robert Hoe, in a small hastily built addition to the stable of Dr. Trudeau until the new fireproof laboratory building was completed. The new Laboratory, a gift of George C. Cooper, of New York, who had been a former patient of Dr. Trudeau, was erected in 1894 and became the first institution of this type in the United States intended specifically for the study of tuberculosis. The library of the Laboratory was a gift from Horatio Garrett, of Baltimore. In 1914 Mr. Samuel Mather made a bequest for the establishment of the Trudeau School, and since that time the Laboratory has been the headquarters of the School and has provided to nearly 1000 physicians basic training in the principles of tuberculosis and also during the past 20 years in the principles of the pneumoconioses and other occupational chest diseases. Through its seven previous symposia on occupational chest diseases, The Saranac Laboratory has, in addition, disseminated a vast amount of original research data and served as a touchstone in this field of inquiry.

Submitted for publication April 4, 1955.
President, McIntyre Research Foundation.

After Dr. Trudeau's death, the Edward L. Trudeau Foundation was established as a memorial endowment fund mainly for the support of the Laboratory. Subsequently the Milbank Memorial Fund and the Black Memorial Fund each contributed \$100,000 as a special endowment for research by the Laboratory. The Laboratory has received generous research grants from industry and support from numerous charitably minded persons and in recent years has been entirely self-supporting.

The Directors of The Saranac Laboratory have been, successively:

Dr. Edward L. Trudeau, the founder, from 1894 to 1915.

Dr. Edward R. Baldwin, from 1915 to 1926.

Dr. Leroy U. Gardner, from 1927 to 1946.

Dr. Arthur J. Vorwald, from 1947 to 1953.

Dr. Gerrit W. H. Schepers, from 1954 to present.

The Laboratory has made three major contributions of great cultural value to this country. The first is the actual research which has been carried on during the past 60 years. The second is the teaching work done formally through the Trudeau School and the Saranac Symposia and informally to the many visitors and students from all parts of the world who have, from time to time, come to the Laboratory. The third is the public service rendered all over the country through the lectures and demonstrations by the staff of the Laboratory at various conferences of physicians, engineers, public bodies, and so forth. In addition, the Laboratory has served as the clinical pathology cen-

CONTRIBUTION OF SARANAC LABORATORY

ter for the local community and even for surrounding towns. From 1893 until 1900 the Laboratory was a private nonprofit institution of Dr. Trudeau's. In 1900 it was incorporated with the State University at Albany, a legal status it has retained to the present time.

The research work conducted by the Laboratory has concerned itself with two major chapters. The first and the longest phase, and in a sense one that is still continuing, is the study of tuberculosis. Dr. Trudeau was one of the first physicians in this country to identify the tubercle bacilli in a patient's sputum, a feat he first accomplished in 1886. He subsequently proceeded to demonstrate the pathogenicity of the bacilli to experimental animals and to prove the pathogenic effect of the bodily secretions of tuberculous patients. The next phase of the study on tuberculosis concerned the environmental influences on tuberculosis. Later, there followed a period of study on artificial immunity in animals. Next came a phase in which a variety of substances were tried as therapeutic agents, ranging from hot air to creosote, iodoform, sulfureted hydrogen, hydrofluoric acid, essence of peppermint, and so forth. The experiments at the Laboratory proved mainly that the majority of these substances, while ineffective against the tuberculous disease, were capable of shortening the lives of the experimental animals. After this phase, the Laboratory concerned itself strongly with the problem of immune reactions and hypersensitivity and participated actively in a search for a possible remedy against tuberculosis. It pioneered the possibility of an antituberculosis serum and, in the course of these studies, discovered the presence of viable tubercle bacilli in imported T. R. tuberculin which was being sponsored in Europe as the result of the work of Koch. Through its support of the work of Dr. P. A. Levene, one of the first workers at The Saranac Laboratory, the Laboratory pioneered the biochemical study of the tubercle bacillus. This work was continued later at other centers, particularly at the Rockefeller Foundation.

The second major contribution to research pertains to the systematic investigation of the pneumoconioses. This phase of the work was truly initiated by Dr. Gardner and concerned itself both with animal experimentation and with the clinical study of industrial personnel who might be exposed to dust.

With improvement in general health conditions among the population of America, it became apparent that a major source of tuberculosis became known to reside in the industrial population, specifically in those concerned with dusty trades. Thus the industrial commitment of the Laboratory tended to become its more important branch of study.

As a result of this approach, the Laboratory proved through its research that the inhalation of quartz dust was a major factor which adversely influenced the occurrence of tuberculosis in industry. Through a series of systematic studies on animals, the Laboratory contributed a tremendous body of information concerning the pathogenesis of silicosis and the distinction between silicosis and other dust diseases. At the same time, the Laboratory continued to pursue its study of the tuberculogenic propensities of industrial dusts and demonstrated forcibly that the main phthisiogenic substance among these dusts remained the quartz particle. This work is still continuing.

Antedating the publication of experiments by Canadian investigators dealing with the use of aluminum for the prevention of silicosis, The Saranac Laboratory engaged in experimental work on this subject. Studies revealed that compounds of iron offered some promise as therapeutic agents for delaying or preventing the development of silicosis. After the report from Canada on the much more promising aluminum prophylaxis, the Laboratory carried on a series of studies on the value of this agent. This investigation is still continuing.

The Laboratory has maintained a field division in the Wisconsin-Minnesota area for many years and thus became intimately involved in the problem of iron mining and the

associated lung disease. This led to the establishment of an industrial hygiene service and the evolution of a radiological division.

The problems of coal miners in particular stimulated research into the field of emphysema and heart disease. This led to the establishment of the physiology department.

Next followed the extensive investigation into the very enigmatical issue of berylliosis, currently still under study. Dr. Gardner had the genius to recognize at this stage the need for inquiry into biochemical pathology, and therefore he created the department of biochemistry. This development of the Laboratory rendered possible the proper study of a

new phase of the occupational dust diseases and prepared the way for investigations into carcinogenesis, with which the Laboratory is currently very much preoccupied.

More recently the Laboratory has undertaken the study of dusts other than mineral and at present has under way an inhalation experiment in which the dusting material is a plastic.

Thus The Saranac Laboratory has striven to keep abreast of the problems of its times. I am told that its approach has ever been pragmatic. The staff is constantly inquiring into fundamental and even academic issues.

Comparative Vascular Pathology of Occupational Chest Diseases

Preliminary Observations

G. W. H. SCHEPERS, M.D., D.Sc., Saranac Lake, N. Y.

INTRODUCTION

It is probably common knowledge that industrial employees who have been exposed to dusts of various kinds have in the past manifested a tendency to die either of a tuberculous complication of a concomitant pneumoconiosis or of cor pulmonale. Such persons may, of course, also die of any of the intercurrent nonoccupational causes. The underlying occupational chest disease may also terminate life through other mechanisms, such as esophageal, bronchial, or arterial erosions by silicotic lymph nodes, with ensuing pulmonary or mediastinal gangrene. The latter category of mechanisms tends, however, to be in the minority. It must be emphasized, too, that no precise information exists today concerning the relative role of cor pulmonale as the causative factor of death in comparison with tuberculosis. This may be because it takes a greater measure of clinical diagnostic ability to diagnose cor pulmonale, and objective findings are less easily identified post mortem. Many cases of tuberculosis may even die through heart failure of the cor pulmonale type. Tuberculosis statistics, on the other hand, are fairly well known, and the mechanisms of death fairly well understood.

It is apparent also that the relative incidence of cor pulmonale in relation to tuberculosis varies markedly from industry to industry. The higher the quartz content of inhaled dust (e. g., cases of gold miners,

ceramic workers), the more probably tuberculosis will be the terminal complication, and the more likely will it be that the infective process will obscure any associated cardiovascular impairment. Where the quartz content of environmental dust is low, as among coal miners, there is a greater tendency to cardiac deaths, and there are fewer tuberculous terminations. But numerous anomalous results may be found where there is no apparent inverted relationship between the two diseases.

There is no necessary relationship between the degree of demonstrable fibrosis associated with pulmonary dust deposition and the prevalence of tuberculosis or cor pulmonale as terminal events. Thus there may be a very marked degree of pulmonary collagenosis associated with asbestosis without a materially enhanced incidence of tuberculosis. Cor pulmonale, on the contrary, is commonly found in association with asbestosis, but its severity does not necessarily parallel the extent of the interstitial fibrosis. Many cases of advanced asbestosis may escape a cardiac complication entirely.

Silicosis likewise is vicarious in its effects on the vascular system. Although a prevalence of tuberculosis in excess of 75% was once a predictable accompaniment of silicosis in South Africa, while tuberculosis may still be found in 21% of first-stage silicotics at death, and whereas it features as the cause of death in more than 50% of second and third stages, the relationship of cor pulmonale to the equivalent grades of silicosis does not follow the same logical pattern. Indeed, it is not uncommon nowadays to find miners with advanced silicosis who have no demonstrable abnormality of the vascular system whatsoever. There may be a simple anatomi-

cal explanation for this. In these cases of uncomplicated silicosis, the fibrotic process is usually almost completely confined to the pulmonary parenchymal lymph nodes, and in these positions it cannot exert any deleterious influence of any consequence on the blood vessels of the lung.

With the steady reduction in tuberculosis mortality among industrial workers all over the world, cor pulmonale has become a relatively more important cause of death. This is an unexpected finding which needs fuller explanation. It is likely, of course, that its higher present-day prevalence is partly illusory and explicable in terms of better diagnoses, electrocardiography, and improved radiographic techniques, rendering possible recognition at a much earlier stage and with greater certainty. The earlier preoccupation of physicians with the socially exceedingly dangerous tuberculous complication, and the overweening importance of the latter, perhaps obscured an even greater earlier prevalence of cor pulmonale. The net present result, however, is that cor pulmonale is the more important sequel to be on one's guard against in dealing with employees who have been exposed to environmental respiratory hazards for protracted periods.

So far these diseases have been referred to primarily as causes of death. All the preceding remarks apply *mutatis mutandis* and with almost equal emphasis to tuberculosis and cor pulmonale as causes of disability, with the proviso, however, that additional causes of functional impairment may coexist, precede, or complicate these conditions without necessarily being capable of causing death directly. Thus one has to think here of conditions, such as emphysema, chronic bronchitis or bronchiectasis, and diffuse fibrosis, which may help to impair the working capacity of the dust-injured employee though but seldom capable of causing death directly. In most instances where the latter three types of complications are present in any sufficiently severe degree, they lead to death through the mechanism of right heart failure.

The riddle of cor pulmonale can only be solved when once we have discovered its precise mechanism of causation in relation to the occupational dust diseases. From the medicolegal point of view, it may be of crucial importance to know whether the cor pulmonale is invariably sequential to a recognized pneumoconiosis or whether it may arise through primary injury of lung vessels by the dust. By definition, of course, the cor pulmonale is invariably sequential to impairment of the pulmonary circulation, and the cardiac result may be achieved either through altered physiological factors or by means of direct anatomical damage either as a sequel of the specific pneumoconiotic reaction or through direct action of the dust on the blood vessels.

The indirect physiological mechanisms whereby the chronic occupational lung diseases can cause heart failure are multiphasic but fairly well understood already. Emphysema may, for instance, mechanically obstruct the circulation of blood through the alveolar capillary network, which effect the right ventricle would attempt to overcome by a process of hypertrophy. Any series of pulmonary infections of long duration and sufficient severity, such as may ensue in any chronic pneumoconiosis, may, through the dual effect of myocardial impairment (cloudy swelling) and the increased cardiac output related to the higher metabolism of the fever state, lead to congestive failure. At the same time the increased oxygen demand created by fever would tend to increase the respiratory effort in the partially anoxic patient. This would create a vicious circle. At the same time any superimposed pneumonic process would further encroach on an impaired pulmonary vascular bed and render futile much of the perfusing function of the pulmonary circulation, inasmuch as such perfusion would now be to nonventilated areas. The bronchial or bronchiolar obstruction attendant on many respiratory tract inflammatory states would further aggravate the ventilatory insufficiency. The main functional mechanism of genesis of cor pulmonale in the occupational chest diseases appears,

however, to be anoxia. Physiologists such as Euler and Liljestrand¹ and also Fishman, McClement, Himmelstein, and Cournand² have conclusively demonstrated that anoxia may directly enhance pulmonary arterial vasomotor tone, with resultant increase in pulmonary pressure. This mechanism may be augmented by associated polycythemia, hypervolemia, and increased cardiac output. Anoxia may further directly impair the efficiency of the cardiac muscle, and when this factor is combined with the enforced need to maintain a greatly increased pulmonary arterial pressure, congestive cardiac failure ensues. Cournand² and McMichael³ have adequately explained these terminal mechanisms. As there is no intrinsic cardiac disease, it is important to realize that the whole process remains reversible, while the pulmonary lesions are yet amenable to treatment. Once the lung disease has advanced too far, not even bed rest can materially ameliorate the cardiac failure, which is not primarily dependent on exertion, as in valvular, coronary, arteriosclerotic, and hypertensive heart disease. Such men only too often tend, therefore, to work until shortly before death, and conventional cardiac supportive measures prove of no value.

In many occupational chest conditions in which cor pulmonale has supervened, the aforementioned functional mechanisms can, however, not be satisfactorily demonstrated. Neither emphysema nor pulmonary fibrosis may be present in a quantitatively significant degree. Physiologists have toyed with the concept of thickened alveolar membranes or have sought to adduce proof of increased resistance to gas exchange across the alveolar membrane. There is some apparent success in this direction, so that we have a further mechanism whereby cor pulmonale may be provoked through anoxemia. Histological confirmation of such damaged membranes requires further elaboration. The physiologists have also drawn attention to the factor of impaired oxygen transport and inequalities of perfusion which presuppose some deficiency of the pulmonary circulation, either functional or anatomical. An attempt to

elucidate the nature of the latter morphological factor, its nature, localization and distribution, prevalence and relative significance in the different occupational chest diseases at various stages, prompted the present inquiry and has yielded the results to be presented.

The study has been conducted on both the human autopsy and biopsy material and the experimental animals constituting the collection of The Saranac Laboratory. In the present account only reference to human lesions will be made. Though the range of material available for analysis is both unique and extensive, no pretense can be made at this stage that more than the fringes of the problem have been touched. Only a preliminary account will be presented, giving prominence to some of the fundamental principles already uncovered and illustrating certain of the more spectacular lesions. While emphasis will be given to these abnormal vascular features, it must be pointed out that it is neither the intention nor within the range of possibility at the present stage of the inquiry to evaluate the relative severity and to quantitate the multiplicity of the lesions to be enumerated. And while reference will be made to the comparative vascular pathology of the different pneumoconioses, it is by no means the objective of this paper to present a final determination of the manner or degree in which the different dusts affect the vascular systems of the lungs. Attention will rather be drawn to the levels of vascular arborization at which significant functional impairment may be engendered through morphological change.

Logically, too, this account should include in detail the major well-known lesions of the pulmonary vascular system, such as pulmonary artery aneurysm with erosion, hemoptysis, rupture or pulmonary artery thrombosis with infarction or dissemination of emboli. These pathological manifestations are well known already, and it must suffice for the present to draw attention to the fact that they occur in association with the various pneumoconioses.

LESIONS OF THE ALVEOLAR WALL

It has been possible to demonstrate obliteration of the capillary network over extensive areas of alveolar walls in many instances (Figs. 1-3). The commonest cause of this disorder in asbestos-, quartz-, cristobalite-, and talc-exposed workers is the abundant deposition of collagen within the wall (Fig. 1B). The collagen fibers make their appearance in the central mural plane intervening between capillary plexuses facing adjacent alveolar spaces. This observation in itself is interesting insofar as it elucidates the fundamental anatomy of the alveolar wall whose contained capillary networks are thus revealed to be of a dual nature in many localities, each alveolus having a generous supply of capillaries of its own. By the abundant thickening of the collagen sheet, these capillary plexuses are apparently pried apart. However, there apparently is more than mere quantitative deposition of collagen to account for the disappearance of the capillaries, as the latter are frequently seen to survive and overlie abundant masses (Fig. 3A). It is possible that in such cases the capillaries have atrophied because of vascular occlusion in an arteriole in close proximity. This seems warranted when one takes cognizance of the fact that capillaries frequently survive excellently in spite of the abundant presence of a central mural collagenous mass. The latter condition has been seen not only in cases of asbestosis but also in association with quartz, iron, and diatomaceous-earth pulmonary reactions.

The commoner mechanism whereby capillaries are obliterated results from a superficial deposition of collagen between the septal cell layers and the endothelial cells of the capillaries (Fig. 2B). Incidentally, the interposition of this layer of collagen leaves no doubt whatsoever concerning the separate existence of a septal cellular membrane. The capillaries become embraced within such collagenous sheaths and are seen to be considerably narrowed, and their continuity throughout the alveolar walls becomes finally interrupted. Even before the capillaries commence thus to atrophy, it is quite apparent

that the functional efficiency of the alveolar wall must be seriously disturbed through the interposition of the collagenous sheath between the alveolar space and the blood cells. This morphological feature would serve to explain the increased gaseous transfer gradients observed in some of the occupational chest diseases.

Another mechanism whereby the alveolar wall capillaries may be occluded is seen in quartz rock, coal, and graphite miners. In such cases carbon-laden koniophore cells infiltrate into the alveolar membrane and by accumulating here in great numbers effectively displace the capillaries (Fig. 1A). Once more it should be stipulated, however, that a possible additional factor in achieving this result may be through the occlusion of arterioles supplying such lung areas.

In talc workers and persons affected by the sarcoid-like granulomata ascribed to beryllium, and also as a result of the inhalation of amorphous ultramicroscopic siliceous particles, the alveolar walls may be markedly infiltrated by cells, mainly macrophages but also lymphocytes, plasma cells, giant cells, and fibrocytes. The abundant presence of such cells effectively strangles all capillaries adjacent to them (Fig. 2A).

A final mechanism whereby alveolar walls are thickened and in which capillaries are implicated may be seen in iron miners, welders and asbestos and foundry workers more particularly. In such cases multiple layers of collagen and capillaries may be present. The capillary plexuses may alternate with collagen layers or may surround them. There may even be pure multilayered proliferation of capillaries (Fig. 3B). It is quite apparent that, in spite of the addition of such excessive vascular components, only the most superficial capillary plexuses are exposed directly to the air of the alveoli. The deeper layers not only become redundant but also may constitute a functionally disadvantageous vascular by-pass. This hyperemic condition is then the very reverse of the ischemia previously described but may equally be a cause of cardiorespiratory functional impairment.

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SMALL BLOOD VESSEL DAMAGE

The lesions of the smaller blood vessels concern changes of the endothelium and intima, alteration of the muscular coats, and perivascular reactions.

Intimal lesions have been most commonly seen in the lungs of deceased persons exposed to quartz, asbestos, talc, iron, and beryllium salts (Fig. 4A).

The quartz type of reaction tends to take the form of a centripetal deposition of concentric collagen bundles, and the advancing broadened intima gradually seals off the vascular lumen. The resultant effect may not be very dissimilar to a mature silicotic nodule, except that the residua of the lamina elastica may be demonstrable by appropriate staining techniques.

The endothelial reaction in iron miners' and foundry workers' lungs may appear as nodular excrescences copiously charged with metallic particles. These swellings may effectively obliterate the lumen. In the asbestos, talc, and beryllium cases there may be a fibrocellular proliferation of the intimal zone without any obvious deposition of foreign bodies, though the latter may be present in great numbers around the blood vessels. Occasionally asbestos and tremolite bodies may, however, be seen within the intima, and iron staining may bring out marked focal prevalence of such elements, especially in talc workers (Fig. 8B). Both in talc and in asbestos workers there is a greater tendency for veins to be similarly affected. Completely occluded venules are frequently seen within larger masses of fibrosis, their lumina being sealed off by abundant intimal tissue composed of a loose web of collagen with interspersed cells (Fig. 10B). Unless such areas are stained by collagen or elastic tissue methods, these features may be missed entirely, as the destroyed vessels ultimately merge completely with the surrounding scar tissue.

Damage to the muscular coats is most commonly seen in association with asbestos and talc exposures. It tends to take the form of a focus of irregular fibrocellular reaction which invades and disrupts the continuity

of the muscle sheets (Fig. 4B). Asbestos or tremolite bodies may be demonstrable within the lesion. The whole mass may bulge prominently into the vascular lumen, almost to the degree of partially occluding it. This effect may be aggravated by a measure of intimal proliferation opposite the nodule, and thrombi tend to form at such sites.

Perivascular reactions stand out, however, as the most important features of the occupational dust diseases. They may be present around the smaller vessels, with or without any narrowing of the lumen. In most cases they commence as macrophage or lymphocytic accumulations in the perivascular lymphatics (Fig. 5).

Deposits of this nature are probably least common in the frankly silicotic cases and most prevalent in association with asbestos, talc, coal, and iron exposures. The reaction occurs either as a cellular deposit or in the form of a collagenous sheath (Figs. 6A and 11A).

The talc and gypsum perivascular lesions are probably the most characteristically cellular examples (Fig. 6B). In instances of virtually pure talc exposure, abundant macrophage deposits accumulate around the smaller vessels and generally do not affect the vascular lumen materially. Provided that quartz has not been inhaled along with the talc or gypsum in any significant amount and provided that the tremolite and anthophyllite content of the talc is low, virtually no collagen is found in these masses, and the encircled blood vessel may show no material adventitial reaction or change in caliber.

Cellular deposits are also characteristic of graphite, coal, and iron miners, with the qualification that these cells are now heavily laden with the appropriate foreign substance (carbon, coal, or iron). The essential lesion of coal miners' pneumoconiosis and of siderosis is such a perivascular koinophore deposit, and this fact emphasizes the error many radiologists fall into when they seek to differentiate between vascular shadows and nodules in these diseases. It is simply not possible to make such a distinction (Fig. 7A).

The perivascular coal lesion may usually be demonstrated in every stage of its evolution in the average case. It commences as a dominantly cellular limited deposit around smaller blood vessels, mainly arteries. By the successive addition of new dust-laden cells, the mass grows progressively until it has the appearance of a stellate nodule. The more quartz there may be, the greater the abundance of collagen fibers which are deposited among these cells and the stronger the tendency for their deposition in the form of concentric whorls. The tendency toward stenosis and virtual occlusion of the blood vessel is enhanced by the presence of quartz along with the coal or iron, but even when the free silica content of such lungs is virtually insignificant, marked stricturing of the blood vessels contained within the pigmented masses commonly occurs. Perhaps the role of these changes has in the past been somewhat overlooked as a cause of pulmonary disability and ultimate cor pulmonale in anthracotics and siderotics.

In asbestosis, the earlier perivascular reaction tends to be cellular and is replaced later by a loose collagenous plexus. Asbestos bodies may frequently be seen both in the cellular phase (Fig. 8A) and also later when the fibrous collar commences to form, the bodies remaining trapped among the collagen bundles. Within this mass the trapped blood vessel either may show no change in caliber and form or may be markedly narrowed and distorted. The concurrent presence of some quartz in the lung tissue markedly enhances the latter tendency.

Perivascular changes provoked by cristobalite, as in diatomaceous-earth disease, tend to be in the nature of a diffuse, irregularly collagenous character, with many cellular elements interspersed among the fibers. The perivascular reactive zone shades off gradually into the more distant lesions.

DAMAGE TO ARTERIES AND VEINS

Blood vessels which may seem perfectly normal to naked eye inspection may nevertheless present a variety of pathological features on microscopic examination of their

walls. In a case where the main exposure was to cristobalite and in another where the causative agent was asbestos, considerable irregular thickening of the intimal layer could be demonstrated in some medium-sized vessels without any simultaneous damage to the elastic laminae but with some fatty infiltration of the muscular coat (Fig. 9A). There was, however, considerable periarterial fibrosis in these cases as well.

More generally the lesions of the intimal coat are atheromatous plaques, and these occur in the main pulmonary arteries or their primary branches. However, one case of an iron foundry worker was found in which atheroma could be traced to the fourth and fifth series of vascular ramifications. No significant atheroma was demonstrable in this case in the aorta or systemic vessels.

A rather spectacular injury sustained by the pulmonary arteries of intermediate caliber may sometimes be seen and takes the form of segmental collagenous infiltration in the muscular coat whose individual bundles may be seen to be separated by intervening fibrous layers (Fig. 9B). Instances of such change have been seen in association with both silicosis and asbestosis. Neither pigment nor asbestos bodies could be demonstrated within these degenerative vascular segments, but this does not exclude their being present. At such segments the vascular walls may be considerably thickened.

Similar changes have been seen in the veins in asbestosis but not in silicosis.

Changes in the vascular adventitia are to be expected, as the specific dust reactions are grouped around the blood vessels. These changes are most frequently observed in asbestosis and diatomaceous-earth disease and may include some damage to the external elastic lamina, especially in the case of the veins coursing through interlobular septa. Such changes are also quite common in cases of silicosis or siderosis where there has been a significant degree of associated infection. The essential nodule of coal miners' anthracosilicosis is also a similar lesion, though the abundance of the perivascular carbon pigment may obscure the associated col-

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agenosis unless special staining is resorted to. The central vessel either may be markedly constricted or may show no material narrowing of its lumen. Arteries tend to show the former type of reaction and veins the latter, though this is not an inflexible rule.

An interesting feature observed more particularly in anthracosis and siderosis concerns the attempted effective recanalization of partially occluded blood vessels through the enlargement of one or more of the vasa vasorum (Fig. 7B). Whether any significant measure of collateral circulation may thus be established remains in some doubt, though Liebow's² researches have given strong support to the fact that the bronchial arterial system may materially supplement and sustain a defective pulmonary arterial system. It is possible that such a collateral circulation may be adequately demonstrated only through injection techniques and that the sites of inoculation are rapidly obliterated. However, in the examples identified in The Saranac Laboratory series, it seems that the communication between the pulmonary and the bronchial arterial systems is definitely via the vasa vasorum.

RELATIONSHIP BETWEEN VASCULAR LESIONS AND SPECIFIC DUST NODULES

The crucial medicolegal issue which emanates from the foregoing demonstration of a variety of pulmonary vascular lesions in persons who have been exposed to different occupational hazards concerns not only the relationship of such lesions to the dust particles which are demonstrable within them but more particularly their relationship to the pathognomonic dust reaction.

The majority of the occupational dust diseases are characterized by the presence of nodules in the lungs. Silicosis is the classical and extreme example, and asbestosis the least conformer. The nodules of siderosis, anthracosis, and talcosis are primarily perivascular in disposition, and the granulomata associated with beryllium exposures, though localized to the alveolar walls, are essentially periarterioles. Shaver's disease and diatomaceous earth disease are less readily related

to the vascular system. They are, in a sense, pericapillary lesions, which accounts for their diffuse character.

The relationship between the silicotic nodule and the vascular system is the most interesting to explore. It has been fairly well established by the work of Simson, Strachan, and Irvine³ that the classical silicotic nodule develops within the pulmonary lymph nodes in man. This accounts for its characteristic location and its discrete or focal character in the average case of moderate exposure to quartz particles. The distribution of these lymph deposits has been fairly well defined by Miller.⁴ They tend to occupy the points of bifurcation or ramification of the pulmonary arteries and also follow the venous system along interlobular septa toward the pleura. In this sense, therefore, while the silicotic nodules are not perivascular, they are at least paravascular in topographic disposition.

Lymph nodes are supplied by arterial twigs from adjacent arteries, and it would be surprising, therefore, to find silicotic nodules which have not at least some semblance of a relationship to the vascular system. The mature hyalinized silicotic nodules appear to be completely avascular, to be true, but the immature nodule almost always has a small arteriole leading to it. Sometimes this vessel is eccentric (Fig. 12A), and at other times it is central in relation to the whorls of collagen (Fig. 11B). What happens to this vessel? When sufficient numbers of nodule sections are prepared by means of elastic stains, it may be possible to demonstrate the remains of such vessels often deeply buried within the mass of collagen (Fig. 12B). The elastic lamina survives the collagen change and leaves a telltale ring pattern.

This discovery has dual significance. In the first instance, it reveals that the very creation of silicotic nodules may be dependent on the existence of a system of nutrient arteries. This may explain partly the progressive growth of silicotic nodules. Secondly, it points to the fact that the maturation of silicotic nodules leads to the interruption of the continuity of smaller arterioles. These may all be end arteries destined to the lymph

nodes in which the silicotic nodule develops, so that final occlusion of the vessel may have no material effect on the pulmonary circulation as a whole. On the other hand, if the shut-off vessels were also required to perfuse areas of lung tissue beyond the site at which the nodules form, their obstruction by the silicotic nodule would be reflected in regional impairment of lung function, whose total effect would ultimately begin to influence the efficiency of the lung as a whole when sufficient numbers of mature nodules have been formed. The foregoing features have been seen in both silicosis and siderosilicosis.

In asbestosis we find an entirely dissimilar state of affairs. The predilection of the asbestotic focus is paravenous (Fig. 13A). The fibrotic area is seldom spherical as in silicosis, though it may be circular in cross section. More generally it presents as an irregular mass adjacent and adherent to the venous adventitia and composed partly of cells and partly of irregularly aligned collagen and elastic bundles with asbestos fibers and bodies among these. The wall of the vein may or may not be materially affected by the presence of the asbestotic reaction. In this respect once more asbestosis differs from silicosis, for when a silicotic nodule comes to lie against a large blood vessel the muscular component of the vessel closest to the nodule becomes considerably thickened and distorted through the deposition of collagen bundles among the muscle fibers (Fig. 13B).

Asbestotic fibrocellular masses are commonly disposed around extensive sections of veins or arteries. The presence of the encircling cicatricial mass distorts and narrows the vessel (Fig. 11A), though not invariably, and it is often surprising to see how little the vessels imbedded within extensive masses of asbestotic granulation may be disturbed. These variations may account in some measure for the lack of correlation between the degree of disability and the extent of pulmonary reaction seen in asbestotics from the same or different industries.

Asbestotic tissue differs further in a vascular sense from the silicotic reaction, in possessing a generous capillary supply (Fig.

10A). Such capillary infiltration into the area of pigment deposition or fibrocellular reaction is entirely lacking in anthracosis, siderosis, berylliosis, and talcosis. In the areas of reaction to gypsum, capillary proliferation may be markedly enhanced.

In the pleura, too, such distinctions are usually demonstrable. The silicotic pleura tends to be avascular, and this tends also to be the state of affairs in siderosis, berylliosis, and anthracosis. In asbestosis, talcosis, and the gypsum lung, the pleura may be focally or diffusely thickened through the addition of a layer of collagen-infiltrated tissue between the lamina elastica and the mesothelium. This zone is richly permeated by vascular and lymphatic capillaries, and within it asbestos and tremolite bodies may often be demonstrated.

PULMONARY ARTERIES

Reference has already been made to atheroma as a relatively common finding in the intima of pulmonary arteries and their primary branches, especially when chronic cor pulmonale is present (Fig. 15A). Such atheroma relatively seldom progresses to thrombosis or erosion, but aneurysmal distentions are not uncommon in silicosis. In all the occupational pulmonary dust diseases, marked distention of the pulmonary arteries and their primary and even secondary branches may be a prominent feature. The vessels may be doubled and even trebled in caliber. Such changes are, however, commonest in berylliosis, silicosis, asbestosis, and talcosis. This condition is rare in uncomplicated siderosis.

Stenosis distortion and fixation of the pulmonary vessels through hilar fibrotic masses or by the presence of enlarged hilar nodes is to be seen most commonly in silicosis, particularly where there has been some associated infection (Fig. 14A). It is an uncommon feature in uncomplicated siderosis, anthracosis, or asbestosis and has not been present in the beryllium series available for examination.

Opposite silicotic nodules these larger vessels often show some measure of mural

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thickening, with or without collagenosis (Fig. 14B) and intimal atheroma (Figs. 14A and 15B). This state of affairs has not been seen in the other occupational dust diseases of the lung.

The range of abnormalities of the larger pulmonary vessels is therefore relatively limited as compared with the multiplicity of changes demonstrable in the smaller vessels. It is indeed apparent that the brunt of pathological stress falls on the least components of the vascular system.

INFECTION AND VASCULAR ABNORMALITIES

The addition of tuberculosis to the silicotic process has a markedly deleterious effect on the pulmonary blood vessels. Tuberculosis *per se* does not necessarily affect the vascular elements, though, when sufficiently advanced, the fibrotic process may obliterate blood vessels. This, however, seldom leads to a cor pulmonale (Gardner*). Even in tuberculosilicosis, cor pulmonale may be a less common accompaniment of advanced disease than, in comparable degrees, of noninfective lesions, though not infrequently the most advanced stages of right heart involvement are seen in connection with the combined disease. The former state is somewhat surprising in view of the extensive loss of vascular bed which accompanies the infective process. The tuberculosilicotic lesion, in particular, is characterized by its virtually complete avascularity.

The manner in which blood vessels may become affected in tuberculosilicosis varies. Where the process is tuberculosilicotic from the start, the vessels are slowly involved by the peripheral expansion of the lesion. It first becomes adherent to the infected nodule, and subsequently dust-laden phagocytes and fibrocytes encircle the vessel while its walls undergo degenerative changes. Through intimal proliferation the lumen is thereafter occluded.

Similar changes are seen in proximity to tuberculous cavities whose walls may contain many degenerated and occluded vessels. Occasionally, however, a blood vessel may be seen to survive within one of the septa of a multilocular cavity, and this tendency is the

greater the more frankly tuberculous the lesion happens to be. These features may explain the relative paucity of frank and massive hemoptysis in tuberculosilicosis as compared with tuberculosis itself.

Blood vessels may also become trapped, degenerated, and occluded by two additional mechanisms in the presence of added infection. Where tuberculosis manifests itself as a transient pneumonic process in a silicotic, the vessels within the inflamed area acquire a dense fibrocellular sheath during the process of resolution or organization, and the proliferation of these cells indicates clearly that they derive some of their stimulus from the presence of quartz in the perivascular lymphatics.

A final manner in which such vessels become affected is discernible in the parenchymal tissue which intervenes between adjacent tuberculosilicotic masses. Here the arteries in particular are seen to acquire thick fibrocellular cuffs within which characteristic tuberculosilicotic tissue reactions may take place, thus indicating the presence of both the dust and the infective components. Such vessels show a marked tendency to endarteritis obliterans.

The infective processes just described in connection with silicosis are demonstrable in siderosilicosis and anthracosilicosis as well but tend to be markedly modified by the presence of the specific iron or carbon deposits. In the case of both anthracosilicosis and siderosis, the carbon and the iron appear, respectively, to enhance the tendency to vascular damage where there is associated tuberculosis. When tuberculosis supervenes in either relatively pure siderosis or anthracosis, the presence of the iron or the carbon has the opposite influence in that these substances tend to retard vascular damage.

Asbestosis is but seldom complicated by tuberculosis, and when the latter is present, there appears to be no specific tendency to added vascular damage. More commonly the infective agent in asbestosis is in the nature of a nonspecific bacterial bronchopneumonia. The repeated recurrence of such inflammatory episodes has the effect of trap-

ping large numbers of asbestos fibers within organizing tissue and thus rapidly to extend the asbestotic granulation reaction. No specific damage is caused to blood vessels in this process, and one gains the impression rather that they are less disturbed in such areas than in the more chronic primary asbestotic process. Similar remarks apply to talcosis, though the tendency for a quartz component to further complicate the matter by forming perivascular fibrotic deposits is relatively strong here. When quartz is present in moderate amounts, the resultant postinfective lesion may initially be a collagenized granulation tissue which is well permeated by capillaries.

RELATIONSHIP BETWEEN VASCULAR CHANGES AND COR PULMONALE

The foregoing account of the variety of vascular changes to be encountered in association with some of the occupational pulmonary dust diseases must perforce incline one to the conclusion that the magnitude of the blood-vessel disease encountered in the lung may play some part in the genesis of cor pulmonale. In theory, one could imagine the right heart laboring against peripheral obstruction in the pulmonary circuit. However, the principle involved is more than one of mere mechanics. By analogy, for instance, the ventricle does not hypertrophy because a patient has had his legs or even all his extremities amputated. Even in the presence of multiple peripheral and organ infarction in atheromatous disease, which presupposes a markedly reduced systemic vascular bed, systemic hypertension does not necessarily develop. Similarly, pulmonary hypertension is often conspicuous by its absence in advanced fibroid phthisis in which a majority of lung blood vessels may be sealed off.

No doubt many subtle physiological mechanisms are brought into action before the right ventricle will tend to hypertrophy in response to rising pulmonary tension. In the case of left ventricular hypertrophy associated with systemic hypertension, there are functional as well as organic peripheral vascular changes and vessels are only partly

stenosed, becoming sporadically occluded as terminal regional phenomena. Perhaps the mechanism in the lungs is comparable with this systemic pattern of behavior, so that partial narrowing of lung blood vessels and segmental injury to their walls may have a more markedly enhanced effect in raising the pulmonary artery pressure than when these vessels are completely occluded in the pneumoconiotic process. The relative ischemia at points distal to such narrowings is bound to influence markedly the capacity of the lung to oxygenate the blood, and the ensuing anoxia and resultant pulmonary hypertension will be proportionately greater if there are at the same time other associated causes of anoxia, such as bronchospasm and emphysema. This will tend to lead to a vicious cycle, for progressive increase in pulmonary artery tension is not likely to improve circulation through distorted, narrowed, fixed, or spastic arteries, arterioles, and capillaries. Whether the vascular damage per se (i. e., in the absence of such associated causes of anoxia) would be sufficient to provoke pulmonary hypertension is not yet proved at this stage, but the anatomical basis for such a possibility does at least exist, and in terms of hydrodynamics it ought to be possible.

SUMMARY

The lungs of persons who have been adequately exposed to industrial dusts, including quartz, iron, coal, talc, gypsum, diatomaceous earth, beryllium compounds, and asbestos, either singly or in combination, show a diversity of lesions of the blood vessels whose prevalence and extent vary according to the nature of the foreign substances deposited in the lungs, their quantity, and associated infection.

The most marked effects are on the smaller vessels and comprise cellular and collagenous lesions of the capillaries in the alveolar walls, damage to the intima, muscular coats, and adventitia of the arterioles and venules, and perivascular deposits of pigments, fibrocytes, and macrophages with variable degrees of associated fibrosis. The effect on these small vessels may be to occlude, stenose, and distort

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them and to create inefficient vascular short circuits.

Larger pulmonary vessels may also show damage, ranging from intimal atheroma to medial segmental hypertrophy and collagen degeneration, cicatricial stenosis, and aneurysmal distention. Such vessels may become eroded and rupture.

In silicosis, the vascular damage is an added lesion over and above the specific collagenous nodules, which latter may, however, show their own peculiar vascular degenerative phenomena. In anthracosis, siderosis, berylliosis, talcosis, and asbestosis, the perivascular lesion is an integral and indistinguishable component of the pathognomonic pulmonary dust lesion.

Specific dust particles or fibers and even asbestos and tremolite bodies may, in most instances, be demonstrated within or in relation to these vascular lesions.

In the presence of superimposed infection, particularly tuberculosis, the vascular damage may be disproportionately great. This effect is enhanced if there has been associated quartz inhalation. Asbestosis does not follow these rules directly.

It is suggested that these vascular changes may be a factor in the genesis of cor pulmonale, though it is not at present established that they may bring about this result in the absence of associated physiological disturbances leading to anoxia.

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DISCUSSION

DR. P. G. BOVARD: Dr. Schepers' discussion was extremely interesting and new. I would like to ask him what causes collagen to accumulate about the arterioles and whether it may be found in persons not exposed to dust.

DR. SCHEPERS: Collagen deposition can occur in the lungs apart from dust exposures. There is a well-known and growing concept of a group of diseases known as the collagenoses. They are characterized by collagen changes not only in the lungs but also in other organs, for instance, in the heart, in the skin, in soft tissues, around joints, and in organs such as the kidneys. One characteristic type is the generalized pulmonary collagenosis of the Hamman-Rich syndrome mentioned by Dr. Van Ordstrand. Others include scleroderma, in which there are collagen deposits in lungs and the skin, periarteritis nodosa, and lupus erythematosus. In coal miners there is also sometimes an arthritis associated with nodular deposits in the lungs. In dermatomyositis, collagen is deposited in muscles, including the diaphragm and intercostal muscles, but no reports concerning lung deposits have been submitted as yet. In those conditions we do not know what the cause of that collagen formation is. There is more speculation than facts in the medical literature. In the case of silicosis we do have evidence that the silica attracts to the sites of its deposition in the tissues the macrophages and the fibrocytes which are normal cellular components of connective tissue. Collagen is formed, as far as we know, by these fibrocytes, and complex enzyme systems may be involved. At least we know that in silicosis the fibrocytes have prior existence in the tissue where the collagen forms. We also know that collagen formation is very largely linked with metabolism of the suprarenal cortex. That is why Dr. Van Ordstrand mentioned the excellent response that he obtained with cortisone and corticotropin.

MR. RAHN: To what type of beryllium was the exposure in the cases illustrated? Was it a beryllium-copper alloy?

DR. SCHEPERS: In the cases of vascular disease to which I referred, the industrial exposure was to beryllium oxide dust and not to beryllium alloy.

DR. E. P. SWARTZ: Dr. Schepers, have you correlated the blood vessel changes with the age of the person?

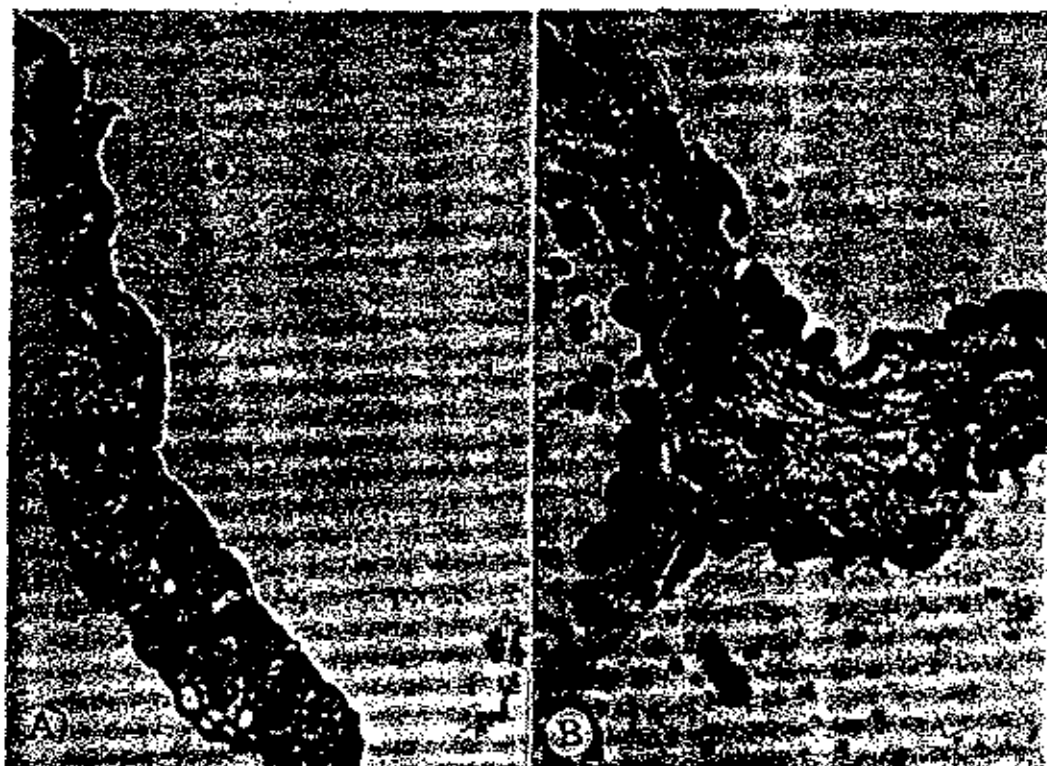
DR. SCHEPERS: My data were all derived from persons who were under 50 years of age at the time of death. I deliberately excluded older persons from my study, as we know that certain degenerative changes take place in the blood vessels of older persons. A study of the incidence of these collagen changes at different ages, compared with their relative prevalence in relation to dusty exposure, is in progress and will be reported later.

DR. S. RISMAN: Assuming that mineral dusts may affect pulmonary vascular structures, does that mean that symptoms may occur without significant or typical roentgenogram changes?

DR. SCHEPERS: When there are no space-occupying lesions in the lung and if there is no radiopaque substance in the perivascular tissues, there will be no shadow on the radiogram. Before the x-ray can record on the roentgenograph film, it has to pass through almost a foot of chest wall and lung tissues. Any substance which will cast a separate shadow must therefore be more dense or occupy a certain amount of space in order to be recorded. These changes which occur in blood vessels are for the

above reasons frequently not demonstrable in the type of radiograms which are useful for routine purposes. On the other hand, if those same radiograms are scanned from a different point of view, i. e., if one searches specifically for evidence of blood vessel damage, it is very frequently possible to recognize changes previously overlooked on merely scanning the same x-rays for nodules. These lesions manifest themselves through the absence of lung markings (representing blood vessels) which were previously demonstrable. Such blood vessel damage may of course very easily be demonstrable by means of arteriography or even by tomography which displays the vascular architecture of the lungs quite well. Moreover, one would have the associated radiographic, clinical, and electrocardiographic evidence of cor pulmonale to provide further clues. It would be entirely unjustified to reason that, because the person in question has breathed a dust, a significant amount of damage to the blood vessels of his lungs must *ipso facto* be present, even though it cannot be demonstrated by any known clinical means. The condition must be provable in order to be diagnosable.

Fig. 1.—Ischemia of alveolar walls. A, obliteration of capillary plexus in alveolar wall through macrophage infiltration (quartz and cristobalite exposure). B, destruction of capillary plexus through collagen deposition within alveolar wall (tremolite talc miner).



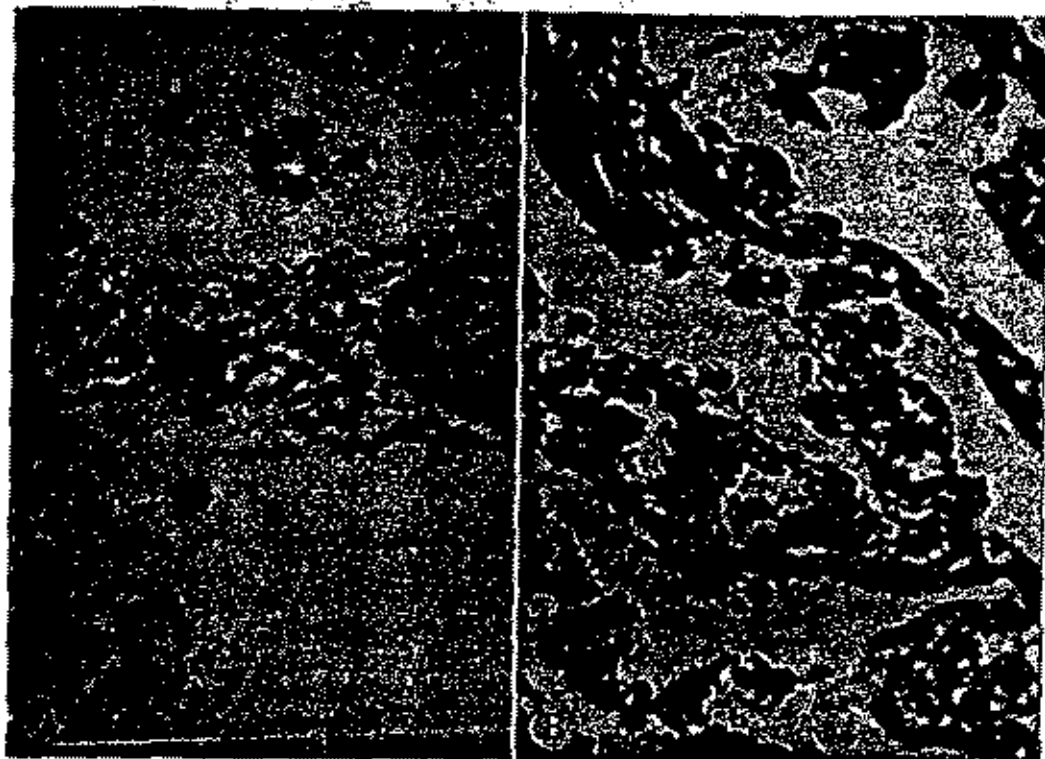
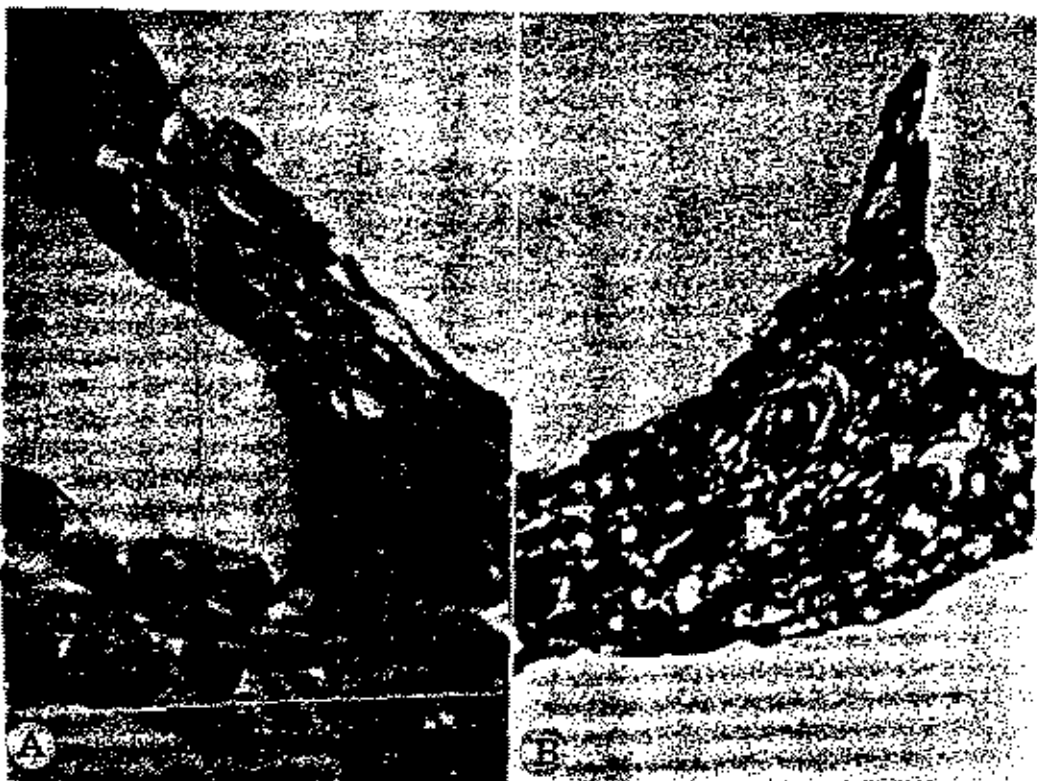


Fig. 2.—Reduced alveolar wall capillary circulation. *A*, impairment of capillary bed through lymphocytic mural infiltration and giant-cell formation (beryllium worker). *B*, alveolar mural capillaries encircled by irregular collagen deposits (asbestos worker).

Fig. 3.—Alveolar wall damage without loss of capillaries. *A*, preservation of alveolar wall capillaries despite copious deposition of collagen along central plane around asbestos fibers (asbestos worker). *B*, multilayered capillary plexuses causing thickening of the alveolar wall (iron welder).



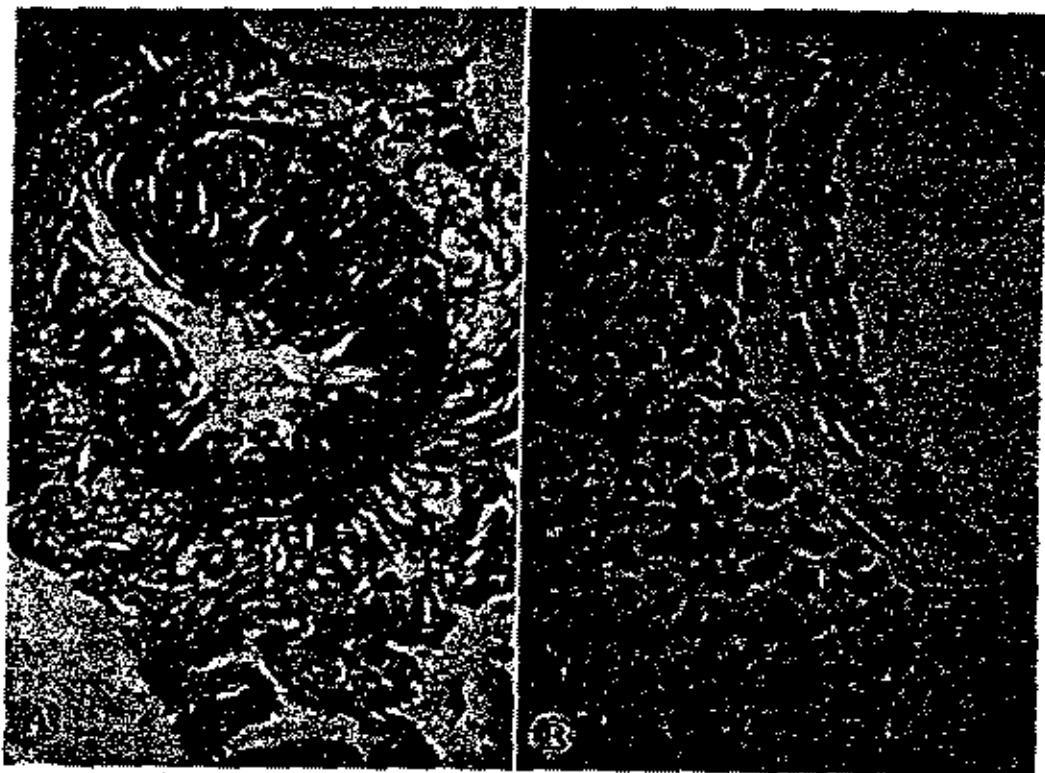
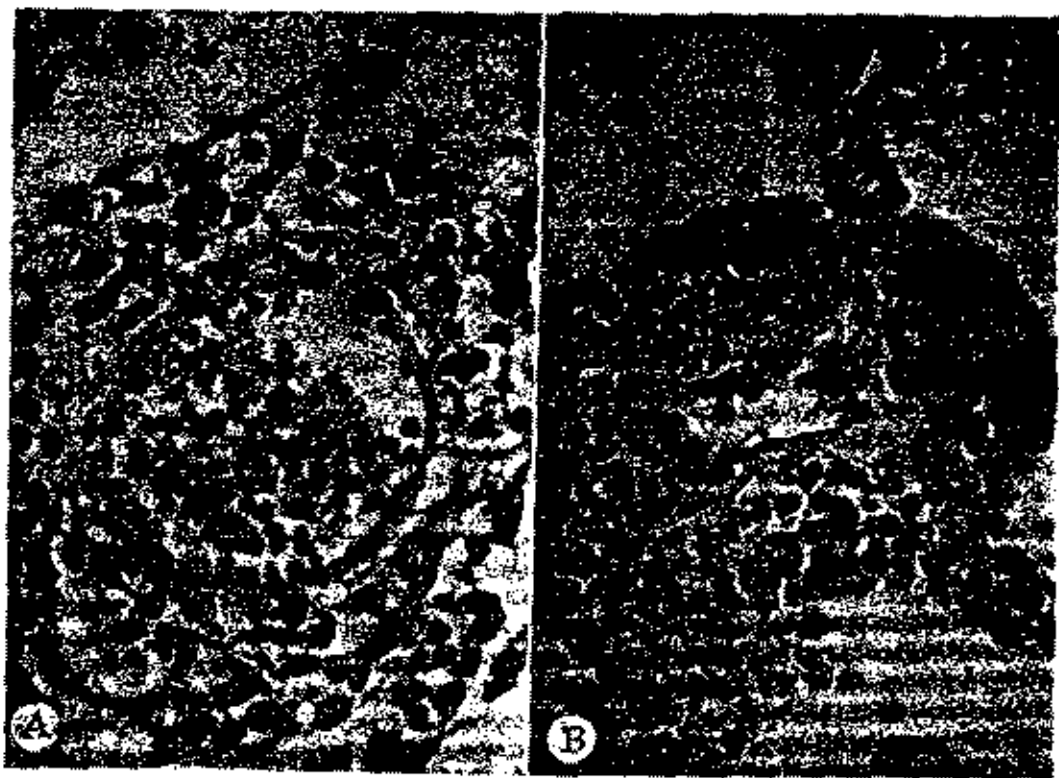


Fig. 4.—Damage to small blood vessels. *A*, proliferation of the vascular intima with partial occlusion of the lumen (talc worker). *B*, cellular infiltration around fibers penetrating the muscularis (asbestos worker).

Fig. 5.—Infiltration of perivascular lymphatics. *A*, plasma cell and macrophage accumulation around a venule (granite worker). *B*, lymphocytic collar around arteriole occupying adventitial lymphatic plexuses (uranium worker).

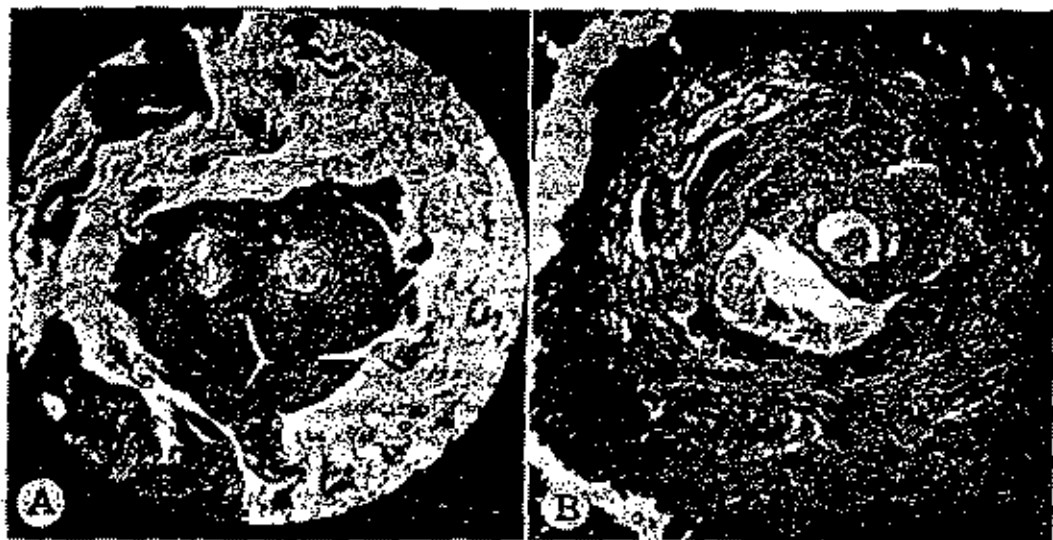


COMPARATIVE VASCULAR PATHOLOGY



Fig. 6.—Perivascular deposits and reaction. *A*, quartz and iron deposited around a blood vessel with abundant collagen reaction (magnetite miner). *B*, cellular accumulation about a blood vessel without collagen formation or vascular stenosis; cells supported by reticular network (gypsum worker).

Fig. 7.—Cumulative perivascular deposits. *A*, abundant deposition of iron around small artery, with some collagen reaction and partial occlusion of the lumen (iron miner). *B*, massive carbon deposit around artery, with partial obliteration of lumen and enlargement of one of the vasa vasorum (coal miner).



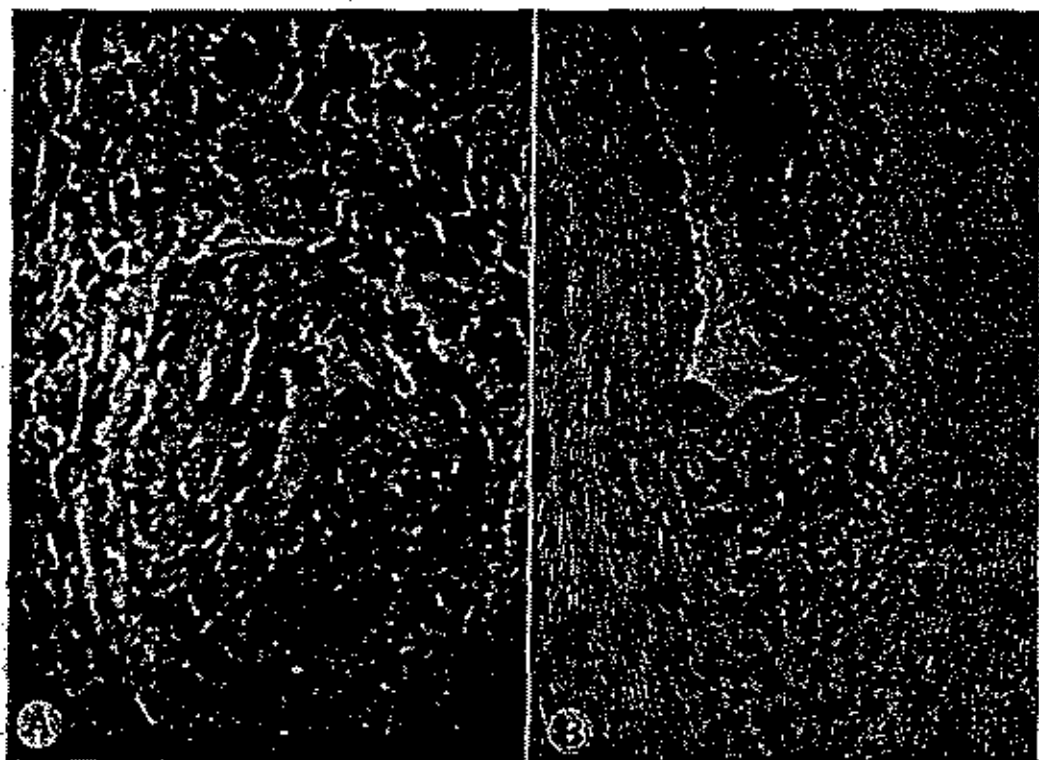
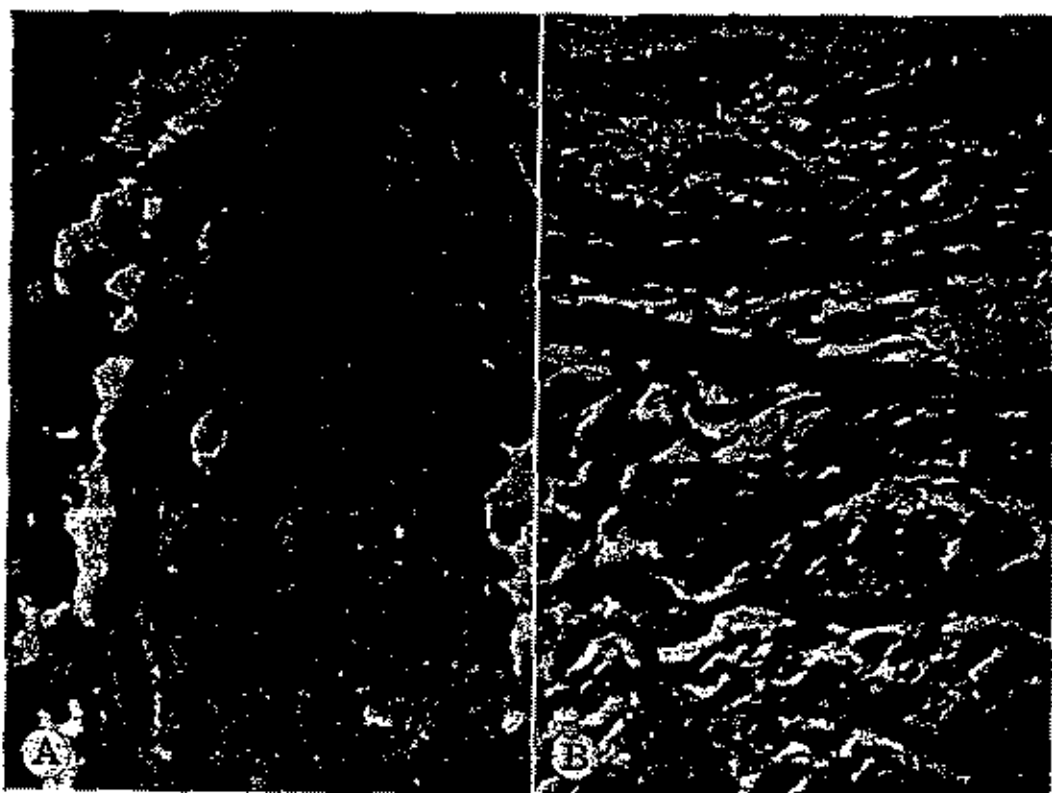


Fig. 8.—Vascular deposition of fibrous dusts. *A*, chrysotile bodies within the adventitia of a small artery (asbestos worker). *B*, tremolite bodies within intima of medium-sized blood vessel (talc miner).

Fig. 9.—Mural damage in small blood vessels. *A*, intimal proliferation and distortion, with fatty infiltration of muscularis (asbestos worker). *B*, deposits of collagen intervening between muscle layers of artery (quartz exposure).



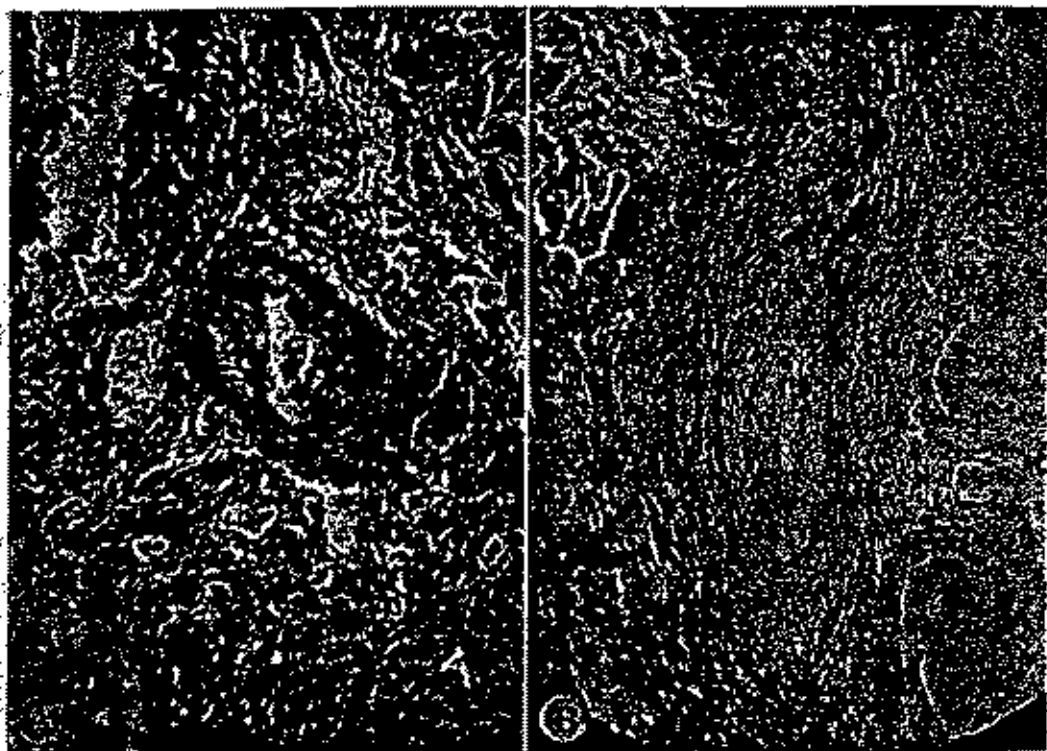
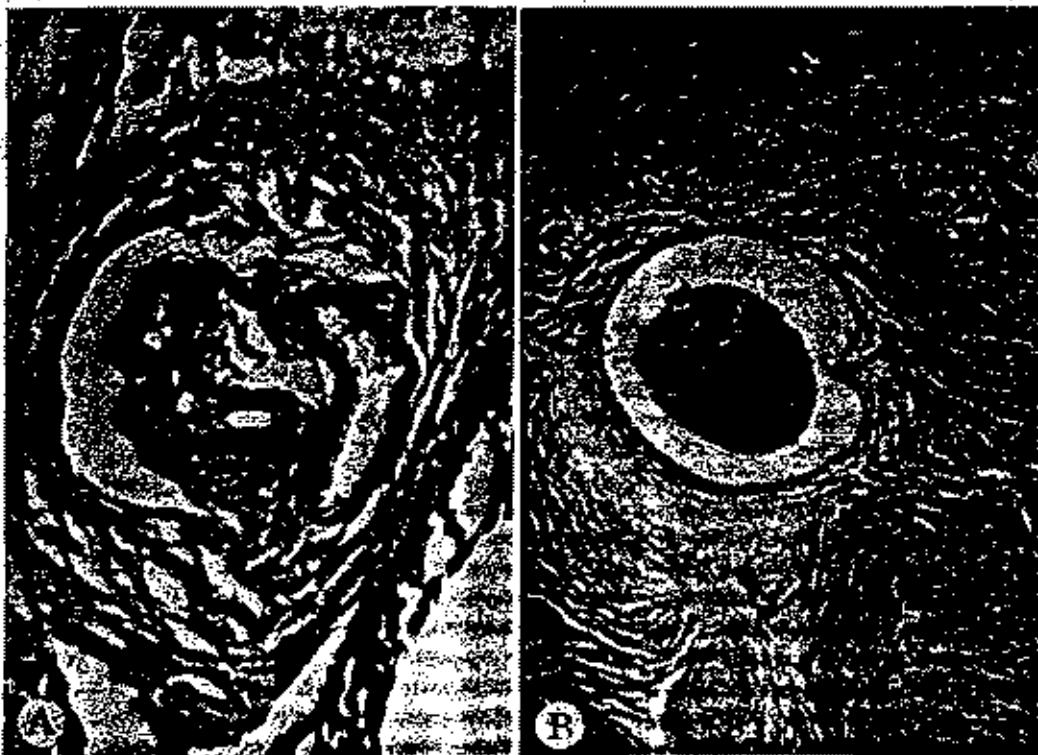


Fig. 10.—Obliteration of blood vessels. *A*, vessel, trapped within area of vascular granulation reaction, undergoing endarteritis obliterans (asbestos worker). *B*, almost completely obliterated vein, displayed within an area of diffuse fibrosis by means of Weigert's stain (quartz-rock miner).

Fig. 11.—Relationship between blood vessels and nodules. *A*, blood vessels trapped within collagen sheath; cristobalite reaction (foundry worker). *B*, blood vessel surviving within center of silicotic nodule (magnetite miner).



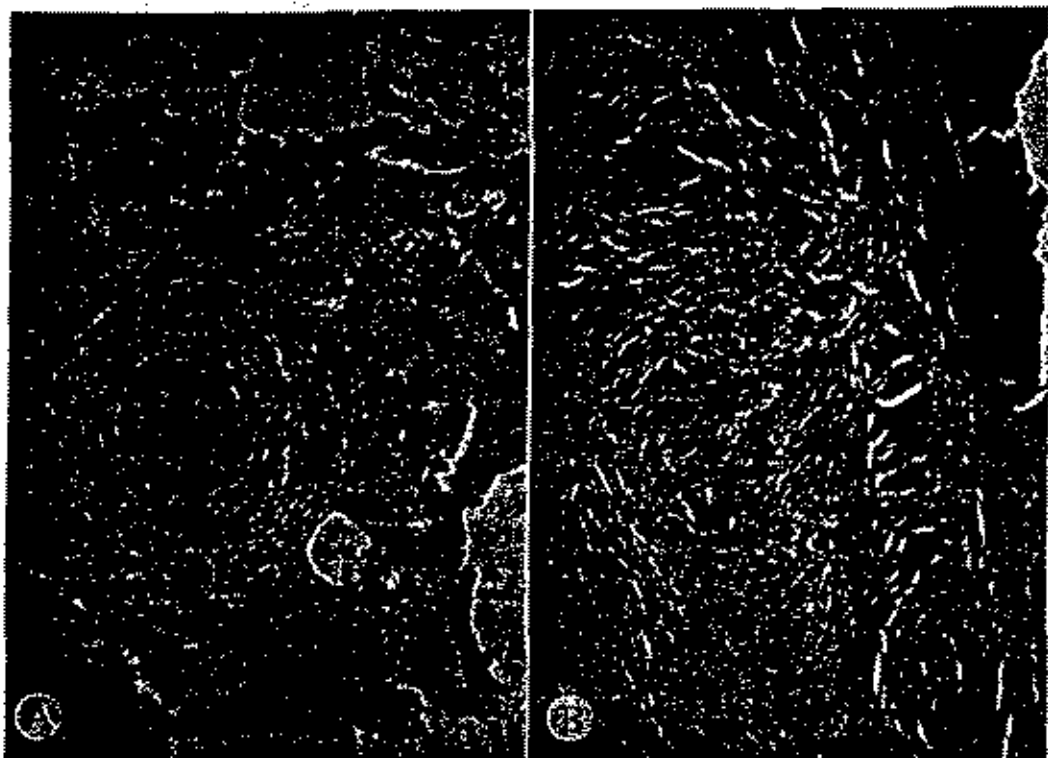


Fig. 12.—“Nutrient artery” simulation in developing silicotic nodule. *A*, silicotic nodule with prominent blood vessel in zone of fibrocellular reaction (flux-calcined diatomite worker). *B*, elastic skeleton of occluded blood vessel, demonstrated by Weigert's stain, within cortical zone of silicotic nodule (quartz-rock miner).

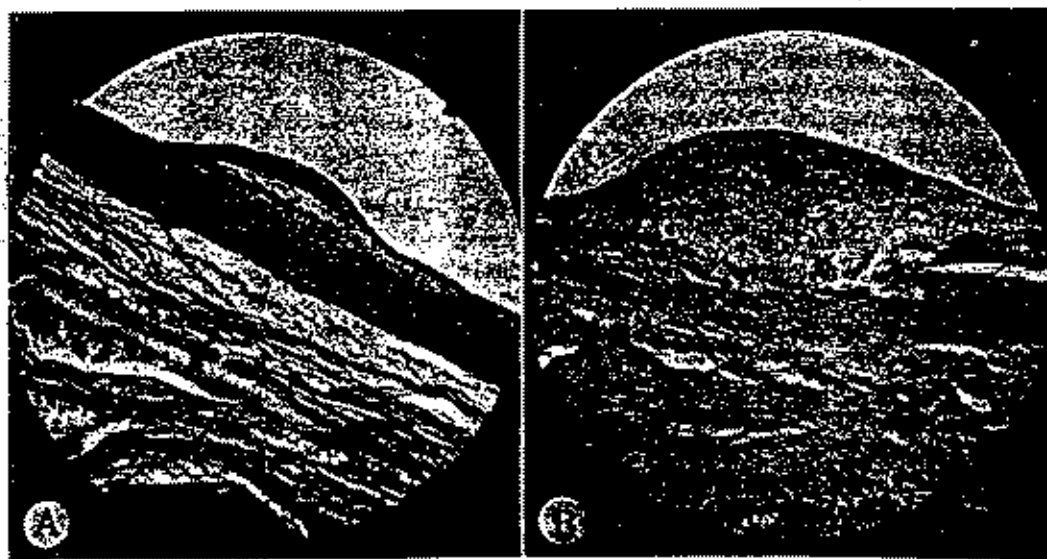
Fig. 13.—Effect of proximity of nodules on vessels. *A*, abortive nodule fuses with collagenous bundles of adventitia of vein (asbestos worker). *B*, silicotic nodule, abutting on blood vessel, thickens proximal walls but does not disrupt elastica externa (quartz and cristobalite exposure).





Fig. 14.—Influence of silicotic nodules on adjacent blood vessels. *A*, Irregular thickening of blood vessel walls where they lie in juxtapposition to a mass of silicotic nodules (granite worker). *B*, diffuse thickening of a blood vessel wall opposite a hilar node (quartz-rock miner).

Fig. 15.—Pulmonary atheroma in silicosis. *A*, atheromatous plaque overlying hypertrophic muscularis; cor pulmonale (quartz-rock miner). *B*, atheroma opposite an adherent silicotic nodule; no cor pulmonale (quartz-rock miner).



The Value of Lung Biopsy in the Diagnosis of Occupational Pulmonary Diseases

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LAWRENCE J. McCORMACK, M.D.
and
JOHN S. HAZARD, M.D., Cleveland

Our forebears as well as our confreres have taught us what the clinical and roentgenographic findings should be in occupational diseases of the lungs. This acquisition of knowledge has been particularly facilitated by the past McIntyre Research Foundation Conferences and the Saranac Symposia.

We are, however, also learning that certain nonoccupational diffuse pulmonary lesions will mimic those of industrial cause, and it is common for the person having pulmonary disease to attribute the condition to an environmental cause. Furthermore, we do not believe that one should be too critical of the physician who, through lack of training and experience in pneumoconioses, may also first think of the possibility that the lesion is of occupational origin. This impression is especially likely in those cases where all diagnostic studies by routine methods have failed to establish an accurate diagnosis.

We have found that a surgical lung biopsy is indicated and usually can establish the diagnosis in these borderline cases. This pro-

cedure usually will prove or disprove an occupational relationship when multiple methods of study are employed. In our hands, needle-aspiration biopsy and scalene node biopsy have not been of significant aid in this particular group of cases. A biopsy of the scalene area can only reveal the disease that will reflect itself in the scalene lymph nodes. A significant number of diffuse pulmonary diseases do not show an affinity for the scalene or any other lymph node group. We believe that a surgical procedure like scalene node biopsy that offers less than a 50% yield in diagnosis does not approach the ideal in efficiency.

We have employed a technique of surgical lung biopsy for a period of five years at the Cleveland Clinic which has permitted study of the lung disease by histopathologic, chemical, and bacteriologic analyses. Although the method is by no means an innocuous procedure it is considerably less radical than the conventional exploratory thoractomy and may be employed in seriously ill patients who are handicapped by a very low pulmonary reserve.

METHOD

The patient is given an appropriate pre-operative sedative; a barbiturate routinely is employed. The pharynx and pyriform sinuses are treated by topical cocaine (4%) by the same technique as is used for bronchoscopic examination. An endotracheal tube is inserted between the cords, and the positive-pressure system is applied; oxygen and nitrous oxide (50-50 combination) routinely are employed. Supplementary anesthesia is

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Department of Pulmonary Diseases (Dr. Van Ordstrand); Department of Thoracic Surgery (Dr. Effler); Department of Pathology (Drs. McCormack and Hazard).

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obtained by intravenous administration of thiopental (Pentothal) sodium in very small doses and a procaine (1%) chest-wall block over the operative site. Emphasis is placed on employment of the lightest possible level of anesthesia.

The site of incision is plotted according to the distribution of disease as it appears on the roentgenogram. Usually an anterior approach is employed with the patient in the supine position. After the skin has been prepared, the area is blocked with procaine (1%) injected intercostally and in line with the proposed incision. The commonest approach is through the anterior chest wall on either side via the fourth or fifth interspace. It is not necessary to remove either rib or cartilage. A small rib spreader is employed for limited retraction, and the pleural space is inspected. The lung may be retracted into the wound, assisted by positive-pressure anesthesia, and a representative area of the disease is selected. The biopsy specimen is obtained after placing a row of hemostatic sutures around the selected site. Under sterile conditions the resected specimen may be divided into two parts and placed in glass tubes for study in the departments of pathology and bacteriology. An additional specimen is removed in selected cases if chemical analysis is desired. We have found that preliminary study utilizing frozen-section technique has improved our results. Although the diagnostic accuracy may not be as great as in more conventional methods, the adequacy of the sample can be assessed immediately and often other methods of study indicated. After the sample has been removed, care is taken to secure all air leaks and bleeding points in the lung bed. The lung is reexpanded, and the incision is closed in layers, using a simple form of closed catheter drainage.

The tissue specimens are studied further in the departments of pathology and bacteriology, and in the majority of cases the information obtained from these examinations will suffice to establish the diagnosis. However, in those cases in which an occupational disease (e. g., berylliosis) is suspected, a speci-

men also is chemically analyzed. The third method of analysis may require a fairly generous biopsy specimen of diseased lung; ideally, a specimen weighing more than 5 gm. should be taken and kept in a chemically clean glass container.*

RESULTS

During the past five years, lung biopsy has been performed in 66 patients at the Cleveland Clinic.†

In 26 of these patients (40%), a question of occupational disease arose on the basis of history, roentgenologic findings, or a combination of the two. In 11 patients, the lung biopsy finally proved a diagnosis of an occupational disease, as shown in the following Tabulation:

Diagnosis	Patients, No.
Asbestosis	1
Siderosis	1
Silicosis	2
Berylliosis	5

It should be mentioned that in each of the berylliosis cases the diagnosis was suspected clinically before lung biopsy. However, since in each instance the patient represented a single case from his or her company or industry, it was our considered opinion that the diagnosis should be established beyond the shadow of medicolegal doubt by both histologic and chemical means. Beryllium patch tests were positive in each case.

Following are reports of two cases that are representative of those patients having occupational disease.

CASE I.—A 46-year-old man was first seen with a problem unrelated to the lungs. The roentgen

* Chemical analyses of the biopsy specimens in this series were performed in the Kettering Laboratory, University of Cincinnati College of Medicine.

† One mortality only resulted from this procedure. There is considerable doubt as to whether the death should be ascribed directly to the surgical intervention, as the patient was actually being kept in hospital for another reason and died of a coronary thrombosis. We do not believe this to have been a complication of surgery. None of the remaining 65 cases showed any postoperative morbidity or deferred complications.

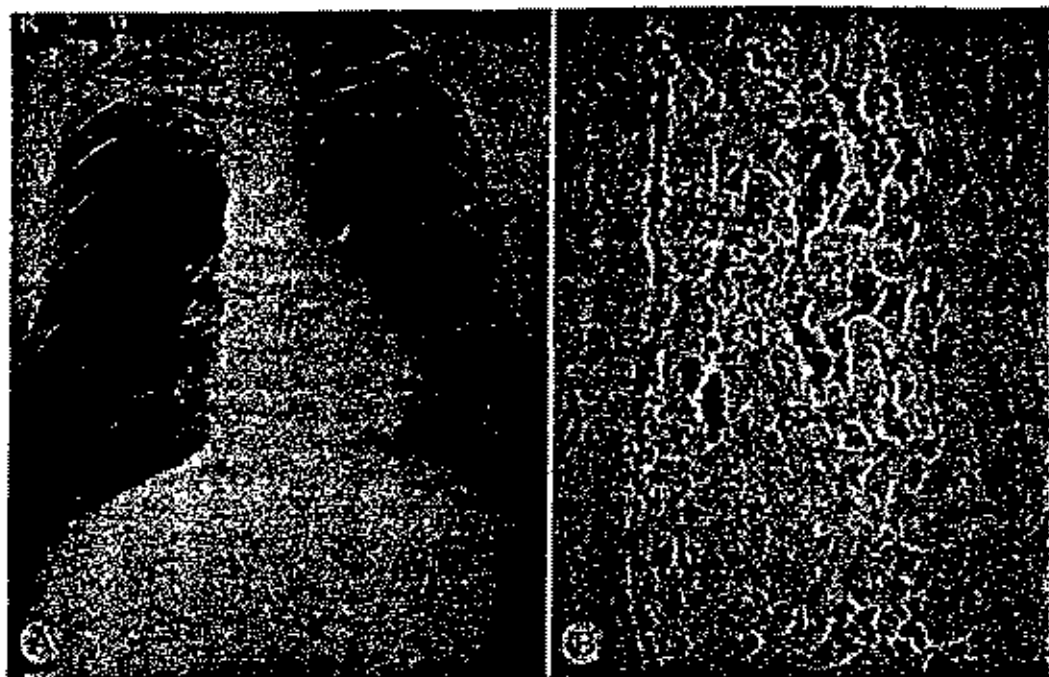


Fig. 1.—A, roentgenogram of chest of Case 1, showing generalized, fine nodulation. Prior diagnoses had always been silicosis, although the patient's only occupation of note had been as a welder. B, siderosis of lung. Numerous macrophages containing a mixture of anthracotic pigment and finely divided iron particles. Iron stain; $\times 130$.

examination of the chest showed a generalized, relatively fine, nodular infiltration. The patient brought with him x-ray films and reports that indicated that his condition had been diagnosed as silicosis for many years. The only history of silica exposure which could be obtained was of only a few months' duration and not of high concentration. For 25 years, his primary occupation had been welding, and he had never worn any protective device. The examination revealed no evidence of impairment of pulmonary function or of disability. The roentgenogram is shown in Figure 1A, and the lung biopsy specimen, confirming the clinical impression of siderosis, is shown by photomicrograph in Figure 1B.

CASE 2.—A 36-year-old man was seen because of a chest x-ray abnormality that had been noted one year previously on a routine mobile-unit x-ray examination and that had remained unchanged. For approximately one and one-half years he had noted a decrease in effort capacity and the onset of a relatively nonproductive cough. The history was otherwise irrelative other than from the occupational standpoint. The significant feature of the latter was a relatively minor exposure three years previously to beryllium oxide which was being used in ceramics work with his company. The occupational history was otherwise negative. According to the pa-

tient and his employer, 25 other employees had had much more contact with the beryllium oxide than had the patient, but they had experienced no symptoms and had shown no x-ray abnormalities. The findings on examination of the patient were essentially negative, with the exception that the chest film showed diffuse, fine, granular nodulation (Fig. 2A). The lung biopsy revealed a typical histologic picture of chronic berylliosis, as shown in Figure 2B. The patch tests to beryllium compounds were all positive. Chemical assay of the lung biopsy specimen revealed a significant amount of beryllium. The patient was capable of light work and has remained in his employment. As he was not significantly disabled and there was no evidence that the disease would progress to that stage, steroid therapy was believed to be unjustified. The patient's subsequent course has been good, with spontaneous recovery from symptoms. Within the past year, more than two years after initial examination, the x-rays show an essential return to normality, as indicated in Figure 2C.

In contrast to the above occupational disease results, a presumptive diagnosis of occupational disease was disproved by lung biopsy

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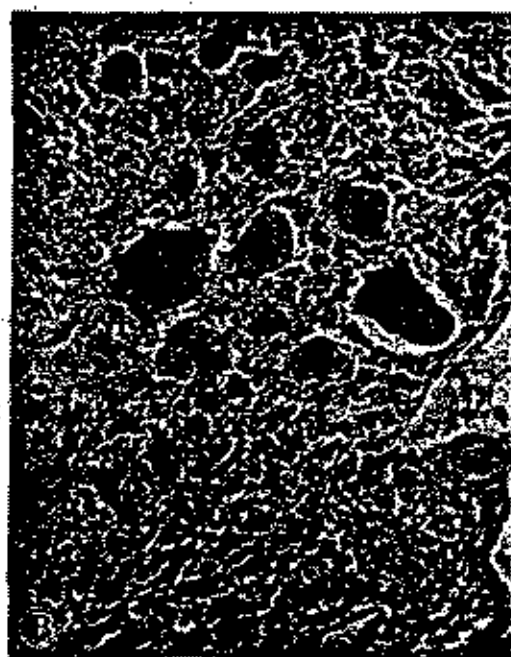
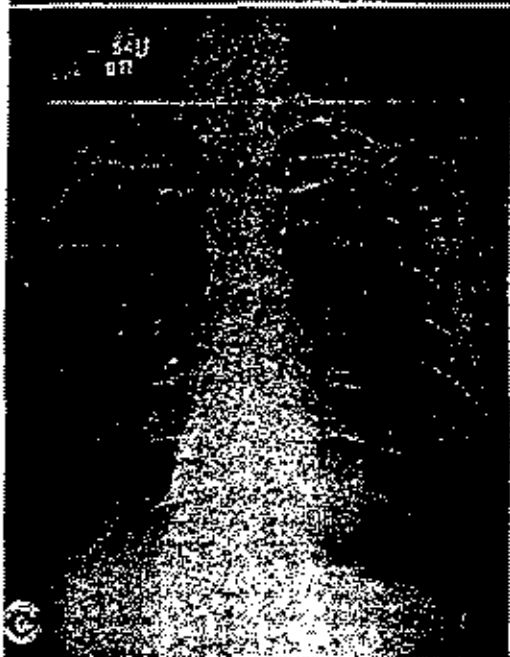


Fig. 2.—A, roentgenogram of chest of Case 2, showing fine, generalized, granular nodulation. Exposure in past to beryllium oxide in ceramics work. No problem in fellow workers. B, berylliosis of lung. Alveolar membrane diffusely distended by granulomas composed chiefly of macrophages and giant cells; a marginal lymphocytic infiltration is present. Hematoxylin and eosin; X 160. C, follow-up more than two years later, showing spontaneous clearing of the roentgen-ray lesion of berylliosis.

CASE 3.—A 48-year-old man was seen because of symptoms of cough, progressively worsening shortness of breath, decrease in appetite, and a 20 lb. loss in weight during the previous six to eight months. The examination was negative with the exception of the roentgenogram of the chest which showed a bilateral diffuse lesion (Fig. 3A). All standard diagnostic studies failed to provide a satisfactory basis for diagnosis. Both the patient and the physician who had been caring for him believed that the patient's condition was a result of his occupation, which for several years had been working with various chemicals. We did not believe that the patient's problem was related to his occupation. However, because a definite diagnosis had not been established by other means, a lung biopsy was performed. As shown in Figure 3B, the biopsy revealed the condition to be sarcoidosis. The patient's subsequent course generally has been favorable.

CASE 4.—A 42-year-old man was seen with the presenting complaints of a relatively nonproductive cough and progressive shortness of breath of one year's duration. The latter symptom had incapacitated him from his work. The occupational history

in 15 cases, as shown in the following Tabulation:

Presumptive Diagnosis	Patients, No.
Suggestive exposure history.....	8
Suggestive roentgen-ray picture.....	6
Suggestive exposure history and roentgen-ray picture.....	4

An example of each of these categories is illustrated in the following case reports.

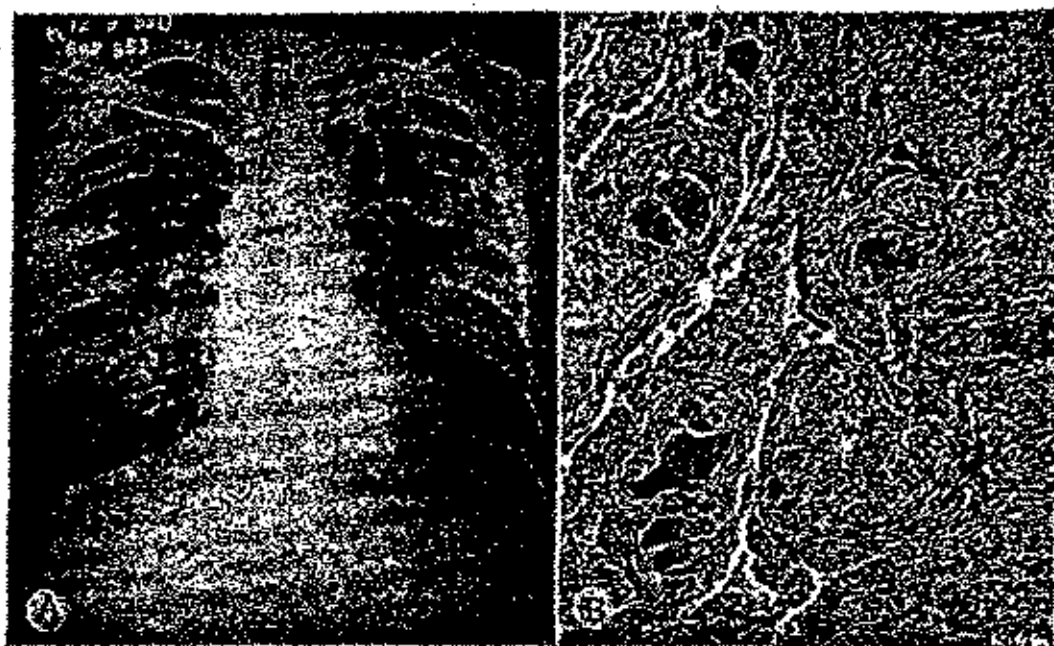


Fig. 3.—*A*, roentgenogram of chest of Case 3, showing diffuse infiltration. Occupational history felt by some to be significant. Lung biopsy disproved. *B*, healing sarcoidosis of lung. Many interstitial granulomas composed predominantly of macrophages and giant cells. In areas the granulomas are surrounded by dense collagen. Hematoxylin and eosin; $\times 100$.

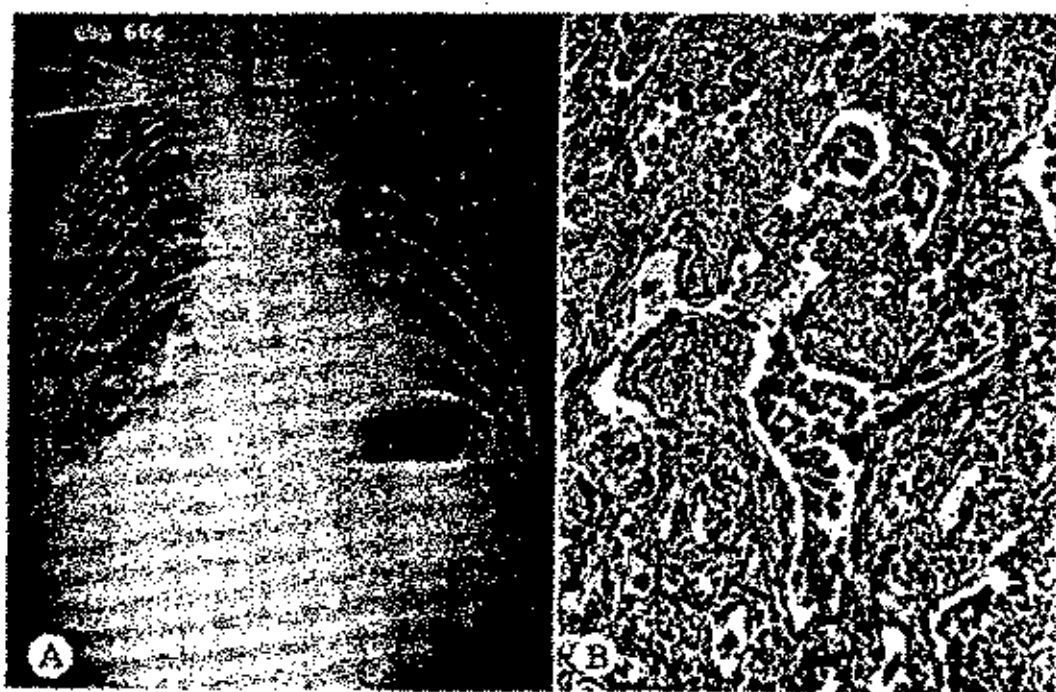


Fig. 4.—*A*, roentgenogram suggestive of a pneumoconiosis. Biopsy disproved. *B*, fibrosing interstitial pneumonitis. Alveolar walls are markedly thickened by an accumulation of lymphocytes and plasma cells. In addition fibrosis is present locally and diffusely. Compressed alveoli contain numerous macrophages. Hematoxylin and eosin; $\times 160$.

VALUE OF LUNG BIOPSY

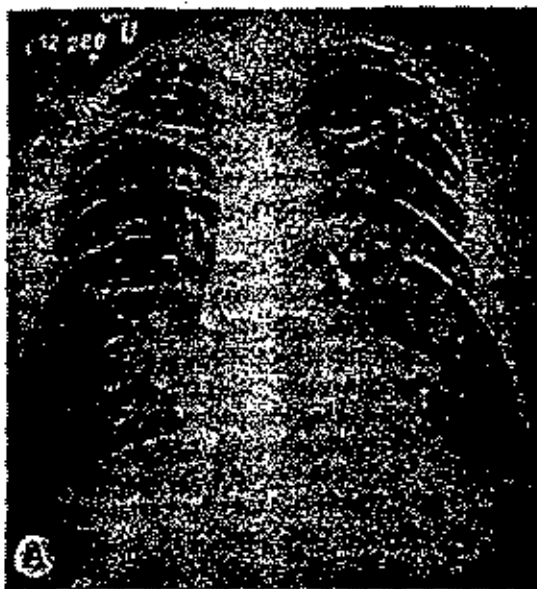
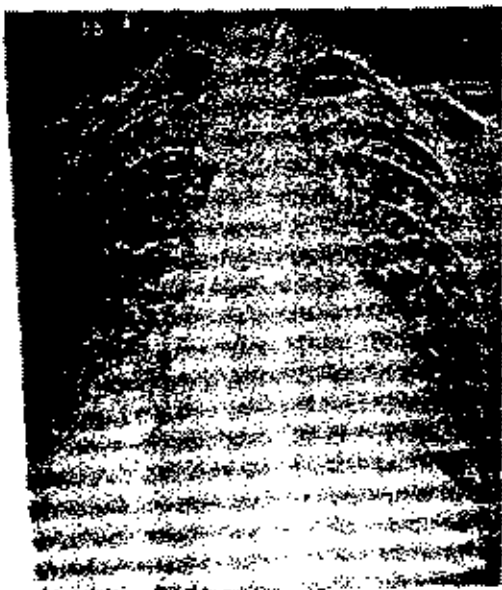


Fig. 5.—A, roentgenogram of chest of 54-year-old man, employed for 35 years in glass industry, showing diffuse, fine, nodular lesion. Biopsy revealed "miliary" metastatic carcinoma. B, secondary carcinoma of lung. Atypical glandular elements in alveoli and lymphatic spaces. Hematoxylin and eosin; X 130.



Fig. 6.—Roentgenogram showing asymptomatic diffuse lesion suggestive of a pneumoconiosis in a 52-year-old housewife. Biopsy revealed primary lung cancer (multifocal bronchiogenic carcinoma, adenocarcinoma in cell type). Also called adenomatosis or alveolar cell carcinoma.



was multiple dust exposures, but they were believed to be of insufficient amount during any one employment to account for the roentgen-ray abnormality, as shown in Figure 4A. The lung biopsy revealed the microscopic picture of a nongranulomatous, fibrosing, chronic interstitial pneumonitis of the so-called Hamman-Rich syndrome, as shown in Figure 4B. The patient died six months after initial examination.

Case 3.—A 54-year-old man was seen with the presenting complaints of a progressive cough, shortness of breath, anorexia, and a 25 lb. loss in weight, of eight months' duration. The history was otherwise noncontributory, other than that the patient's life-long occupation had been with a glass company. Analysis of his jobs with the company appeared to indicate that they had not entailed a significant degree of silica exposure. However, the patient and his family thought that the roentgen-ray picture (Fig. 5A) was the result of his employment. Examination was otherwise negative. The lung biopsy showed no evidence of silicosis and revealed that the diffuse, fine nodulation in his lungs was metastatic adenocarcinoma (Fig. 5B). The primary site was never determined. The patient died one year after initial examination, and autopsy was not obtained.

It can also be mentioned with reference to roentgen lesions simulating pneumoconioses that there were also five cases in women in which the x-rays were suggestive, although in each case the woman was a housewife who

had a completely negative occupational history. The following case report is an example of this group.

CASE 6.—A 52-year-old woman was seen because of the finding on a routine mobile-unit chest x-ray of the diffuse nodulation, as shown in Figure 6. She was experiencing no symptoms of any kind. The occupational history was negative; she was a housewife. Routine examinations failed to indicate a definite diagnosis. The lung biopsy revealed the patient's condition to be primary lung cancer in the form of multifocal peripheral bronchiogenic carcinoma (adenocarcinoma in cell type) or so-called pulmonary adenomatosis or alveolar cell carcinoma. The patient died of her disease six months after initial examination.

SUMMARY

Surgical lung biopsy is a direct approach to the diagnosis of diffuse pulmonary disease where routinely used studies fail to arrive at a diagnosis. It is a particularly important procedure in borderline cases where it is otherwise impossible to prove or disprove the presence of an occupational disease. At Cleveland Clinic, surgical lung biopsy established a diagnosis of occupational disease in 11 such borderline cases. During same period of time, surgical lung biopsy disproved a presumptive diagnosis of occupational disease in 15 cases.

Occupational Chest Diseases in Gold Miners

A Review of Progress in the Union of South Africa

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INTRODUCTION

From the purely scientific point of view, the influence of engineering and medical intervention on the course of occupational chest diseases among miners in the gold mines of the Union of South Africa is of paramount importance because of the magnitude of the mining venture, the stupendous numbers of men involved, the determined governmental efforts to prevent disease, and the long period over which this project has been in operation.

The popular misconception is that these gold mines are at Johannesburg. It is true that there still are some great mines at this city, but they have long since been dwarfed by numerous mines strung out along the Witwatersrand Reef in the Transvaal, over an area of about 180 miles from Heidelberg in the east to Klerksdorp in the southwest. Some of the more fabulously wealthy mines are at the periphery and have been in operation in recent years only. In addition to this central series of mines, a new and promising gold field has in the past decade been mushrooming in the Orange Free State at a distance of a little more than 150 miles south of the Witwatersrand. It is not known yet how extensive this field will prove to be, but rumor has it that it may eventually eclipse the Witwatersrand in its gold and uranium yield. It is to be hoped that its disease-provoking potential will be brought under control from the start. Not to be forgotten also is the eastern Transvaal (Barberton area) where gold was first discovered and

mined in South Africa. Gold is mined on a smaller scale also in other isolated localities, and in the Rhodesias numerous mines have been developed.

Another popular misconception, which needs correction, is that gold occurs in the form of nuggets. I doubt whether any but a few miners ever see nuggets of any great size today. They were common in the earlier years of superficial mining, but today most of the gold is recovered from a banket and occurs in a form which can be readily missed by the inexperienced. Extraction of the gold involves arduous toil, power crushing and milling operations, and elaborate and expensive chemical procedures. The composition of the banket, apart from its precious metal content, is approximately as follows: quartz, 80%-90%; silicates, 10%-20%; pyrites, 1%-5%.

Not only are the mines numerous and spread over a large area, but they are also mostly extremely deep. Depths in excess of 7000 ft. are quite common, and in some mines 10,000 ft. levels are being worked. Plans are afoot to descend even farther, but the sharp geothermal gradient is proving a discouraging obstacle.

Long-term governmental studies on the effects of environmental hazards on the personnel operating these mines have been made for the scheduled mines only; but most of the studies on the Negro laborers are extremely inadequate for the reason that these men work at the mines transiently and interruptedly and because of the vast numbers employed, the excessive annual turnover, and the insufficiency of medical, technical, and clerical personnel available to cope with the problem. Less than 2% of the Negroes are radiographed annually by the Bureau from the point of view of silicosis. All are, however, subjected to 35 mm. radiography

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Director, The Saranac Laboratory.

at a central repository are studied periodically the mines, and Mine Medical Officers who at these mines the Bureau, as well as to are responsible.

the mine man. These studies have been recorded in the annual, and special reports of the (Miners' Phthisis) Medical Bureau, Government Mining Engineers, and the independent or special Government Commission, and Mining Associations, and Medical Officers. In conducting this review of the trend of progress in the occupational chest in the suppression of the accumulated in those re-diseases, the ~~data~~ has been achieved. The reports will be ~~emphasize~~ emphasize the historical review will ~~see~~ and will cover observations which ~~extend~~ over a period of about 60 years in ~~form~~ recognition, enlightenment, stasis, and ~~stagnation~~.

AL. YEAZES
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Recognition of the Problem.—With this more or less familiar period everyone is already. The ~~first~~ ^{first} decade following the discovery and inception of gold was not too disastrous ~~from~~ ^{from} the point of view of chest diseases, as ~~much~~ ^{much} of the mining was in the nature of open ~~pit~~ ^{pit} and quarry working and a search for ~~minerals~~ ^{minerals} while power-drilling tools were not ~~yet~~ ^{yet} ~~in~~ ⁱⁿ use. ~~But~~ ^{But} had tuberculosis experienced ~~its~~ ^{its} ~~first~~ ^{first} ~~as~~ ^{as} an infecting agent made its ~~improbable~~ ^{improbable} ~~in~~ ⁱⁿ ~~the~~ ^{the} ~~early~~ ^{early} gold on any ~~sign~~ ^{sign} ~~of~~ ^{of} indigenous stock diggers being ~~totally~~ ^{totally} ~~at~~ ^{at} that time a healthful, and South Africa ~~was~~ ^{was} ~~at~~ ^{at} that time a healthful, and South Africa ~~remained~~ ^{remained} ~~comparatively~~ ^{comparatively} ~~however~~ ^{however}, soon brought

[illegible]

force. They were at a later stage repatriated, and it has been a medical mystery what their fates were in respect of silicosis or tuberculosis.

The next decade brought with it the Anglo-Boer war for the possession of the mineral wealth of South Africa. In its wake and following the first flush of military conquest came a growing awareness that for many the price of gold was death. This problem was soon recognized not only in South Africa but also in England, where returning miners frequently did not survive long enough to enjoy to the full their, by British standards, fabulous savings. Some, of course, went home both sick and broke.

Not all the labor struggles in those first 10 years of the century were on account of politics or wages. There was growing restlessness and a crescendo clamor for an inquiry into the cause of unexplained disability and death. Government commissions took over and defined the condition of miners' phthisis as a dual disease involving both silicosis and complicating tuberculosis. The condition became certifiable as a compensable disease, and virtually every medical practitioner on the Witwatersrand of the pioneer group had some share in pronouncing indisposed or dead miners as suffering, or as having suffered, from this condition. Not all who were thus certified had the disease at that time, and a few such are yet alive today. There were no proper x-ray facilities universally available, and each physician had notions as to what should rate as pathognomonic criteria. The physicians did not always follow the same standards, and there was no reason why they should have done so, as few knew with any measure of certainty what it was all about.

Enlightenment.—The preceding phase of confusion and legalized medical haphazardness was brought to a close with the establishment of the Miners' Phthisis Bureau in 1914 at the suggestion of Brig. A. G. Orenstein. The purpose of the Bureau was to standardize procedures and diagnostic criteria, to take certification of silicosis and tuberculosis victims out of the hands of in-

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interested parties, thus also eliminating court actions, and to conduct research on the prevalence, nature, causation, and prevention of these diseases. Under the able direction of its first Chairman, Dr. W. Watkins-Pitchford, the Bureau rapidly brought cosmos out of the medicolegal chaos.

Meanwhile, engineering research had made great strides, chiefly under the stimulus of the Chief Government Mining Engineer, Sir Robert Kotzé, best remembered today as the inventor of the *komimeter*. Adequate proof had by then been produced to suggest a quantitative relationship between extremes of atmospheric dustiness and the prevalence of miners' phthisis. Heroic efforts were consequently instituted to combat the factors which tended to engender dust. This problem was, of course, continually aggravated by the ceaseless growth of the mines, the increasing numbers of personnel involved, and the greater rate at which excavation could be effected and gold extracted by means of improved pneumatic drills and high explosives and the elaboration of ever more powerful and efficient crushers and stamp mills. The Government enforced the application of safety precautions through the various Mining Acts and the Regulations under them. Engineers responsible to the Chief Government Mining Engineer ensured that the recommended hygiene procedures were carried into effect and the regulations properly observed.

The Bureau's contribution to progress in this phase of enlightenment comprised primarily the rapid elimination of cases of tuberculosis, tuberculosilicosis, and advanced silicosis and disability from the ranks of active miners. By virtue of its control over the miner's working permit, which it could either issue or revoke, and because it enjoyed the status of a compensation tribunal, from whose decisions financial benefits flowed automatically, the Bureau had absolute power in controlling who could work in the mines. Besides this, the Bureau commanded the best available x-ray facilities and pathology laboratories. Large numbers of infected cases were thus weeded out rapidly from the start.

Through its function of screening all recruits, the Bureau could ensure that no new cases of tuberculosis entered the industry, and through its system of semiannual, periodical, physical and radiographic examinations, a careful check could be kept on all working white miners with the object of finding the incipient disease.

It is possible that the Bureau, preoccupied as it was with the prevalent more serious grades of these diseases, was at first too strict in its interpretations of x-rays in the incipient or less severe cases. Within 10 years from its creation, the government (a recent new one) consequently agreed to the creation of an Appeal Board, and the concept of what constitutes a scintilla of silicosis was formally defined by the Minister of Mines, who ruled that, though scintillas may be ignored, the benefit of medical doubt should invariably be accorded the miner. The legal stages of silicosis had by then already been expanded to embrace not only a primary and a secondary but also an anteprimary stage.

This phase of enlightenment was also highlighted by the researches of A. Mavrogordato, F. W. Simson, and A. S. Strachan more particularly. Watkins-Pitchford, who had held down the dual posts of Chairman of the Bureau and Director of the South African Institute for Medical Research, was succeeded on retirement by his able first assistant, Dr. L. G. Irvine. Sir Spencer Lister, the new Director of the Institute for Medical Research, had meanwhile contributed valuable help to the industry through the elaboration of a vaccine to immunize the Negro laborers against the prevalent and frequently fatal *Pneumococcus mucosus pneumonia* which decimated the ranks of new recruits brought in from distant native territories. By now the South African group of researchers had attracted so much attention through their publications and the success of their campaign against mining diseases that Johannesburg became a veritable mecca for those who sought guidance in the control of the occupational chest diseases. The Bureau's status as a leading world authority was con-

led through the fact that the 1930 International Conference on Silicosis was held in 1930. Dr. L. U. Gardner, of Saranac Lake, N. Y., was a delegate to this Conference.

Silicosis.—All was not, however, well on the horizon from even in the midst of triumph. The Bureau had gained the victor's laurels, but soon appeared to be resting on them. The tempo of research declined. By comparison with what had been happening in previous two decades, miners were surviving and working longer. The general production rate for silicosis at the time of the conference had dropped to 13.79 per 1000 (from 27.87 per 1000, 10 years earlier). The average age at first certification had risen to 47 years, as compared with 39.5 years in 1920, and the victims had managed to live an average of 157 months of work, compared with a mere 116 months 10 years before. The average dust counts in the mines had also been reduced to 284 particles per cubic centimeter (about 7,000,000 particles per cubic foot). Predictions were that silicosis would soon be eliminated. Tuberculosis and tuberculosilicosis were already considered as properly under control. Over the 10-year period 1920 to 1929, the number of cases of tuberculosis annually diagnosed among white miners who had no silicosis had been reduced from 44 to 32 (i. e., rates of 322 and 207 per 100,000, respectively). The production rates for tuberculosis combined with silicosis had also been reduced from a high of 163 per 100,000 in 1920 to a mere 12 per 100,000 in 1930. In the 10 years preceding 1919, the new case rate had been 860 and 852 per 100,000, respectively. This seemed like terrific progress and truly was. It seemed as though the answer to the problem had been found and that, if the Bureau merely continued along the course which had been set for it and the engineers persevered in ensuring the good housekeeping which reportedly had been achieved, the problem would soon be in sight. This became the official point of view, and those who protested that men were nevertheless being disabled and yet were dying the risk of being viewed as meddlers

and malcontents. It became the duty of the departmental officials to maintain the *status quo* while a constant political struggle went on all about them. The Bureau's findings were under constant criticism. Scarcely any of the miners and few of their family physicians came to have confidence in the Bureau, which in many quarters was regarded as "an instrument of capitalism" designed to keep the men working whether they were diseased or not. Not even those who had been declared silicotic or tuberculosic were all invariably grateful, many protesting that they were certified too late.

Under constant pressure from the public the government eventually in 1946 revised and consolidated the Miners' Phthisis Acts and made this probably the most liberal of all comparable legislation in the whole world.* No legislation is without flaws, and there were errors also in the new Silicosis Act, some of which were amended in successive years. It was perhaps a mistake, however, to incorporate the Bureau into the civil service. The intention was, of course, good, but the results were poor. Because of the stratification of seniority and authority apparently necessary to any civil service, the Bureau could no longer attract the type of skilled personnel needed for its gigantic and specialized task. As the Bureau was, in a sense, also a cul-de-sac within the service, the men who joined it found that they could not readily be promoted to other departments. There was no incentive for younger personnel to stay, and the turnover of the better men was calamitous. The dissatisfaction of the miners slowly mounted to organized political opposition. Self-criticism by members of the Bureau could not ward this off, which was most discouraging to those who perceived the need for research. The Bureau seemed to outsiders to be in the doldrums. Officially, however, there was nothing to worry about, as certification rates for silicosis and tuberculosis were continually diminishing, suggesting that all was fair.

Reaction.—Relief came in 1949 when a new government acceded to the pleas of the miners that if silicosis and tuberculosis were

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not the cause of disability and death among them some other mysterious disease of occupational origin was surely decimating their ranks. A Governor General's Commission, under the chairmanship of Dr. Peter Allan, was appointed to inquire into "the occurrence of certain diseases, other than silicosis and tuberculosis, attributable to the nature of employment in and about mines." Accidents were, of course, excluded, as they fell under the purview of the Department of Labor. The Commission inquired into environmental factors, such as ventilation, mine dust, mine water, blasting fumes, heat, humidity, bacterial content of mines, and work stresses. It also examined claims concerning the prevalence of heart disease, arthritis and rheumatism, dermatitis and other skin diseases, debility, nephritis, parasites, lung cancer, bronchitis, emphysema, and the psychological consequences of mining work.*

While the Commission did not find overwhelming prevalence of most of these diseases, it did conclude that "there is strong presumptive evidence that there is a disabling respiratory condition occurring among miners, which is not recognizable by the usually accepted means of detecting the earliest specific signs of silicosis and which may become permanent." It recommended legislation to provide for the inclusion of such "pulmonary disability" in the Silicosis Act as an independent new compensable entity, and it recommended that the Bureau should be placed in charge of diagnosis and certification of this condition, adding the proviso that "the methods of medical examination at the Silicosis Medical Bureau would have to be modified."

While the miners welcomed the finding of the Commission in respect to pulmonary disability, they repudiated the suggestion that the Bureau be allowed to administer the necessary legislation and pressed for an inquiry.

Once more the government acceded. A Governor General's Commission, under the chairmanship of a judge of the Supreme Court, Mr. D. O. K. Beyers, undertook this delicate task in 1951. The result was un-

favorable for the Bureau. Reorganization was recommended and put progressively into effect by the government.*

After the Beyers report had been completed, pulmonary disability was incorporated into the Silicosis Act (1952) as a separate medicolegal entity, and certification and research concerning its nature and prevalence were entrusted to a special committee, whose officers were no longer required to be members of the civil service.* By 1954 more than 700 new cases of such pulmonary disability had been identified among white miners and about 100 cases among the Negro laborers.

One of the effects, however, of the creation of this committee was that its much more thorough methods of investigation revealed that many pulmonary-disability applicants (especially Negroes) suffered instead from silicosis or tuberculosis, which had not previously been detected by the Bureau. The Bureau, which was meanwhile undergoing reorganization, succeeded in finding these diseases in ever larger numbers, and between 1952 and 1954 certification of new cases of silicosis increased from a little more than 200 per year to more than 1000 among white miners alone. Tuberculosis and tuberculosis combined with silicosis, which had by 1952 virtually become negligible entities, were found in more than 70 white miners in the year 1953-1954. Not only were these conditions found in such large numbers of men not previously declared to be affected by occupational diseases, but in those who in previous years had been declared silicotic or tuberculous the stage of the disease was rapidly upgraded. Thus the rate of monthly reclassification of first-stage silicotics to the second stage (white miners only) increased at accelerating pace from less than 30 per month to more than three times this rate. Second stages became upgraded to the third stage from a rate of less than 5 per month in 1952 to more than 60 per month toward 1954. During this period tuberculosis was demonstrated as a clinical complication of silicosis in more than 40 cases within a single year. This was not unexpected, as large

numbers of silicotics were previously known to have tuberculosis at death, but by 1952 the condition had become a rarity as a diagnosis during life.

The figures for Negro laborers underwent similar drastic revision. During 1953-1954 more than 1700 new cases of silicosis were demonstrated, more than 1100 new cases of tuberculosis were discovered in working Negroes, and tuberculosis and silicosis were detected in combination in an additional more than 800 cases. This meant that the annual production rates of these diseases were almost trebled.

These stupendous results confirmed the suspicion of the miners that all had not previously been well.

A last chapter in the phase of reaction, and which, it is to be hoped, may presage a phase of reconstruction, has been the appointment of a further Governor General's Commission of Enquiry under the chairmanship of Dr. S. Oosthuizen, Professor of Radiology at the University of Pretoria. The purpose of this Commission is to recommend a more efficient type of organization of the Medical Bureau, to revise the legal definitions of silicosis, pulmonary disability, and tuberculosis, and to inquire concerning the need for intensified research concerning the causation, nature, and prevention of these diseases. It is particularly hoped that the Commission's report on the latter issue will be favorable, for only through research and more research can there be any hope of finding answers to the extant problems concerning the occupational chest diseases.

South Africa certainly has a great deal at stake. Apart from the personal wage loss, the discomfort and suffering, and the premature death caused the victims, these diseases are a tremendous economic burden to the mines. Thus the outstanding liability for the mines in respect of compensation for these diseases has exceeded \$150,000,000, and currently the mines are paying, in addition, more than \$10,000,000 per year in direct costs. To these figures must be added the vast sums expended annually on engineering hygiene measures and the capital which is tied

up unproductively toward this end. These figures, moreover, reflect the state of affairs for only scheduled gold mines whose approximate statistics are available. The impact on other mines is by no means known yet.

It must be realized also that the rapid certification of such large numbers of men may have serious consequences not only on the earning capacities of the victims but also on the working efficiency of the industry they service. The Silicosis Act does not, however, prohibit white miners from continuing their employment in mines except when certified to be suffering from silicosis in the third stage, from pulmonary disability in the second stage, or from tuberculosis. All Negro laborers are, however, excluded on first certification. Many of the white miners continue in their jobs for the simple reason that they cannot readily obtain alternative surface employment. Many who do depart, with every firm intention never to return, nevertheless tend to drift back to the mines after variable periods.

This medically deplorable state of affairs is due to the fact that the Silicosis Act has never truly attempted to "compensate" the affected men for wage loss or diminished working capacity but instead it pays a system of "benefits" which take no true cognizance of the financial loss incurred. The prophylactic purpose of the Silicosis Act is thereby often frustrated. On the other hand, the system has many advantages for certain persons.

STATISTICAL TRENDS

To facilitate recapitulation of the events of the past 40 years, certain features of these diseases have been graphically portrayed in Figures 1 to 7.

Occupational Chest Diseases. — White Miners: The spectacular initial decline in the annual rate of production of silicosis, tuberculosis, and silicosis combined with tuberculosis among white miners is well shown in Figure 1. In respect to both tuberculosis and tuberculosis combined with silicosis, it should be pointed out, however, that the rates reflected in this chart do not represent the total incidence of tuberculosis on the

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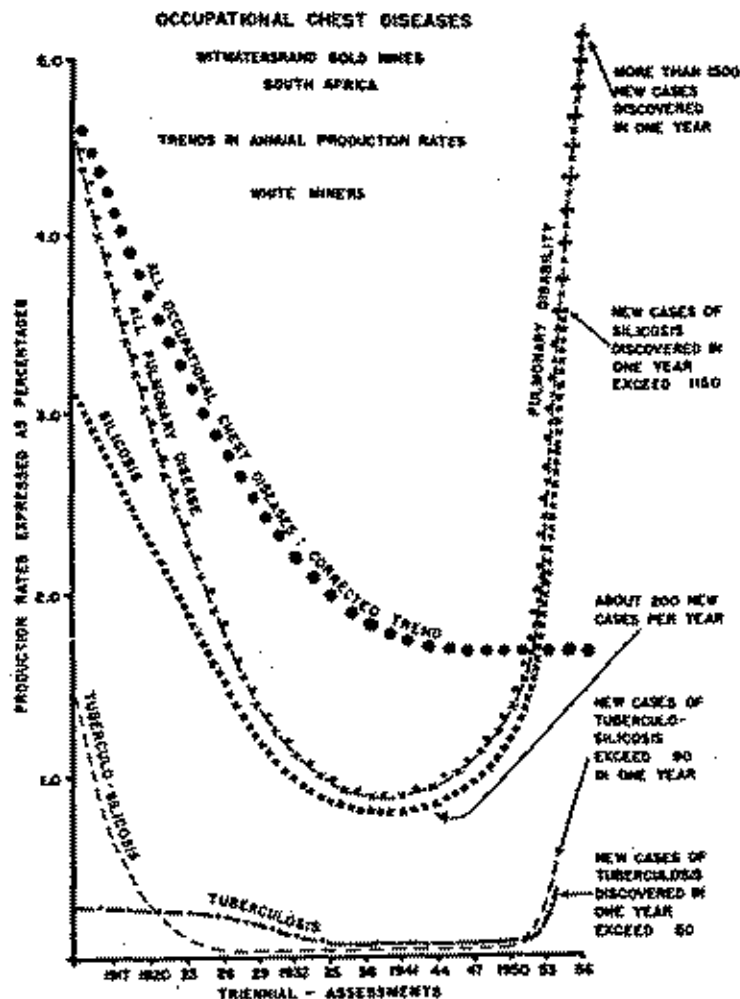


FIGURE 1

mines. The only cases included here are those which were discovered for the first time in miners who previously did not have silicosis. A tuberculous complication in the latter group has consistently been much higher, and in 1948 it was still Bureau experience to find tuberculosis at death in the lungs of 21% of first-stage silicotics, while this rate more than doubled in second- and third-stage silicotics, being quite commonly a factor in the cause of death in the latter cases.⁴

Having attained a comfortable all-time low of about 200 cases toward 1950, it is rather disconcerting to find that by 1954 the annual rate of certification had exceeded by three times the highest rate ever recorded at the

time when pulmonary disease was previously present at its worst. Of the 789 cases certified in 1917, for instance, among 15,000 miners, 257 were in a stage equivalent to the second stage, and 382 were in the third stage. In the year 1953-1954, more than 770 second-stage silicotics and more than 400 third-stage silicotics were discovered, though the total body of men from whom these numbers derive now exceeds 30,000. Against 150 new cases of silicosis found in 1917, more than 1050 first-stage silicotics were discovered during the year 1953-1954. To these totals must be added the more than 490 men certified as suffering from pulmonary disability in the first stage (equivalent to silicosis in the second stage) and the

more than 200 cases found to be suffering from pulmonary disability in the second stage (equivalent to silicosis in the third stage).

The question may be asked whether the Bureau was perhaps applying new standards of diagnosis or compelled by changes in the law to certify these diseases at such an alarming rate. In the case of pulmonary disability the latter stricture naturally applies, as the law came into effect in 1952 only, but the criteria for neither silicosis nor tuberculosis had been altered since 1946; prior to this the wording in the legal definitions was slightly different, but there had been no intentional material relaxation in legal standards since 1919, except in respect of second-stage silicosis certification, which was facilitated in certain instances since 1946.

The answer, therefore, is to be found in the fact that the Bureau itself had commenced to apply new diagnostic criteria in interpreting the existing definitions. This

reduces one to the conclusion that either the Bureau has recently become too lenient, now perhaps including disease at "the stage of imagination," or else it previously had been "too strict," failing to acknowledge the existence of established disease until unreasonably rigid criteria had been complied with. On the latter assumption, a statistical interpretation would possibly be that cases now certified for the first time in such large numbers represent persons whose disease had been recognized only some time after the earliest detectable sign or the relevant degree of disability had first become manifest. The trends shown on these curves, therefore, more truly represent annual certification rates rather than annual production rates. At some future period when it has become known whether these trends are maintained or abruptly deflected and after belated certifications have been appropriately antedated, it should become possible to decide whether the curve of progress should

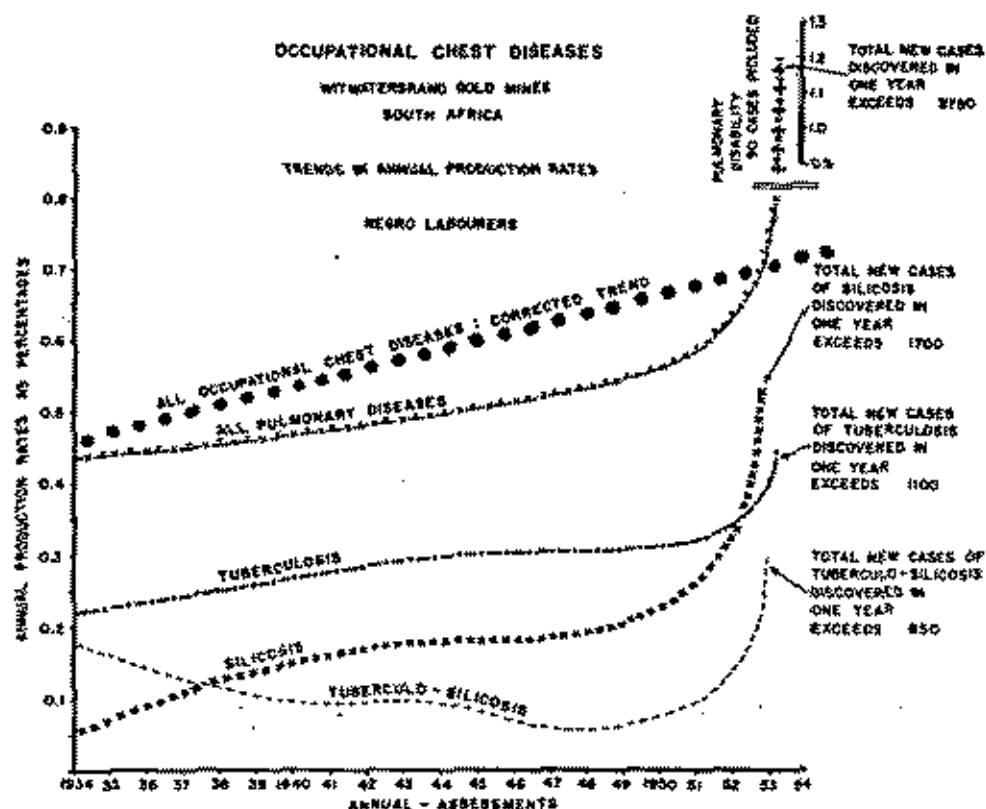


FIGURE 2

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be redrawn at a generally decelerated rate, as suggested in Figure 1. Clinical and autopsy experience tends to favor the latter prospect, for the disease at present diagnosed is not as florid a malady as it was in the earlier decades of the century, if only for the reason that tuberculosis now plays a less important role in the incipient stages. The recrudescence of tuberculosis and tuberculo-silicosis, shown in Figure 1, likewise does not mean a sudden spread of the infectious element but a prompter diagnosis. In other words, though these cases are now recorded as occurring in greater numbers than they were encountered during the past 30 years, the disease has not necessarily become more prevalent, and perhaps all it means is that the tuberculosis will no longer be reported for the first time after death.

Occupational Chest Diseases. — Negro Laborers: In the case of the Negro laborers (Fig. 2), the production rates of all the pulmonary occupational diseases (silicosis combined with tuberculosis at the outset excluded) have shown a slow but steady increase during the past 20 years. The terminal upsurges shown on the graphs may have explanations comparable to those given for white miners in the preceding paragraphs and reflect altered Bureau diagnostic standards rather than epidemic fulmination of these diseases. The position is, however, materially more serious than among the white men for the reason that these annual production rates are virtually based on new groups of employees, the annual turnover of laborers being in excess of 80%. The total labor force exposed to mine dust had increased by about 20% during these years, being now about 300,000 (scheduled gold mines only). A discovery of more than 3750 cases of occupational chest disease among 300,000 men means an incidence but a fourth as high as among the whites. To this must, however, be added the fact that not all laborers were examined by x-ray and less than 2% were screened by the Bureau itself. No accurate statistics are available concerning the average dust exposures of these men, but it is probable that the white miners spend

three times as many years in the mines as do the Negro laborers before silicosis may be demonstrated. Tuberculosis, in particular, tends to be a young man's disease among the Negroes. However, during this shorter period the Negroes are probably more directly in contact with dust, as they are truly the miners (drilling holes, shoveling rock), whereas the white men assume the role of supervisors.

The steady increase in the total incidence of these diseases among the Negroes may possibly correlate with a tendency toward longer average periods of service performed by each Negro.

The increasing prevalence of tuberculosis among the Negro laborers is a discouraging observation. It may be noted that tuberculosis has constantly been more prevalent than silicosis. The Chamber of Mines has taken pains to ensure that these men have adequate living quarters and well-balanced diets. Often, however, when first detected, the disease is far advanced. Many of the cases are of the fulminating primary type, with a rapid course. But often advanced chronic disease may be discovered too late, and such cases are a source of infection to others. Not until all Negroes are periodically radiographed will this problem be disposed of.

The tuberculosis situation assumes even more disastrous proportions when it is realized that facilities for the reception and treatment of these men are conspicuous by their paucity. Most of the tuberculous are repatriated, with consequent risk of infecting others at their tribal villages. Others mercifully die within a short time. Yet when modern therapy is instituted, many of these cases respond excellently. It is a travesty of medical idealism that all this should still be happening at a time when the campaign against tuberculosis has made such progress in the United States that even Trudeau Sanatorium had to be closed for lack of patients. The new cases found among the gold miners of South Africa in any two-month period would fill this vacant Sanatorium.

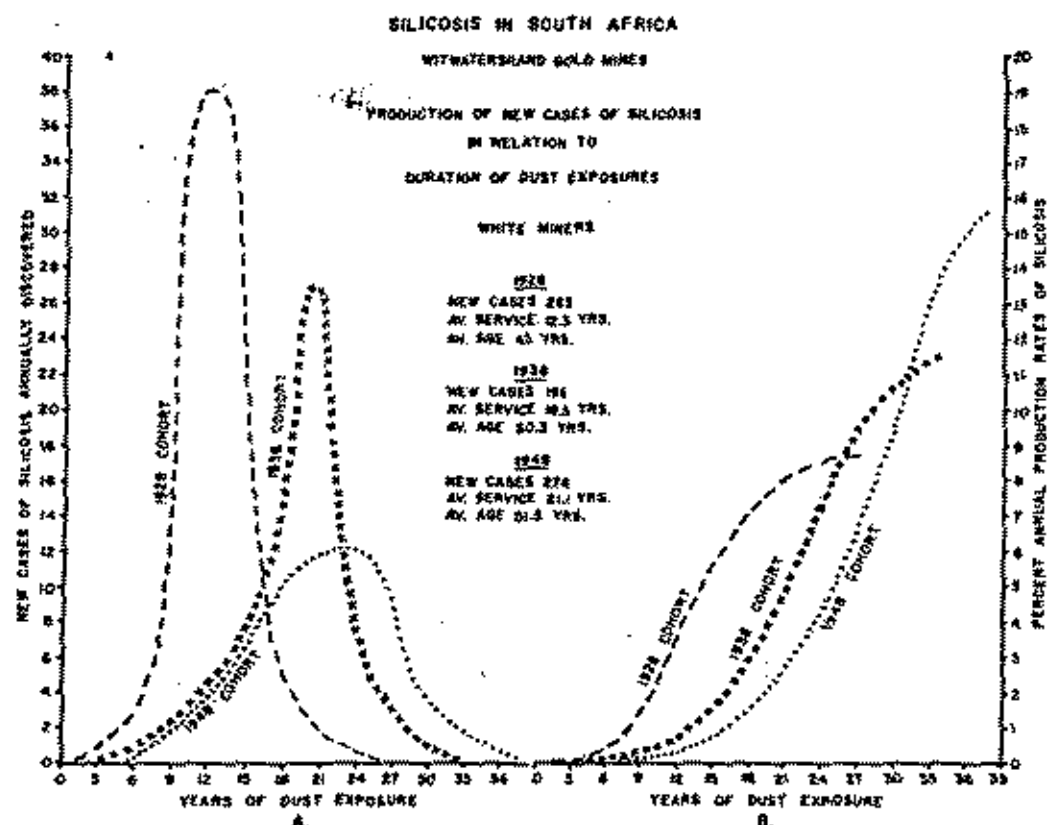


FIGURE 3

Effect of Duration of Service.—Progress in the campaign against silicosis is shown also in respect to its changing prevalence in relation to duration of dust exposure (Fig. 3). The decennial cohorts for 1928, 1938, and 1948 illustrate well how miners have been enabled by improved mining hygiene to work longer periods before silicosis manifests itself as a nodular radiographic disease (Fig. 3 [A]). The tendency in recent years has been not only to double this period, to judge by the modal peaks of the histograms, but also for greater dispersion in the occurrence of the radiographic stage in relation to the duration of service in a dusty environment. The men have also been enabled to survive almost a decade longer before certification. This is real progress.

However, it must be recalled that the total number of men working at each dust-exposure phase diminishes rapidly as the years go by. When the decennial cohorts of silicosis cases for the years 1928, 1938, and

1948 are converted to per cent annual production rates (Fig. 3 [B]), the difference between 1938 and 1948 is not quite so marked as would appear to be the case when the occurrence of new cases is compared by means of histograms. It is shown that the production of silicosis is a function of duration of exposure, being relatively more prevalent among those miners with the longest mining service, even in the case of the 1928 cohort.

Progression of Silicosis.—Retardation of the rate of progression of first-stage silicosis to higher stages would be another feature showing progress in South Africa as a result of better mining hygiene or medical supervision. Figure 4 shows this factor to be discouraging in respect of the cohorts for the years 1921, 1931, and 1941. It is revealed that when silicosis advances beyond the first stage it does so relatively rapidly, and within 10 years after first discovery the majority of cases have already advanced. In this respect

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SILICOSIS IN SOUTH AFRICA WITWATERSRAND GOLD MINES TREND OF ANNUAL PROGRESSION OF SILICOSIS

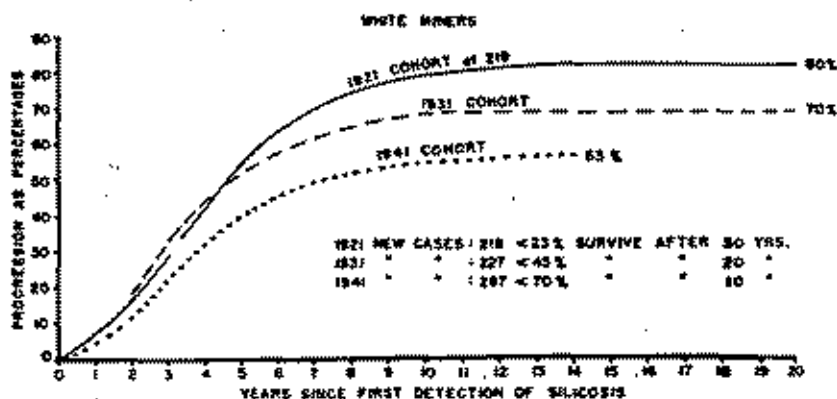


FIGURE 4

the disease had not materially changed its character over the past three decades. Reference has already been made to the fact that during the year 1953-1954 the Bureau found it necessary to reclassify more than 760 first staggers into the next two advanced categories of the disease. In addition, almost 400 second-stage silicotics were reclassified as third staggers, while an additional approximately 70 previously certified miners were found to have tuberculosis complicating the silicosis. This gives a total reclassification of silicotics to higher stages in excess of 1240. During the year 1947-1948, by comparison, the Bureau reclassified but a total of 75 silicotics, and a decade earlier yearly totals of 250 or more reclassifications were considered to be high rates of progression.⁷

Once more this exaggerated rate of advance must be viewed as a belated correction of previously retarded certification of disease which had advanced but which had not been admitted by the Bureau to have done so. Such cases should for statistical purposes be carried back to earlier historic periods, as they were derived mainly from the ranks of the surviving annual cohorts of new cases certified since about 1938. When this has been done, the differences in rates of progression of the diseases in recent years as compared with progression among the case cohorts from earlier decades will probably

be largely eliminated. In other words, though silicosis occurs less frequently among miners today and takes a greater period of exposure before it becomes radiologically demonstrable, it tends to progress to a stage of disability at virtually the same inexorable rate as characterized its behavior in earlier years. This conclusion may be modified by the consideration that the miners today are older when they eventually become disabled than was the case three or four decades ago, when silicosis first made its vicious character manifest. Perhaps it takes less added pulmonary damage to disable an elderly miner than is required to cripple a young man.

Death Rates.—Silicosis: Progress in respect of the control over silicosis is further manifested through the diminishing proportion of cases that die from silicosis and the longer survival of the silicotics. Thus of the 1917 and 1921 cohorts of new silicotics, less than 23% survived after elapse of 30 years, the majority having died within the first 10 years, whereas of the 1941 group only about 30% had died within 10 years from the date of certification (Fig. 5). The rates at which miners died, respectively, from causes ascribable to silicosis and from other causes became reversed during the past three decades. Thus of the 1917 cohort of silicosis, more than 60% had died from silicosis within 20 years and less than 10% from

SILICOSIS IN SOUTH AFRICA

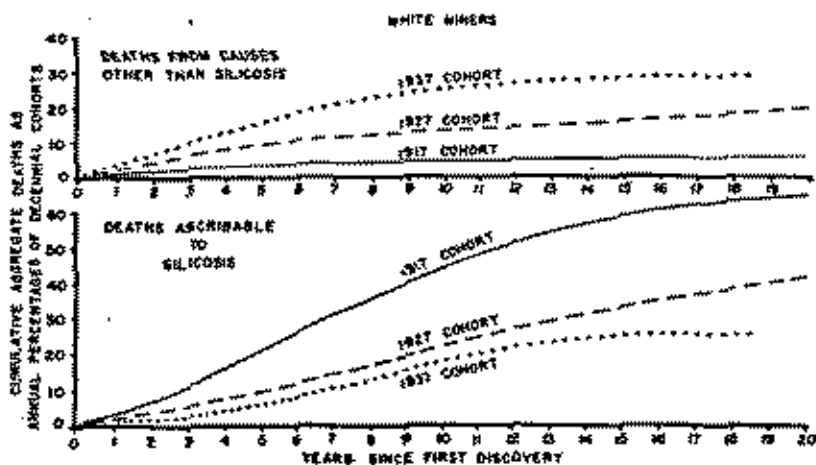
WITWATERSRAND GOLD MINES
DEATH RATE TRENDS

FIGURE 5

other causes.* By 1937 these ratios had become inverted so that fewer than 20% of the 1937 group of new silicotics had died from silicosis within the succeeding 15 years of follow-up, whereas more than 20% of this group had already succumbed to other causes within the first 10 years. This reversal is partly explicable on the basis that the average age at certification of the 1917 group of silicotics was less than 39 years, whereas the 1937 group had on an average attained the age of 50.8 years when first diagnosed as silicotic.

Tuberculosis.—The problem of tuberculosis is interesting and merits further comment. Argument has often been advanced in South Africa that its statistically alarming prevalence among working Negro laborers is illusory, because inadequate cognizance is taken of the fact that more than 300,000 of these men are annually in the service of the gold mines and that the annual labor turnover of more than 80% may exaggerate the number of cases prevalent among working laborers, many of the infections being brought in from outside. During 1953-1954 the Bureau discovered more than 1100 new cases of tuberculosis and more than 880 new cases of tuberculosis combined with silicosis among less than 2% of the approximately

300,000 dust-exposed Negro laborers. Even if these approximately 2000 tuberculosis cases are to be related to the whole 300,000, rather than merely the 2% examined, we are still dealing with a new case rate in excess of 600 per 100,000, which is 10 times the attack rate for tuberculosis among the white population of South Africa and twice the rate found among the Negroes in the worst peri-urban slums where malnutrition and overcrowding prevail. The mine laborers are well quartered and fed and are selected, on first recruitment, for their robusticity and radiographic freedom from disease. The high tuberculosis rate must therefore relate to their occupation, and the fact that almost half of the cases were instances of tuberculosis combined with silicosis at the outset gives the show away.

Among the white miners, tuberculosis is not quite the statistical menace it is among the Negro laborers, though, of course, it is always a serious problem for the person who falls a victim to its ravages. It is fortunate, therefore, that the disease has been so relatively successfully eliminated. Figure 6 shows graphically that since about 1923 tuberculosis has not been materially modified in its ability to attack the young miner. These men tend to be about 40 years of age, and

CHEST DISEASES IN GOLD MINERS

TUBERCULOSIS AND TUBERCULO-SILICOSIS

WITWATERSRAND GOLD MINES
SOUTH AFRICA

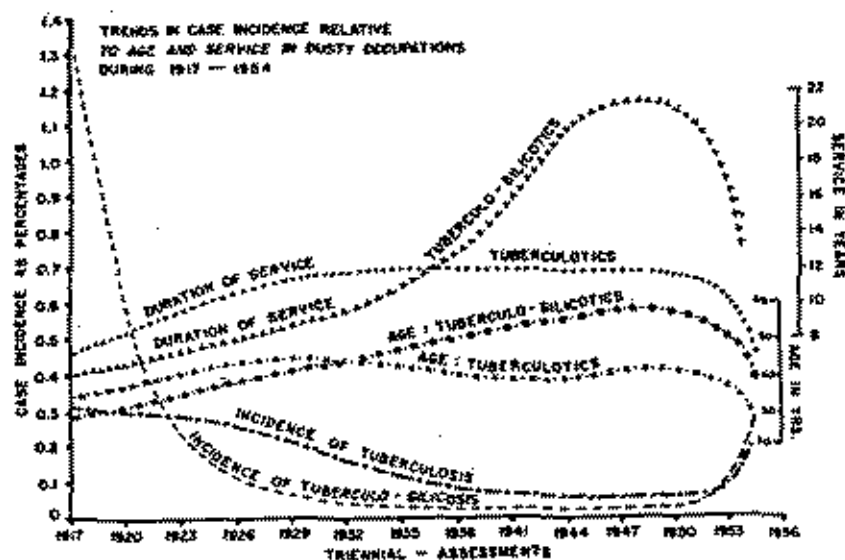


FIGURE 6

TUBERCULOSIS IN GOLD MINERS FROM THE WITWATERSRAND, SOUTH AFRICA DEATH RATE TRENDS

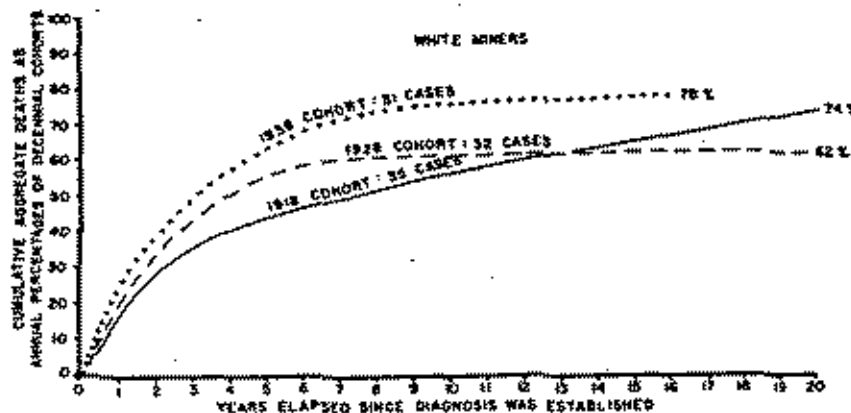


FIGURE 7

the disease appears after about 12 years of dust exposure. Though it assumes the pathological character and clinical course of non-occupational tuberculosis, it is almost invariably based on some macroscopically demonstrable preexisting silicotic damage in men with five or more years of service. For this reason South African law wisely treats all tuberculous miners with more than 10 years of dusty occupation service as cases

of silicosis complicated by tuberculosis, whether or not the silicosis has been demonstrated in life. It is almost invariably found in the lungs of such men after death. Many tuberculous with less than 10 years' service are reclassified as suffering from silicosis as well as from tuberculosis at later stages.

Tuberculosilicosis, i. e., silicosis and tuberculosis developing *pari passu* and manifesting simultaneously as a combined disease, com-

menced originally as a disease of younger miners and is now most prevalent among the older age group (fiftieth decade). Whereas it originally was the main source of death among short-service miners, it tends at present to be a more benign, more chronic disease occurring in men who had been exposed to dust almost 20 years (Fig. 6). It is by no means the same highly fatal entity as the tuberculosis which becomes grafted onto pre-established silicosis, and many miners affected by tuberculosilicosis may be completely symptom-free for many years, whereas those in whom tuberculosis supervenes on silicosis almost invariably die within six months to two years in spite of sanatorium care. The modern chemotherapeutic and antibiotic remedies have shown some temporary capacity to arrest such tuberculosis.

The death rate among tuberculosics has failed to show any significant abatement during the past four decades and may even be worse today than formerly (Fig. 7). Thus, whereas only 26% of the 1918 cohort of tuberculosic miners were surviving after 20 years, less than 22% of the 1938 cohort were alive at the end of 16 years, the majority having died within the first 10 years and at a materially more rapid rate than applied in the case of the 1918 cohort. No immediate explanation for this phenomenon presents itself.

CONCLUSION

The foregoing review of the occupational chest disease problem in the gold mines of South Africa may be summed up as revealing over-all favorable progress. Conquest is, however, by no means yet in sight. The fact that large numbers of the extremely robust white miners nevertheless develop disabling disease within about 20 years indicates but one thing: There is still too much harmful dust being breathed by these men. Assuming that the generally "satisfactory" dust levels reported in official statistics are representative of mining conditions at all times, one is forced to the conclusion that the "ideal" dust level of 200 particles per cubic centimeter (approximately 5,000,000 particles per cubic foot) is not yet satisfactory. The engineers

may have to adjust their sights once more. It is difficult to imagine precisely how this can be done, having regard to the rigid precautions which are already being enforced by government and the fabulous amounts already being spent by the mine owners to meet the specified requirements.

Pessimism concerning the increasing prevalence of these diseases among the Negro laborers may be tempered with the thought that in the absence of existing engineering and medical control the situation would have been infinitely worse. It is rather obvious, however, that the occupational diseases among these employees need much more exhaustive study. This is logical but rather more easily proposed than carried into effect, having regard to the rapid personnel turnover, language and cultural barriers, and the difficulty in obtaining technically qualified personnel for such an ambitious project. It does not, however, seem beyond the range of reasonability to insist on regular periodic chest x-rays for all Negro laborers. If it is considered a *sine qua non* for the white miners, who are much less closely in contact with dust-generating processes, it should be so much more necessary in the case of the Negro laborers. The rapid elimination of cases of tuberculosis should be the first objective, and it is to be hoped that some effort will be made to hospitalize and treat all tuberculosics after the disease has been officially certified by the Bureau. The pernicious practice of allowing such patients to go "home," where they constitute a source of infection to their families and friends in remote tribal villages beyond the control of civilized medical skills, should be stopped. Tuberculosis was not brought under control in civilized countries by *laissez faire* or without heartaches and frustrations, and the period of isolation can today be greatly reduced through the application of the modern therapeutic agents.

Although elaborate prescriptions are given concerning financial benefits for affected mine employees, the basic approach of the South African silicosis legislation with respect to the occupational chest diseases is

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prophylaxis rather than compensation. It has been shown how this ideal can be frustrated through administrative inadequacies, and it is to be trusted that precautions will in the future be taken to obviate the recurrence of events referred to. Research only can solve the puzzle of persisting disability, despite all the precautions that have already been taken.

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Accomplishments in the Epidemiologic Study of Silicosis in the United States

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Should an early investigator of silicosis return to the industrial scene, he might justifiably be surprised that, after many decades of study, this disease has still not been vanquished. Yet there are some who, though not removed from the industrial scene, have yielded to the complacency that full control of silicosis has been achieved. It is therefore timely, as we move farther into a technologic era in which radiation and other modern hazards compete for attention, to review the status of this old industrial plague.

In the United States, many groups, both nongovernmental and governmental, have made noteworthy contributions to the elucidation of the problem of silicosis. A review of all their efforts would not be practicable at this time. It is therefore the purpose of this paper to review only the accomplishments of the United States Public Health Service and to inquire into the present status of silicosis in the United States with the use of data made available to this agency.

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EARLY SILICOSIS STUDIES

For this group there is little need to report the chaotic situation that existed when the United States Public Health Service, in cooperation with the United States Bureau of Mines, undertook its first investigation of silicosis in the tri-state area of Oklahoma, Kansas, and Missouri in 1914.¹ At that time, medical knowledge was far ahead of our techniques for measuring the workers' exposure. Consequently, in this early investigation, very little information was developed about the environment. Even at this early date, however, the investigators realized that the ultimate solution of the problem would depend on the correlation of the medical findings with dust concentration. This study was one of the earliest attempts to apply x-ray to mass diagnostic procedures.

It is of historical interest that, of the 720 miners examined, 433, or 60%, were diagnosed as having "miners' consumption." In 103 of these cases, tubercle bacilli were demonstrated in sputum samples. In addition, there were 43 miners with a doubtful diagnosis; 26 were suffering from miscellaneous nonpulmonary diseases, and 39 had uncomplicated tuberculosis. Of the 433 miners, 120, with an average age of 31 years, showed first-stage silicosis; 142, with an average age of 33, were second stage; and 68, with an average age of 38, were third stage.

To reemphasize the drastic social consequences of the disease during this era, let us briefly review several case histories. Mrs. C. lost two husbands, aged 38 and 48; one son, aged 28, and one son-in-law, aged 34. Mrs. L. lost four brothers, aged 40, 42, 44, and 46. Mrs. T. lost two brothers aged 30

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and 28; a half-brother, aged 30; a husband, aged 29, and a brother-in-law, aged 28. Those are but a few of the many cases of family hardships caused in this one particular area by silicosis. This is not given as scientific evidence bearing on the problem but to illustrate the social and economic implications of silicosis of that time.

Conclusions drawn from this study are also interesting in view of our present knowledge of silicosis. Some of these were stated as follows:

1. Miners' consumption is an important occupational disease widely prevalent among the hard-rock miners of the Joplin district, affecting probably 30% to 35% of them.

2. Miners' consumption is essentially a pneumoconiosis due to the inhalation of siliceous rock dust and resulting in a fibrosis with loss of function.

3. The disabilities and other factors of miners' consumption are due primarily to silicosis, infection being usually a secondary and often a terminal process.

4. Infection, both tuberculous and pyogenic, is common in miners' consumption, the tendency toward infection increasing as the disease progresses.

The tri-state study formed the basis for a series of Public Health Service investigations in the dusty trades during the 20's and 30's, which included the cement, asbestos, coal, talc, and granite industries. Fortunately, by 1922 dust quantification methods had been improved, and it was thus possible to include in these studies fundamental investigations of the environment. The study of the granite industry, undertaken in 1923 by the old Office of Industrial Hygiene and Sanitation of the Public Health Service, was the first epidemiologic study of silicosis in which it was possible to correlate definitely the worker's physical condition with his environment.² This introduction of epidemiologic methods, which considered both the worker's environment and his physical condition, probably represents the most significant contribution that the Public Health Service has made to the study of silicosis. The granite industry study served to add materially to our knowledge of the pathology of the disease by constructing a graphic picture of what happened to men working for

many years under dust hazards of a known character. Among the significant factors were the following:

- (1) The long period of service before the liability to tuberculosis became manifest, generally 20 years or more.

- (2) The sharp correlation between the length of exposure to the dust and the prevalence of tuberculosis, and also the death rate from this disease.

- (3) The close correlation between the extent of dust exposure and the health of the miner.

- (4) The universal occurrence of silicosis among the workers exposed to concentrations above 40,000,000 particles per cubic foot (pcf) of air.

- (5) The large proportion of workers who finally succumbed to tuberculosis.

- (6) The almost invariable fatal form of the disease (silicosis) within a short time after the onset.

- (7) The different character of silicosis, as manifested by x-rays, compared with that where the exposure was to a dust with a much higher content of free silica.

This last conclusion was contested by Gardner in 1939, his thought being that it may have been due to improvement in x-ray techniques.³

On the basis of this study, it was possible to form some rough ideas of the limits of dustiness which may be regarded as reasonably safe from a health standpoint. Silicosis was universally present in those groups where the average dust content of the environment varied from 40,000,000 to 60,000,000 pcf of air. There was little indication of any serious effect on the men with average exposure of about 20,000,000 pcf. In the group where the average concentration was 6,000,000 pcf, there was no indication of any unfavorable effects on health. Thus, it appeared from the analysis of the data that a safe limit to this particular dust, with a free silica content of approximately 35%, was between 9,000,000 and 20,000,000 pcf of air.

Out of the granite study grew an extensive silicosis-control program, instituted by the Industrial Hygiene Division of the Vermont Department of Health. Briefly, this program was based on an agreement between the granite manufacturers and the labor unions to initiate dust-control measures, which would be periodically checked by the Ver-

ment Department of Health, and to provide annual x-ray examination of workers. It is interesting to note that, insofar as records show, not a single case of silicosis has developed in a granite-shed worker whose initial exposure followed the installation of dust controls.* This is the only known example of a United States industry in which it appears that no new cases of silicosis are developing. However, there are a number of factors which must be analyzed before we can assume that such success has been or could be attained in other industries.

The Public Health Service studies of dust diseases, conducted between 1913 and 1935, made several important contributions to the study of silicosis. These studies served to confirm the findings of many independent investigators and assisted in determining the pathology of the disease. They helped immeasurably in the assaying of dust exposures and in defining the role of such factors as particle size, composition of the dust, and duration of exposure and led ultimately to the adoption of 5,000,000 pcf of air as a maximum allowable concentration for silica dust. The year 1935 or thereabouts saw recognition and acceptance of the five cardinal factors in the etiology of silicosis: composition of the dust; the concentration of the dust; size of the dust particle; duration of exposure, and individual susceptibility.

Because of the need to concentrate on other disease entities, 1935 also saw a diminishing emphasis by the Public Health Service on epidemiologic studies of silicosis. This decision was undoubtedly influenced by the assumption that the silicosis problem was largely solved and that prevention was simply a matter of applying the necessary environmental controls. This feeling apparently was shared by others, for at the Fourth Saranac Symposium Drinker stated, "To be sure, the clinical and biological aspects of silicosis leave many problems unsolved, but the preventive aspects are now in fair order."¹ The middle 30's also marked the introduction of extensive dust-control pro-

grams by the larger mining and industrial companies.

The 20 years that have elapsed since the institution of dust-control measures may be regarded as a period of observation for determining whether these accepted preventive techniques are in reality adequate. It is therefore timely to appraise the effectiveness of control methods for silicosis.

PRESENT STATUS OF THE SILICOSIS PROBLEM

As a prefatory note, it should be recalled that statistics on the incidence of occupational diseases, including silicosis, have always been notoriously poor in the United States. With 48 states with differing requirements or none at all, it is not feasible to set up a central collecting system. In the states that have some kind of reporting scheme, lack of compliance, problems of interpretation of case histories, and differences in classification of the disease and in nomenclature are other discouraging factors. Despite the fact that medical reporting to Health and Labor Departments is compulsory in many states, it is ineffective as a source of incidence statistics. Numerical information, however, is available on silicosis incidence, but it is uncoordinated, scattered, and subject to various interpretations. The main sources are compensation records, medical and environmental investigations in specific industries, and routine examination programs.

We have been attempting to overcome the gap by gathering statistical data on the extent and scope of the silicosis problem today. This study, under way since November, 1954, seeks to determine how many silicotics there are as well as when they received their major dust exposure—whether it was before or after 1935, which we are arbitrarily setting as the year when industry began on a substantial scale to install dust-control equipment.

At the Fourth Saranac Laboratory Symposium on Silicosis, Cummings ventured a guess that not more than 50,000 employed men might be found in the United States at the present time with definite evidence of silicosis.² Exact knowledge of the number

* Ashe, H. B.: Personal communication to the authors.

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of potentially exposed workers in the United States then, as today, was not available. Among the more reliable estimates was the one based on the preliminary survey (1936-1939) of the industrial hygiene problem in the United States by the Public Health Service; the number of persons potentially exposed to silica dust was estimated to be 1,500,000.*

In terms of today's status of the silicosis problem, the implication in these earlier estimates can give rise to deep concern. In view of the slow clinical course of silicosis, workers who received their major dust exposure in the 30's or early 40's could be expected to show signs of the disease and disability at the present time. Although dust-control equipment was beginning to be installed in

laws in the states, it is not possible to make comparisons and draw valid conclusions. For this reason, only a description of the data can be presented.

In Colorado, in a 30-month period July, 1952, to December, 1954, there were 34 cases of silicosis processed. Of these, 11 were compensated; 18 were dismissed or denied owing to late filing, to absence of total or permanent disability, or for other reasons, and 5 were pending decision. Sixteen of the affected workers were reported to have begun their employment in industries with exposure to silica dusts after 1935. Twenty of the men worked in mines, 10 in foundries, 2 in smelters, and 2 in the firebrick industry.

In Utah, the medical panel of the State Industrial Commission made a diagnosis of silicosis in 24 workers during a three-year period preceding 1954. Four hard-rock miners were alleged to have received their exposure after 1935; one worked at his job 6 years, another 14 years, and two others 17 years each. The other 20 workers received their exposure before 1937 or both before and after. Eighteen of this group were hard-rock miners, and two were mill workers. Six of the miners also had tuberculosis.

In West Virginia, the Industrial Commission processed 1523 cases of silicosis in 1953 and the first 10 months of 1954. Fifty-eight were fatal. West Virginia compensates for partial disability, and, of the total processed, three-fourths received compensation.

In Pennsylvania, during the three-year period 1950, 1951, and 1952, a total of 305 cases of silicosis and 1115 cases of anthracosilicosis were compensated. In Illinois, 87 compensation claims for silicosis were closed during the three-year period 1951 to 1953. In California, the Industrial Accident Commission issued 87 original decisions involving pneumoconiosis during the fiscal years of 1953 and 1954. Only cases in which there is a dispute come up before the Commission. It is of interest to note in connection with these compensation data that, although we have no recent figures for Montana, in 1947 some 600 persons were receiving benefit payments as silicotics.

TABLE 1.—Compensation Data on Silicosis

State	Years	Type	Cases, No.
Colorado	July, 1952-Dec., 1954	Cases processed	34 silicosis
Utah	1952-1954	Cases processed	24 silicosis
West Virginia	1953-1954	Cases processed	1,523 silicosis
Pennsylvania	1950-1952	Compensated cases	305 silicosis 1,115 anthracosilicosis
Illinois	1951-1953	Compensated cases closed	87 silicosis
California	1953-1954	Disputed cases before the Commission	108 pneumoconiosis
			2194

the middle 30's, the achievement of universal coverage was many years removed. A big educational job lay ahead. Management and labor had to be taught not only how to prevent and control dust diseases of the lungs but also that certain dusts in excessive exposures were dangerous. As a matter of fact, the job is still incomplete, for two decades later many plants can be found without dust control. In other words, despite whatever progress may have taken place in cleaning up dusty working conditions, we are likely to inherit for years to come a sizable prevalence of silicosis.

Compensation Data.—A major source of information on the extent of the current silicosis problem is compensation records. Table 1 summarizes the experience in six states within recent, but differing, periods of time. Because of differences in compensation

X-Ray Examination Data.—Another source of information is the x-ray examination data accumulated by the divisions of industrial hygiene in the state health departments of Vermont and North Carolina.

Table 2 shows a comparison of x-ray findings of workers in the granite sheds of Vermont in 1937-1938, when dust control equipment was being installed by the manufacturers, and again in 1954. X-ray examinations in 1937-1938 of 805 workers disclosed 365, or 45%, with silicosis; examinations in 1954 showed 20% with silicosis. In 1954, the incidence rate based on the payroll employment of 1809 granite-shed workers was 16%; insofar as it can be determined from occupational histories, all the affected workers re-

TABLE 2.—*Silicosis (All Stages), Granite-Cutting and Finishing Industry of Vermont*

Item	1937-1938	1954
Average payroll employment.....	1,100	1,809
Workers x-rayed, no.....	805	1,437
Workers x-rayed with diagnosis of silicosis, no.....	365	283
Workers on payroll with silicosis x-rayed at least once but not in indicated year, no.....		75
Total with silicosis.....	365	358
Workers x-rayed found with silicosis, %.....	45	20

ceived their initial exposure to dust prior to the installation of dust-control equipment. Of the 294 workers with silicosis who are still employed, 42 also have some form of possible infection, such as tuberculosis. In 1937-1938, the corresponding number was 143.

A workmen's compensation law was passed recently in Vermont providing compensation for total disability due to silicosis. Relatively few claims have been filed, however, since the granite cutters either are not totally disabled or prefer to remain at their jobs as long as they can.

The Vermont Division of Industrial Hygiene also takes routine chest x-rays of workers in other industries. In 1951-1952, there were 16 to 419 quarry workers x-rayed who showed evidence of silicosis. The years of exposure were long in all instances. Eleven

out of 1216 workers in the foundry industry and 38 of 318 slate workers showed evidence of silicosis in one stage or another. The period of major dust exposure has not been ascertained for these cases.

Since 1936, the Division of Industrial Hygiene of the North Carolina Board of Health has been x-raying workers and conducting studies of the working environment in dusty trades applying for or carrying workmen's compensation insurance for silicosis. This responsibility is delegated by law. Legal provision is also made for physical examinations of prospective employees and periodic examinations of those engaged in industries with harmful dusts, with a stipulation for the removal of employees in the very early stages of the disease. The program is carried out in conjunction with the Industrial Commission. On the average, 2500 to 3500 workers appear for x-rays annually. Most of these workers are engaged in the mining and milling of tungsten, mica, and pyrophyllite and the quarrying and cutting of granite and stone.

Since 1936, as a result of the state's physical examination program, 446 workers were diagnosed as having silicosis. Table 3 gives a distribution of cases for major industry groups according to five-year intervals during which positive diagnosis was first made. The five-year grouping is for convenience rather than to show any increase or decrease in incidence, because the number of new cases uncovered is dependent to a great degree on the coverage of industries by the x-ray survey. Unlike the data collected in Vermont, the available information for North Carolina does not lend itself to determining incidence rates. Workers found with silicosis are denied a workcard and either file a claim for compensation or find employment in non-dusty industries. Thus, they do not always reappear for periodic examinations.

An opportunity was given to review individual records of 40 cases diagnosed as having silicosis for the first time in 1953 or 1954. Occupational histories indicated that 20 of these workers began employment in

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dusty trades after 1935. Five of the recently affected workers were under 40 years of age and had a mean average exposure to dust of 13 years; 5 were between 40 and 49, and 10 were over 50 years of age.

Mortality Statistics.—Further information in the form of unpublished data on deaths from occupational respiratory diseases in the United States has been provided by the National Office of Vital Statistics. These data are shown in Table 4. Over the four-year period 1949-1952, they reflect an average of more than 1200 deaths per year from silicosis and anthracosilicosis combined, about 600 deaths per year from respiratory tuberculosis

was the only cause of death mentioned on 21 of the 64 certificates; silicotuberculosis was given on 26, and for the remaining 17, other causes were also stated.

A rough distribution by occupation revealed that 18 were miners and another 18 worked in the granite industry, foundries, and other trades generally associated with silica-dust exposure. Another 18 were reported in occupations not usually associated with silica exposure, such as farmers, janitors, store clerks, and guards. Ten certificates did not state occupation or gave the occupation as "laborer" without further explanation. The inadequacy of the kind of

TABLE 3.—Number of Cases of Silicosis (All Stages) According to Period When First Diagnosed and by Industry in North Carolina

Period	Total	Miner and Milling of Minerals	Granite and Stone Industry	Foundries	Other
1936-1939	89	42	17	13	5
1940-1944	124	77	37	8	5
1945-1949	75	60	31	9	5
1950-1954	158	91	56	3	9
Total	446	270	160	33	20

TABLE 4.—Deaths from Occupational Respiratory Diseases, 1949-1952, for United States (National Office of Vital Statistics, Public Health Service)

Cause of Death	1949	1950	1951	1952
Respiratory tuberculosis with mention of occupational disease of lung	658	647	635	694
Silicosis and anthracosilicosis	1,203	1,208	1,206	1,227
Other pneumoconioses	225	220	225	247

with mention of occupational disease of lung, and 225 deaths per year from other pneumoconioses, probably chiefly silicosis. Age or occupational analysis of the deaths is not available.

An analysis of 64 death certificates naming silicosis or pneumoconiosis as a primary or contributory cause of death in one state (Kentucky) shows that silicosis is present at all ages but tends to increase in importance in the older age groups. Five of the workers were between 30 to 39 years of age; eight were between 40 and 49 years. For six of these workers, the cause of death was given as silicosis or pneumoconiosis without mention of other conditions; for five, silicotuberculosis; and for the remaining two, other disease conditions. Silicosis

information contained in death certificates is readily apparent.

CURRENT INVESTIGATIONS AND STUDIES

It was not meant to imply earlier in this paper that since 1935 the Public Health Service has had no interest in silicosis and other dust diseases. With its extensive history of research in dusty industries, the Occupational Health Program of the Public Health Service has every intention of pursuing appropriate studies whenever it is indicated that a significant public health problem exists. In 1949, evidence pointed to the foundry industry as a significant source of exposure to silica dust. Consequently, the Public Health Service, in cooperation with the Illinois Department of Public Health, undertook a study of silicosis in the various

foundries of Illinois.⁵ As might be expected, the most significant findings pertained to the respiratory system. Pulmonary fibrosis of occupational origin was found in 9.2% of the 1937 men examined. The clinical and environmental findings revealed that there was reason to believe that the dust conditions in the foundries had improved in the past 10 to 20 years. Thus, it is likely that in most instances the pulmonary fibrosis observed was due in great part to the higher dust concentrations which probably had existed 10 or 15 years previously. The conditions noted, however, generally left room for improvement in the control of silica as well as other hazards.

In 1953 and 1954, in cooperation with the health departments of California, Nevada, and Oregon, the Public Health Service conducted a comprehensive clinical and environmental study among workers engaged in the mining and processing of diatomaceous earth in five plants, three handling salt-water diatomite and two handling fresh-water diatomite. Approximately 900 employees were examined. The prevalence of pneumoconiosis, similar in type to that reported in 1952 by Smart and Anderson,⁶ was sufficiently high to confirm the existence of a pulmonary hazard in this industry.[†] Preliminary indications are that the major danger lies in the crystalline forms produced by calcining of the amorphous natural diatomite. Prior to the study, recognition by the industry of the need for rigid controls led to progressive reduction in dust exposure, and so correlation of current environmental and clinical data is misleading. Plans are now in effect for periodic follow-up observations to determine the effectiveness of control measures now being applied.

From the foregoing statistics, crude as they may be, it is apparent that silicosis is yet a major occupational disease in the United States. Our limited information, however, indicates that tuberculous infection

is not so prevalent as it once was among silicotics, and, needless to say, because of our present compensation laws and enlightened employment practices, the disease no longer has extreme and unique social consequences. Examination of the data also indicates that there is a longer period of development of the disease than was true in the early days. You may recall the average age of those suffering from third-stage silicosis in the tri-state study was 38 years. Although we have not compiled an average age for present-day silicosis, it would appear that it is somewhat higher.

UNRESOLVED QUESTIONS

The continuing occurrence of relatively large numbers of cases of silicosis raises some questions. It is not the purpose of this paper to attempt to answer these questions, but simply to pose them as areas in need of further study. A number of questions follow:

1. Do the initial exposures in these cases date back to pre-dust-control days? If so, do these cases represent progression of the disease due to continued exposure to low concentrations of silica dust? Certainly, the age range of many of the cases indicates that they may have received their initial exposure before dust controls were generally adopted by the mining and manufacturing industries.

2. How extensive and efficient is dust control in relation to recommended standards? Doubtless, there is a large volume of data available in official and private industrial hygiene agencies which would have bearing on this problem. As yet, however, these data have not been analyzed on a mass scale.

3. Do our standards need revision? There is no ample evidence at this time to indicate that the 5,000,000 particles per cubic foot (pcf) of air are not adequate. However, as with other industrial hygiene standards, this standard should be under constant scrutiny.

4. Are there other factors to which we are not giving proper consideration, such as particle size of the dust? Mention of this problem is frequently found in the literature.

[†] Occupational Health Program, Division of Special Health Services, U. S. Public Health Service: Unpublished data.

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The Third International Conference of Experts on Pneumoconiosis pointed up the need for additional research in this field, stating that "the lower size limits of injurious particles had not yet been determined."[†]

5. What is the actual toxicity of silica? The diatomaceous-earth pneumoconiosis study indicated that noncrystalline forms of silica, as well as cristobalite and tridymite, produce a pneumoconiosis which is not silicosis *per se* but closely related to it. The predominate opinion of investigators of coal miners' pneumoconiosis is that the small concentrations of crystalline silica to which the worker is exposed have no significance in the etiology of the disease.[‡] There are others, however, who maintain that these small concentrations may have a significant relationship to the problem. This point still needs to be resolved.

These are questions which are of real interest to the scientist and must be answered if silicosis is to be completely eliminated as an industrial disease. In the compensation field also there are problems which will need scientific evaluation before the compensation and social aspects of the disease are completely resolved. These problems are associated primarily with the need to devise practical means of assessing disability. This question becomes more acute as more states compensate for partial disability. Indeed, there is still great need for the development of a satisfactory x-ray classification. As you know, this problem is being considered by a committee of experts in the United States, and an international classification system has been proposed by the International Conference of Experts on Pneumoconiosis.[§]

CONCLUSION

From this review of dust studies of the Public Health Service and the data made available by other sources, it may be concluded that the problem of silicosis in the United States is still far from being solved. Several obstacles yet remain to be hurdled,

primarily in the resolution of technical questions.

The following agencies cooperated in providing information relating to the silicosis problem: Industrial Hygiene Division, Vermont Department of Public Health; Division of Industrial Hygiene, North Carolina Board of Health; State Compensation Insurance Fund, Industrial Commission of Colorado; Utah Industrial Commission; Industrial Commission of West Virginia; Bureau of Research and Information, Pennsylvania Department of Labor and Industry; Division of Labor Statistics and Research, California Department of Industrial Relations; Division of Statistics and Research, Illinois Department of Labor; Kentucky State Department of Public Health, and National Office of Vital Statistics, Public Health Service, U. S. Department of Health, Education, and Welfare.

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Silicosis in Canada

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The statistics on the incidence of silicosis in the Province of Ontario and in the rest of Canada over the last quarter-century are somewhat lacking. The reasons for this are twofold, and they seem to be equally common in other parts of the industrial and mining world. They are as follows:

1. In our mining industry from 1926 to 1930, the exposure time needed to produce silicosis was about 15.4 years. In the interval 1951-1953, it increased to nearly 25 years.
2. The number of employees in gold mines in the Province of Ontario varied greatly during the period 1926-1953 (Fig. 1). The

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average employment was about 13,200, and it ranged from nearly 22,000 in 1941 to as low as 11,000 in 1944.

In addition to the changes in total employment, labor turnover makes for lack of continuity of history obtainable from annual examinations. It may result in complete loss of contact with many who leave the industry, unless and until some of them may return claiming silicosis which developed in the interim.

It is perhaps fair to say that approximately 70% of the total employees in gold mining are engaged in what are designated as dust-exposure occupations*; this number includes

* The Mining Act, Ontario, Section 135, reads in part, as follows:

- (c) "Dust exposure occupation" shall mean,
- (i) employment underground in a mine,

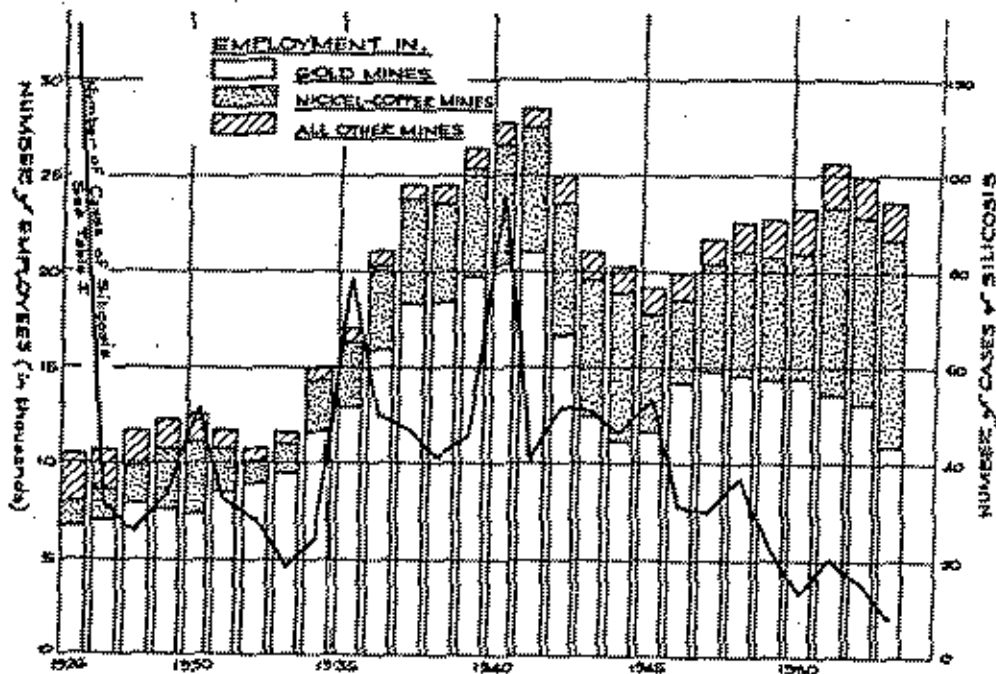


Figure 1.

SILICOSIS IN CANADA

all underground workers as well as those working in crusher houses, in milling, and in the assay office.

A recent survey of a number of gold mines operating in the Porcupine Area of Northern Ontario showed that among a total of 3757 employees

	Per Cent
1,231 had been employed for less than 10 years.	59.1
443 had been in continual employment for 10 to 15 years.	11.8
159 had been continually employed for 15 to 20 years.	11.2
634 had been continually employed for more than 20 years.	16.9
3,757	100

Despite this discouraging approach to the subject, I believe that nowhere in Canada is there as much factual information available on the progress and extent of silicosis as may be found in the mines of Ontario. Some appreciation of this can be conveyed from the following facts:

1. For all practical purposes, gold mining may be said to have commenced in Ontario in 1908. For the first 20 years no special attention was paid to chest examinations of employees, with or without x-ray. Commencing in 1928, however, the Mining Act of the province was amended to require that every person employed in a dust-exposure occupation in a mine must have preemployment examination, including x-ray of the chest, by an examiner appointed for the purpose and must be certified

(a) Before a preliminary certificate is issued

"to be free from diseases of the respiratory organs and otherwise fit for employment in dust exposure occupations";

(ii) employment at the surface of a mine in ore or rock crushing operations where the ore or rock is not crushed in water or a chemical solution which constantly keeps it in a moistened or wet condition.

(iii) employment at other locations, as designated by the Chief Inspector, at the surface of a mine or in a pit or quarry;

(b) Before a final certificate is issued, after two years' employment, "to be free from tuberculosis of the respiratory organs."

Thereafter the certificate is kept in good standing only if annual chest examinations, including x-ray, are submitted to by the holder.

There is, in consequence, a complete chest history of every man employed in a dust-exposure occupation, commencing with his preemployment examination and continuing with annual examinations during the complete period of his employment. The films are all retained in the files of the local examiner of the Workmen's Compensation Board of Ontario, together with a card record of these examinations kept up to date annually or oftener, as intermediate examinations may have been indicated and carried out.

2. In Ontario, the Workmen's Compensation Board operates as a semigovernment function. An independent board has been set up under an Act of Parliament and is empowered to pay compensation for industrial accidents and to assess the employers the full cost of same, to include not only compensation but also medical aid and rehabilitation.

Silicosis was made an industrial disease under the Act of 1926. The Board's decision on all claims thereafter has been given to the employers, so that the Ontario Mining Association, an organization of these employers, has full information on the ultimate disposal of these claims.† Further, the Compensation Board has been able, through the cooperation of the Silicosis Referee Board and, in particular, of Dr. A. R. Riddell, a member of that Board, to set out the year in each case in which silicosis was first deemed to be present.

† A paper, "The Prevention of Silicosis in Ontario Mines," by N. F. Parkinson, read at Timmins in January, 1951, and published in the Proceedings of the McIntyre Research Foundation for that year, provides further details respecting the position of silicosis and the measures taken in its prevention.

TABLE 1.—Number of Cases by Years in Which Silicosis, as Defined by the Workmen's Compensation Act,* First Occurred†
(Table Includes Average Age, Average Dust Exposure, and Number Who Had Died at End of 1953)

Year	Cases of Silicosis, No.	Average Age, Yr.	Average Dust Exposure, Yr.‡		Workers Who Started Mining After 1928,‡ No.	Workers Dead at End of 1953, No.
			In Ontario	Outside Ontario		
1920.....	127	39.7	12.0	1.4	0	120
1921.....	31	43.1	12.3	1.0	0	20
1922.....	25	41.7	13.3	1.7	0	23
1923.....	23	41.5	10.7	0.9	0	31
1924.....	30	44.3	13.8	1.0	0	29
1925.....	33	45.3	17.5	1.3	0	30
1926.....	28	45.2	16.1	1.3	0	23
1927.....	19	44.5	15.1	0.9	0	13
1928.....	23	43.4	17.0	0.5	0	18
1929.....	79	45.3	17.7	2.0	0	47
1930.....	62	45.0	16.1	0.8	0	31
1931.....	47	44.3	17.2	2.6	1	32
1932.....	41	44.7	16.1	3.4	2	24
1933.....	48	43.6	19.7	3.0	0	26
1934.....	56	43.6	19.5	2.7	1	29
1935.....	60	44.4	17.1	1.8	2	28
1936.....	53	43.4	16.9	2.3	3	39
1937.....	51	40.7	19.9	2.3	2	39
1938.....	45	40.2	17.4	1.8	4	30
1939.....	52	40.0	20.4	1.5	0	15
1940.....	32	40.2	19.2	0.7	7	5
1941.....	30	40.7	20.0	1.8	5	5
1942.....	28	41.0	21.4	0.5	7	11
1943.....	22	40.3	21.5	1.1	3	6
1944.....	14	43.6	24.7	1.2	1	5
1945.....	20	47.8	24.7	1.2	1	5
1946.....	16	45.5	22.4	1.0	0	3
1947.....	1	55.0	24.7	0.1	1	2
Totals.....	1,146	45.7	17.6	1.6	45	623

* "Silicosis means a fibrotic condition of the lungs sufficient to produce a lessening capacity for work caused by the inhalation of silica dust."

† The year when a man is first considered to have developed silicosis is determined by the Silicosis Review Board of Ontario usually after physical examination and a study of the records and the chest x-ray films of the man concerned. Those still at work and so not yet eligible for compensation are included, as are also persons whose claims have been allowed after death.

‡ Average time spent in dust-exposure occupations up to the time of developing silicosis, as determined from the employers' records and information obtained from the man himself.

§ The amendment to the Mining Act, making compulsory annual chest examinations and certification for all men working in dust-exposure occupations in the mining industry of Ontario, came into force on Jan. 1, 1929.

AVAILABLE INFORMATION ON SILICOSIS IN ONTARIO MINES

In the Province of Ontario, most of the cases of silicosis developing in the industry have come from the gold-mining group. Of the total of 1146 accepted cases shown in the accompanying Tables, only 128 have been allocated to the mining of other materials than gold (Table 1).

Note particularly Column 6 of Table 1, which shows the number of cases included in the total of Column 2 who started to work in the mines after 1928. The significance of this group is that they all received preemployment examination, including chest x-ray, in accordance with the requirements of the Act which became effective on Jan. 1, 1929.

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The workers have all received at least annual chest examinations, including x-ray, over the whole period of their later employment in the mines.

It is worthy of comment that, of the total of 1146 known cases accumulated in the industry from the time of commencement of mining activities in the early 1900's, there have been to the end of 1953 only 45 men who commenced mining in 1929 or later who are known to have contracted silicosis. One must not become too enthusiastic about such a showing, as the final story on these cases will not be known for some years. There are bound to be additions made to the number of those attributed to some past years. There will be some men who, silicosis-free, left the industry for a number of years, then developed silicosis, and sought treatment and compensation. These men are fully protected under the Act. If, as, and when disablement may develop in the future, provided that they were actually exposed to silica dust in their employment in Ontario for periods amounting in all to at least two years preceding, they are entitled to compensation.

To permit a more graphic demonstration of the trends, some of the figures in Table 1 have been grouped by five-year periods in Table 2 as follows:

An examination of the data in Tables 1 and 2 provides some interesting indications.

The number of cases has shown a marked decline since the period 1941-1945. If, for example, the number of cases developing in 1954 and 1955 are the same as occurred in

each of the years 1951 to 1953, the figure for the last five-year period will be 72.

We can be almost certain that as years pass more cases will be added to a number of these prior years, but the trend seems clear and the decrease in the rate of production gives all the indication of being substantial.

There is no uncertainty about the increasing average age at which the new cases of silicosis are developing. The trend is substantial and steadily upward. In less than 30 years the average age for the development of silicosis has increased by approximately 36%.

Also there is no uncertainty about the great increase in exposure time required to produce silicosis in Ontario mines. In less than 30 years the dust exposure required has been lengthened by more than 60%.

No special reference has been made as yet to death cases, as shown in Table 1. A special study of these has been prepared, which demonstrates certain other trends of interest than those disclosed in a simple listing of the number of deaths as at the end of 1953. One feature of interest is that 11 of the 127 men who were found to have developed silicosis in 1926 or before were still alive at the end of 1953.

The 623 cases have been grouped under certain classifications and by five-year periods in Table 3.

A review of these figures emphasizes some trends already noted and indicates some new ones.

The 1946-1950 period shows the occurrence of 162 deaths from silicosis, while in the same years (Table 2) only 136 cases of silicosis were shown to have developed. As a matter of fact, in 1947 for the first time since 1926 the number of deaths occurring among silicosis cases was greater than the number of new cases developing in that year. The comparable figure for the three-year period 1951-1953, when 98 deaths occurred, was 43 cases of silicosis that developed, as shown in Table 2.

The age at time of death shows the same remarkable trend upward as the age at which

TABLE 2.—Consolidation of Some Statistics on Cases of Silicosis Contained in Table 1 into Five-Year Period Groups (1926-1953)

Five-Year Period	Cases of Silicosis, No.	Average Age, Yr.	Average Dust Exposure, Yr.	
			In Ontario	Outside Ontario
1926-1930.....	260	41.5	18.7	1.7
1931-1935.....	182	45.5	17.5	1.5
1936-1940.....	278	48.9	16.1	2.5
1941-1945.....	240	48.8	16.8	2.0
1946-1950.....	130	51.2	20.5	1.2
1951-1953*.....	43	56.5	23.2	1.0
Totals.....	1,140	46.7	17.6	1.8

* Three-year period.

TABLE 3.—Number of Deaths Among Persons with Silicosis by Five-Year Periods (1926-1953) in Which Deaths Occurred (Average Age, Elapsed Time from Silicosis to Death, and Proportion of Total Deaths Due to Silicosis or Silicosis plus Tuberculosis)

Five-Year Period	No. of Deaths	Average Age at Death, Yr.	Average Elapsed Time from Silicosis to Death, Yr.	Deaths from Silicosis and Silicosis plus Tuberculosis, Per Cent
1926-1930.....	49	44.8	5.0	61.8
1931-1935.....	90	47.8	5.4	61.1
1936-1940.....	105	50.7	7.2	69.5
1941-1945.....	119	54.4	8.6	78.6
1946-1950.....	162	58.9	9.8	86.0
1951-1953.....	30	62.2	11.6	86.1
Totals.....	623	54.4	8.2	69.9

* Three-year period.

silicosis develops but exaggerated here by the fact that the length of time elapsing between the development of silicosis and death is also increasing.

Elapsed time between silicosis and death, as shown in Column 4 of Table 3, has in-

creased from an average of 2 years (1926-1930) to 11.6 years in the period 1951-1953, or by nearly six times. Age at time of death (Column 3 of Table 3) increased for the same periods from 44 to 62.2 years, or by 41%.

The last column, dealing with the cause of death, shows a marked trend away from tuberculosis as a governing factor. Actually, in Ontario mining experience, silicosis of itself has never been an important cause of death. Of the total of 623 deaths shown in these groups to the end of 1953, only 18 have been attributed to uncomplicated silicosis. In a number of these, especially where compensation payments have not resulted, the diagnosis might be questioned.

Some interesting research work might be undertaken to determine the reason for the trend here shown, but there would seem to be two outstanding causes which might be considered to have influenced the situation. They are as follows:

1. After men develop silicosis, they now live for nearly 12 years instead of the average

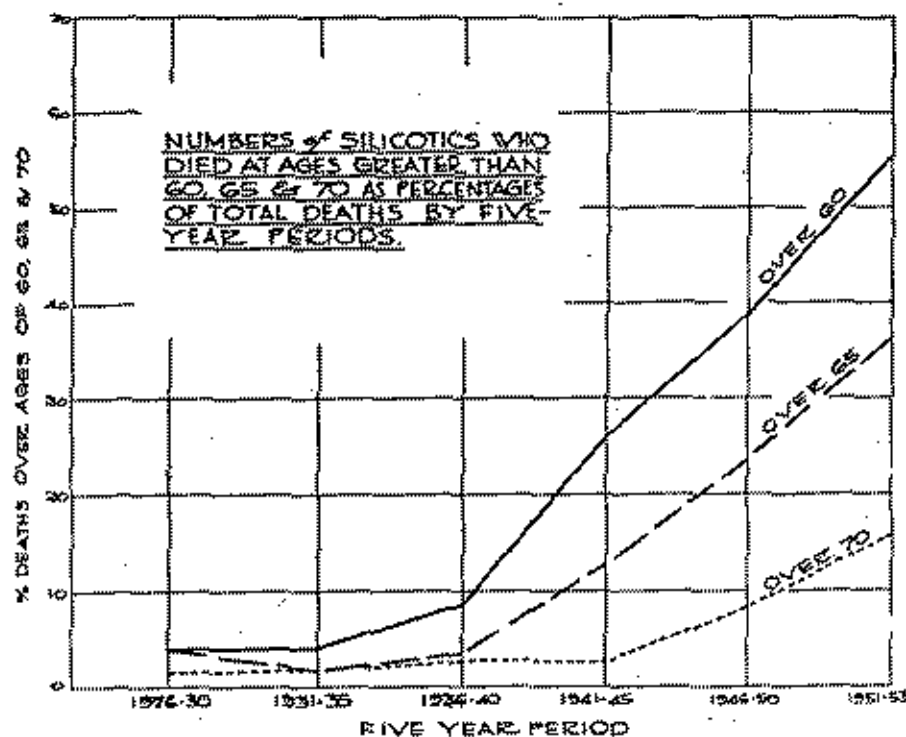


Figure 2.

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of 2 shown in the early years. This means that they have nearly six times as long to live and, therefore, six times the chance of dying of accident or some other disease or cause not related to their silicosis.

2. The work done under the auspices of the provincial government in the field of the prevention of tuberculosis has brought about a marked change in the position of this disease. Mortality rates in the province in 1930 on account of tuberculosis were 57 per 100,000 of population. The comparative figure for 1953 was seven. On the assumption that prevalence has been similarly affected, the opportunity of our silicotics to become infected by contacts has obviously been reduced.

On the subject of age, Figure 2 shows the percentage of cases 60 years of age or over making up the total deaths of our silicotics in each year. Using averages, it is apparent that there must be a fair number among those whose deaths occurred in each year whose ages were less than and greater than the average figure shown. The graph, however, again substantiates the trend toward greater age at time of death. For example, in the three-year period 1951-1953, of the total deaths 55% were among men over 60, 37% were among men over 65, and 15% were among men over 70 years of age.

Actually, with the average age at which the Ontario miners now develop silicosis—56.5 years (1951-1953)—and the average age at which death occurs in the same period—62.2 years—silicosis can no longer be, if it ever was, looked upon as a menace to our youth. While the comparison is obviously not a fair one, it is nevertheless a fact that the average age at death of all males in Canada as per the census figures in 1951 was 56.4 years.

I would call your attention again to Figure 1. This shows the mine population from 1926 to 1953, inclusive, with subdivisions representing those employed in gold mines, nickel-copper mines, and all other mines, respectively. All other mines include, in the main, those mining iron ore and the silver-

cobalt group. Superimposed on the population figures is a graph showing in each year the number of cases of silicosis taken from Column 2 of Table 1.

The mere statement that 1146 cases of silicosis have been found in the mining industry of the province gives perhaps an erroneous impression. The length of time over which these cases have accumulated is of interest. Of these 1146 cases, 1018 have been attributed to gold mining, in which there has been an average of 13,200 men employed per annum for a period of some 28 years.

SUMMARY OF ONTARIO MINING EXPERIENCE

From the records certain obvious developments have, I believe, been demonstrated, as follows:

1. The number of cases of silicosis developing each year has been decreasing at a rapid rate.
2. The average age at which silicosis develops has increased from 41.5 years (1926-1930) to 56.5 years (1951-1953), or by 36%.
3. The average number of years of dust exposure required to develop silicosis among the few who contract the condition has increased from 15.4 years (1926-1930) to 24.8 years (1951-1953), or by 60%.
4. Only 45 cases, or less than 4% of the 1146 known cases of silicosis in the industry, have occurred among those who commenced mining after 1928.
5. The average age at death has increased from 44 years (1926-1930) to 62.2 years (1951-1953), or by 41%.
6. Life expectancy after silicosis develops has increased from 2 years (1926-1930) to 11.6 years (1951-1953), or by six times.
7. The proportion of cases that died of silicosis or silicosis plus tuberculosis has decreased from 91.8% (1926-1930) to 55.1% (1951-1953).

That these developments are of importance to the men employed in the industry and to the industry itself needs little emphasis. They have not been achieved without effort. The most important changes that have been made since 1925, when silicosis was recognized as being present among employees in mining, are briefly summarized as follows:

1926 Silicosis was made an industrial disease for compensation purposes (at industry's request).

1928 Legislative provision was made for compulsory preemployment x-ray examinations and certification for dust-exposure occupations (at industry's request).

1925 and continuing

(a) Dust prevention.

(b) Dust collection.

(c) Design of machines to avoid making dust. Improvements in mine ventilation have been such that in many mines a greater tonnage of air is now pumped underground than the tonnage of ore hoisted.

1944 General application of aluminum powder prophylactically in Ontario gold mines.

The mines would like to be able to assess the value of any one of these changes in the over-all improvement in the silicosis situation as demonstrated. The long period of exposure required to develop silicosis and the practical difficulties in setting up controls make such an appraisal at this time difficult, if not impossible.

We are satisfied that preemployment x-ray examinations, practiced since 1929, are important.

We are satisfied that the control and removal of dust, together with improved ventilation taken in hand in 1925 and worked at assiduously since then, are important factors. After nearly 30 years, however, silicosis has not been entirely eliminated.

In the light of the more rapid improvement in the silicosis situation since 1946 (Tables 1 and 2), we are satisfied that aluminum prophylaxis administered generally to all gold-mining employees since 1944, demonstrated to be effective in the prevention of silicosis in animals, may have been a factor.

More time will be required to demonstrate the actual position of aluminum prophylaxis in this regard, but, in the meantime, after some 11 years of continual application, no cases have arisen which demonstrate or even indicate any ill effects.

SILICOSIS IN ONTARIO FROM OTHER INDUSTRIES THAN MINING

In preparing this review of silicosis in the mining industry of Ontario, there has been

available factual information in the form of x-ray films, listed results of physical and x-ray examinations, records of dust exposure from the mining companies, and decisions of the Workmen's Compensation Board of Ontario over the years as to compensability on account of silicosis of the persons concerned. There has also been available the expert opinion of members of the Silicosis Referee Board of Ontario as to the date when silicosis as defined in the Act first made its appearance. In these circumstances, the story of the history of the known cases of silicosis that have occurred over the years may, for all practical purposes, be considered factual.

To use this material, however, in assessing the position of silicosis in the rest of Ontario, let alone in the rest of Canada, raises real difficulties.

In no other area, nor among any other group of workmen employed in a complete industry, of which I am aware, do any such records exist as have been available in the preparation of this material.

First, in Ontario other industries than mining have their silicosis problems, and while dust exposure may in some be severer than that found in mining, one can be sure that the gross amount of silicosis found in all such would be only a fraction of that found in mining by reason of the great disparity in the total number of employees.

SILICOSIS IN THE REST OF CANADA

Omitting references to provinces where mining and other forms of industry involving exposure to dust are not found on as comparable a scale as in Ontario and where little, if any, silicosis would be expected, it has been found that in 1951, for example, the proportion of the total Canadian population in Ontario and other provinces that might be classed together was as follows:

Province	Per Cent
Ontario.....	22.8
Quebec.....	29.0
Alberta.....	5.7
British Columbia.....	8.2

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On the basis of the actual value of mineral production, the corresponding figures for these provinces in 1953 were as follows:

Province	Per Cent
Ontario.....	44.5
Quebec.....	29.0
Alberta.....	18.5
British Columbia.....	12.1

Lacking more definite information, it might be assumed that the production of silicosis in these other provinces bears some comparable relation to the figures covering population or value of mineral production.

As a check in part to estimates made on the basis of any of the above figures, the Workmen's Compensation Board of the Province of British Columbia for the year ended Dec. 31, 1953, reported that, during

the 18 years since silicosis became a compensable disability in that province, 616 workmen have been given compensation for impairment therefrom. The only comment I would make in this regard is that, even though some of the 616 cases arose through other industries than mining, the proportion in relation to Ontario mining cases seems high at about 54% of our 1146, while their population is just over 25% of our Ontario population and their value production of minerals about 35% of our value production. Unfortunately, I have no similar figures to give you on the situation in Quebec or other provinces.

Assistance in the preparation of data was rendered by Dr. A. R. Riddell and other members of the Silicosis Referat Board of Ontario.

COMMENTARY ON REFERENCES BY N. F. PARKINSON CONCERNING THE SILICOSIS PROBLEM IN ONTARIO

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Mr. Parkinson has asked me to enlarge on some features of the mining situation and, in addition, to say a few words in regard to silicosis in industries in Ontario other than mining in which workmen encounter silica dust.

We are advised that 1164 persons are known to have contracted silicosis in the Ontario mines. Forty-five of these entered the industry and, as far as is known, were first exposed to silica dust after 1923, when the preemployment examination of prospective miners was instituted. This group represents a very small fraction of the miners who commenced work in the industry after 1923. They developed the disease in spite of greatly improved working conditions and special arrangements for the selection of persons suitable for dust exposure. What is the explanation?

The medical records on each of these cases are very complete. They include clinical data and serial chest radiograms prepared at the time each miner entered the industry and at yearly intervals during his employment there. Each miner in the group has filed a claim with the Workmen's Compensation Board, in connection with which he was further examined and x-rayed. Subsequent

to his initial examination for compensation purposes, each has been under periodic medical supervision. Most have had periods of observation and treatment in sanatoria or general hospitals. All the deceased have been autopsied. Thirty-four of the miners are still living; eleven have died.

Some of the important data on these cases are listed in Table 1.

All the miners in the group developed silicosis rapidly after periods of dust exposure which were, on the average, about half the period given by Mr. Parkinson as average for miners at the present time. Evidently these persons were especially susceptible to injury by silica. Although tuberculous infection may not explain the susceptibility in all these cases, it appears significant that 28, or slightly more than 60% of them, were definitely suffering from tuberculosis and that in 8 others, or almost 18%, tuberculosis was suspected. These cases are not, at least in the first instances, cases of what in this country often is termed silico-tuberculosis. Rather are they cases of tuberculo-silicosis. The term seems to have considerable merit. Most of these cases are not overtly tuberculous when first seen. Nevertheless, in our experience tuberculosis should always be suspected as a factor in cases that develop quickly after short exposures or in those in which the pulmonary fibrosis continues to progress long after exposure has ceased. Silicosis and tuberculosis are peculiarly related. This should always be kept in mind by those concerned with the medical selection of persons for exposure to silica dusts. A review of

Recorded for publication June 20, 1955.

Division of Industrial Hygiene, Department of Health for Ontario.

TABLE 1.—Data on Forty-Five Cases of Silicosis Contracted in Ontario Mines

Miners with Tuberculosis		Whole Group		Miners Apparently Free from Tuberculosis	
28		8		9	
Age at Commencement of Exposure, Yr.	Average, Yr.	Age When First Silicotic, Yr.	Average, Yr.	Exposure, Yr.	Average, Yr.
Youngest..... 19	25.3	Youngest..... 26	41.9	Shortest..... 5	11.7
Oldest..... 44		Oldest..... 60		Longest..... 21	

Deaths					Cause of Death
Age at Death, Yr.	Age at Which Exposure Commenced, Yr.	Age When First Silicotic, Yr.	Exposure, Yr.		
32	22	37	15		Pulmonary tuberculosis
33	30	39	9		Bronchogenic carcinoma; active tuberculosis
35	21	34	13		Pulmonary tuberculosis
39	30	46	16		Lung infarct following operation for intestinal obstruction; no tuberculosis
43	25	35	9		Pulmonary tuberculosis
54	29	45	23		Bronchogenic carcinoma; active tuberculosis
57	27	44	11		Right heart failure; cor pulmonale; obsolescent tuberculosis
60	23	40	17		Pulmonary tuberculosis
62	24	46	18		Pulmonary tuberculosis
63	22	38	9		Pulmonary tuberculosis
67	30	52	7		Carcinoma involving sacrum; no tuberculosis

* Not yet definitely determined.

medical data and the serial chest radiographs on this group of cases suggests that some of the persons concerned were poor risks for exposure to silica dust at the time they were hired.

Our information in regard to the silicosis situation in Ontario in industries other than mining is, at best, approximate. Until the Silicosis Act of 1952 was passed, the records pertaining to this matter were imperfect. The institution of pre-employment examination of candidates for employment in most industries covered by the legislation and the periodic examination of workmen already employed, as is required by the Act in certain industries, has added to our information, but some time must elapse before our records are built up to the point where they are of much value.

Even as things stand, our records have some value, however. Prior to the passing of the Act, many workers in these industries had been examined by the Division of Industrial Hygiene of the Ontario Department of Health. Beginning in the early 1920's, surveys were conducted in many plants where workmen are exposed to silica dust. From 1940 onward, periodic examinations were made in some of these plants. Unfortunately, the examinations were conducted on a voluntary basis by arrangement with the managements of the participating plants. As they were done at irregular intervals, the coverage was not complete. Compensation claims also have supplied considerable information.

For many exposures, however, the period covered by compensation claims dates back only to the neighborhood of 1935. This source of information, therefore, has many limitations and is not as useful as it is in the case of miners.

In Tables 2, 3, and 4, which follow, information regarding silicosis in these industries is displayed.

The data contained in these tables seem to warrant, insofar as the Ontario experience is concerned, the following conclusions:

TABLE 2.—Distribution of 572 Known Cases* of Silicosis and Other Occupational Pulmonary Diseases in Certain Hazardous Industries in Ontario

Industry	Workers in Exposure, Approx. No.	Workers with Silicosis, No.	Workers Still at Work, No.
Foundry	10,000	425	236
Granite cutting.....	800	37	20
Porcelain and pottery manufacturing.....	2,100	59	53
Silica brick making, etc....	800	31	19
Miscellaneous	2,300	261	70

* These were still alive in January, 1953.

† Includes silicosis and other forms of pneumoconiosis.

1. Many persons with silicosis can continue in gainful employment in their accustomed occupations or at other suitable work.

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TABLE 3.—Analysis of 356 Silicosis Claims*

Industry	No.	Average Age When Examined After Claim Filed, Yr.	Average Age at Commencement of Exposure, Yr.	Average Age When First Silicotic, Yr.	Average Exposure, Yr.
Foundry workers.....	275	58.5	22.8	55.6	30.7
Stone cutters.....	28	57.8	17.7	55.4	24.1
Porcelain and pottery makers.....	55	58.3	23.1	47.8	21.0
Spica brick handlers.....	14	55.4	25.4	53.1	22.4
Other ceramic workers, mixers, grinders, etc.	1	52.4	30.4	49.5	17.3
Makers of abrasive powders†.....	5	48.9	34.5	46.9	15.5

* These persons had filed claims for workmen's compensation and were living when the compensation was made.
† One had 25 years' exposure; with this case omitted, the average years of exposure were 22 years.

TABLE 4.—Mortality Statistics for 385 Deceased Persons with Silicosis from Three of the More Important Exposures*

Industry	No.	Average Age at Death, Yr.	Average Exposure, Yr.	Deaths Contributed to by Silicosis
Foundry.....	275	55.1	31.8	69.1, including 23.1% due to the
Granite and sandstone cutters.....	38	50.7	22.7	66.2, including 44.5% due to the
Ceramic industries.....	25	51.0	20.5	70.0, including 41.0% due to the

* Autopsies were conducted on slightly more than 25% of these cases.

2. The incidence in most industries in which workers encounter silica dust in Ontario is not high.

3. In general, exposures in which casual labor is used are severer than are those in which skilled labor is employed.

4. Although silicosis sometimes contributes to the early death of affected persons, in general it does not at present appreciably decrease life expectancy.

5. Silicosis is much more important as a cause of disablement than as a direct or contributory cause of death.

6. Tuberculosis is still the most disabling factor and the chief cause of death in silicosis.

From time to time inquiry is made concerning the incidence of silicosis in the various Ontario exposures. Mr. Parkinson has explained the difficulties which surround any attempt to arrive at a reliable incidence rate for the mining industry, in connection with which records covering a period of more than 25 years are available. It is even more difficult to determine incidence in other industries. You were advised that no records comparable with those for the mining industry are available in these industries. In industries such as the foundry industry, labor turn-over is high, and fluctuation in production constantly alters the number of persons in employment. The majority of foundry workers in

Ontario who have contracted silicosis entered exposure early in the century. Some, in fact, began foundry work in the late 1890's. In a few instances, exposure had occurred in Europe, in the United States, and elsewhere, as well as in Ontario. Special difficulties are encountered in regard to the granite-cutting industry. A large proportion of the Ontario cases from that industry occur in persons who were initially employed cutting stone in Aberdeen, Scotland, or in Barre, Vt. It is impossible at this time to determine which exposure was the more important. Where so much is unknown and not obtainable, incidence rates have little meaning.

Mr. Parkinson's observations in regard to the present situation in the Ontario mining industry, particularly that branch concerned with gold mining, are very encouraging. The improvement that has occurred during the period under review warrants the belief that further improvement may be expected. It cannot be looked for, however, unless the preventive measures now in force are continued and vigorously pursued. It is our hope that over the years the control measures recently instituted in Ontario in respect of the other silica industries may prove equally effective.

It has been a pleasure to contribute something to the discussion of this very interesting paper.

Talc Pneumoconiosis

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Since Thorel's original study in 1896,¹ when talc pneumoconiosis was first recognized as a distinct pathologic entity, numerous clinical and experimental reports have continued to appear in the literature. The bulk of these reports have related to workers in talc mills and mines and to those engaged in the rubber industry.* Three investigations of the talc industry were carried out in New York State.† Dreessen's study of 57 men exposed to tremolite revealed an incidence of fibrosis above average (67%) but of a non-disabling character. In contrast to Dreessen's* observations, the findings of Porro, Patton, and Hobbs,* based on 15 cases with 5 postmortem examinations, showed that pneumoconiosis causing disability and death does occur in talc workers and that pathological tissue changes are principally due to talc itself. In 1943, Siegal, Smith, and Greenburg* reported on the dust hazard in tremolite talc mining, including roentgenologic findings in talc workers, and their findings and conclusions were similar to those of the latter.

Since the roentgenograms and histories of the 32 cases reported on by Siegal and associates* were still available after 14 years, a follow-up study was undertaken in order to (1) ascertain the health status of this group, (2) evaluate the present operations and dust concentrations of the talc mines and mills,

and (3) do a comparative study of the workers employed before and after the newer engineering techniques had been introduced (1943). The present paper deals largely with the first two objectives; the third is now in progress and will be reported at a later date.

FINDINGS

Environmental Data.—A study of the operations and dust concentrations of the talc mills and mines at this time shows a marked improvement in the engineering techniques from that found in 1941, and this is reflected in an appreciable decrease in the dust exposure. From 1943 to 1948, a number of corrective measures were instituted to reduce the dust concentrations and included the following: (a) wet drilling in mines; (b) enclosure of elevator and chutes; (c) installation of automatic bagging machines; (d) conveyORIZED car loading; (e) discontinuance of blow rooms, and (f) provision of local exhaust ventilation. The dust concentrations obtained at the mills before and after improvements were instituted are summarized in Table 1.

Medical Data.—Deceased: Of the original 32 patients, 19 have since died, and the causes of death obtained from the hospital records, physicians' files, or death certificates are given in Table 2. No necropsy data are available to confirm the clinical diagnosis. The ages of the 19 that died ranged from 48 to 84 years, and in the 4 whose cause of death was believed to be due to pulmonary failure associated with talc pneumoconiosis, the ages varied between 60 and 79 years.

Living: Thirteen of the original 32 are still alive, and of these 7 have retired and 6 are gainfully employed. The ages of the retired group vary between 63 and 83 years; the ages of the actively employed, between

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From Division of Industrial Hygiene, New York State Department of Labor.

* References 2 and 3.

† References 4 to 6.

TALC PNEUMOCONIOSIS

TABLE 1.—Comparative Dust Count^a Data at Several New York State Talc Mines and Mills

	Original Study (1941)				Follow-up Study (1956)			
	Low	Medium	High	Average	Low	Medium	High	Average
Mines								
Drilling	85	418	2,800	808	0	2	8	2
Mucking	2	86	478	180	8	4	5	4
General air	4	18	80	19	..	..	..	..
Mills								
Crushing	22	69	600	180	2	15	200	63 [†]
Screening	43	51	130	62	3	23	69	27
Grinding mills	22	75	271	92	5	15	40	20
Garnets and separators	58	70	728	238	8	9	21	11
Bagging	30	120	620	181	4	15	90	23
Blow room	118	1,196	2,480	1,227	Discontinued			
Open chutes	21	83	440	185	Discontinued			
General air	65	70	85	60	5	18	40	19

^a Dust counts are in million particles per cubic foot.
[†] High count due to leakage from conveyor enclosure.

TABLE 2.—Causes of Death in Talc Pneumoconiosis

Patient	Age, Yr.	Cause of Death *	Patient	Age, Yr.	Cause of Death *
L. A.	Unknown	Fractured skull	F. L.	62	Acute myocardial infarction
G. B.	63	Carcinoma of G.I. tract	O. L.	57	Carcinoma of stomach
W. H. D.	64	(1) Hypertensive cardiovascular disease (2) Cerebral hemorrhage	J. M.	65	Carcinoma of pancreas
P. D.	58	(1) Cerebral hemorrhage (2) General arteriosclerosis	W. M.	66	Pulmonary failure associated with pneumoconiosis
B. Y.	60	(1) Pulmonary insufficiency— <i>pneumoconiosis</i> (2) Congestive heart failure	W. O.	46	Duodenal ulcer
A. G.	Unknown	Unknown	L. S.	72	Pulmonary failure due to pneumoconiosis
G. J.	68	Acute myocardial infarction	J. B. S.	79	(1) Pneumoconiosis (2) Myocarditis
D. K.	66	Acute myocardial infarction	O. T.	Unknown	Unknown
H. L.	56	Acute myocardial infarction	O. B.	58	Carcinoma of G.I. tract
P. V.	Unknown	Mesothelioma of pleura— <i>pneumoconiosis</i> (bilateral)			

* Causes of death were obtained from the following sources: (1) private physicians; (2) hospital records, and (3) death certificates.

45 and 64 years. A summary and analysis of the clinical and laboratory findings are seen in Table 3.

COMMENT

In view of the comparatively small number comprising this investigation, no significance can be attached to age incidence of the deceased and living groups. It is noteworthy, however, that the age range in the retired workers was between 63 and 83 years and that in the four deceased, whose cause of death was believed to be due to pulmonary insufficiency associated with talcosis, the ages varied between 60 and 79 years. Although no statistically significant correlative data can be formulated between the duration of tremolite talc exposure and longevity, it is of interest that an above average life span

may occur, following prolonged exposure to talc dust and associated with pulmonary dysfunction (Tables 2 and 3).

Analysis of the medical data of the living shows many similarities to those reported in the literature.[‡] Clinically, the outstanding features are dyspnea, productive cough, abnormal chest findings (diminished breath sounds, basal rales, limited chest expansion), clubbing, and a roentgenographic picture descriptive of pneumoconiosis. Clinically, the course is relatively slow but progressive, and, similar to silicosis, the clinical picture does not retrogress with marked improvement of the industrial environment or upon retirement. Dyspnea is present in 100% of the group and is sufficiently pronounced to limit

‡ References 5 to 7.

Table 3.—Symptomatology of Talc Pneumoconiosis

Patient	Age	Status	Environmental Exposure, yr.	Symptoms			Signs			Roentgenologic Findings			ECG			Peripheral blood		
				Cough	Wheeze	Other	Heart	Chd.	Progression	Complications	Plaques	Fluorescence	ECG	ECG	ECG	Hgb.	RBC	WBC
P. E.	33	R	Talc mill—27	M			Enl.	S					Normal	Normal	Normal	15.5	5.5	4.1
M. G.	34	W	Talc mill—25 Alumina—21	None			Not enl.	None	MI	Hilar nodes enl.	Pr.		Normal	Normal	Normal	15	5.15	11.1
W. H.	35	W	Talc mill—15 Steel mill—5	Mo			Not enl.	MI	Mo	Hilar nodes enl.	Pr.		Normal	Normal	Normal	16.5	5.35	8.5
J. J.	40	W	Talc mill—50	S			Enl.	S	S	Cor pulmonale	Pr.		Normal	Normal	Normal	16.5	5.35	14.5
R. J.	40	W	Talc mill—35	MI			Not enl.	Mo	MI	None	Not Pr.		Normal	Normal	Normal	15	5.05	11.5
C. K.	43	R	Talc mill—40	S			Not enl.	MI	Mo	None	Pr.		Abnormal rhythm	Abnormal rhythm	Abnormal rhythm	15.5	5.05	9.5
V. L.	45	W	Talc mill—35	Mo			Not enl.	None	S	Hilar nodes enl.	Pr.		Normal	Normal	Normal	15	5.15	7.1
S. Z.	53	R	Talc mill—25 Talc mill—25 Zinc mill—2	S			Not enl.	MI	Mo	None	Pr.		Normal	Normal	Normal	16.5	5.1	7.5
G. B.	53	R	Talc mill—25 Other quartz—17	MI			Not enl.	None	Mo	None	Pr.		Normal	Normal	Normal	15	5.15	5.1
W. W.	59	R	Talc and zinc mines—51	MI			Enl.	Mo	S	Hilar nodes enl.	Pr.		Normal	Normal	Normal	16.2	4.65	8.5
S. W.	63	W	Talc mill—50	Mo			Not enl.	MI	Mo	None	Pr.		Normal	Normal	Normal	16.4	4.75	12.1
H. M.	72	R	Talc mill—35	Mo			Not enl.	MI	Mo	Hilar nodes enl.	Pr.		Normal	Normal	Normal	16.5	4.85	10.1
R. R.	72	R	Talc mill—35	None			Not enl.	MI	MI	Hilar nodes enl.	Pr.		Normal	Normal	Normal	16.5	4.85	10.1

* Status: R—Retired; W—Working; MI—Minimal; Mo—Moderate; S—Severe; P—Productive; Pr—Present; † Exposure to talc only.

TALC PNEUMOCONIOSIS

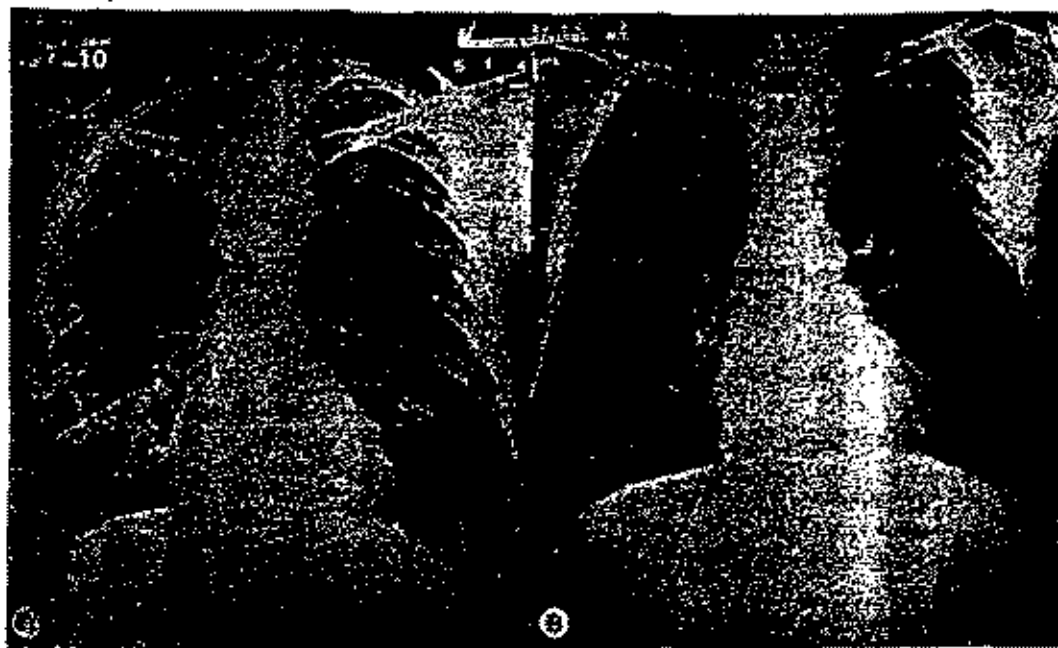


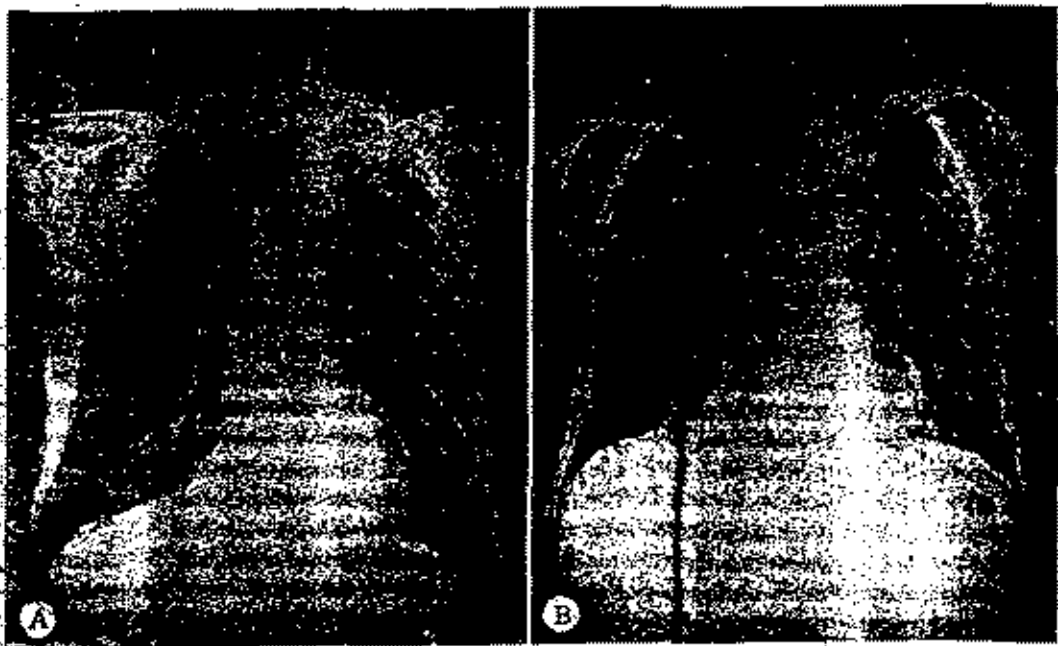
Fig. 1.—*A*, Patient S. W., 1941, characteristic basal infiltrations are seen. *B*, Patient S. W., 1954, note giant bulla in R. U. L. and prominent hilar markings.

the ordinary routine physical activity of the worker to a moderate degree.

Of extreme interest are the findings in the chest x-rays. The basic lesion is an interstitial infiltration of variable intensity,

located basally and in the midlung fields and of bilateral distribution, with the apices relatively spared. In several, the infiltration is nodular in character. Emphysematous bullae of varying sizes are observed in four (Fig.

Fig. 2.—*A*, Patient B. M., 1941, pericardial and diaphragmatic plaques are seen. *B*, Patient B. M., 1954, pericardial and diaphragmatic plaques are more pronounced.



1A and B). A most striking finding is the presence of opaque densities, varying from single linear strands in the region of the diaphragm to massive deposits—bizarre in shape, extending over a large part of the lung field and occasionally on the pericardium (Fig. 2A and B). These deposits, referred to as talc plaques by Siegal and associates,⁶ are observed in all but one of the cases studied. Cardiac enlargement is present in four persons, in two of whom the cardiac configuration is suggestive of cor

1941. As mentioned previously, two of the present chest x-rays showed cardiac configurations suggestive of cor pulmonale, but of even added significance, a markedly decreased cardiac silhouette is noted in one patient (G. S.) and is strongly suggestive in another. The cause for this is not clear. It is possible that pleural pericardial adhesions, associated with the plaque formation, and subsequent retraction and limitation of the pericardium may possibly account for this decreased cardiac silhouette.

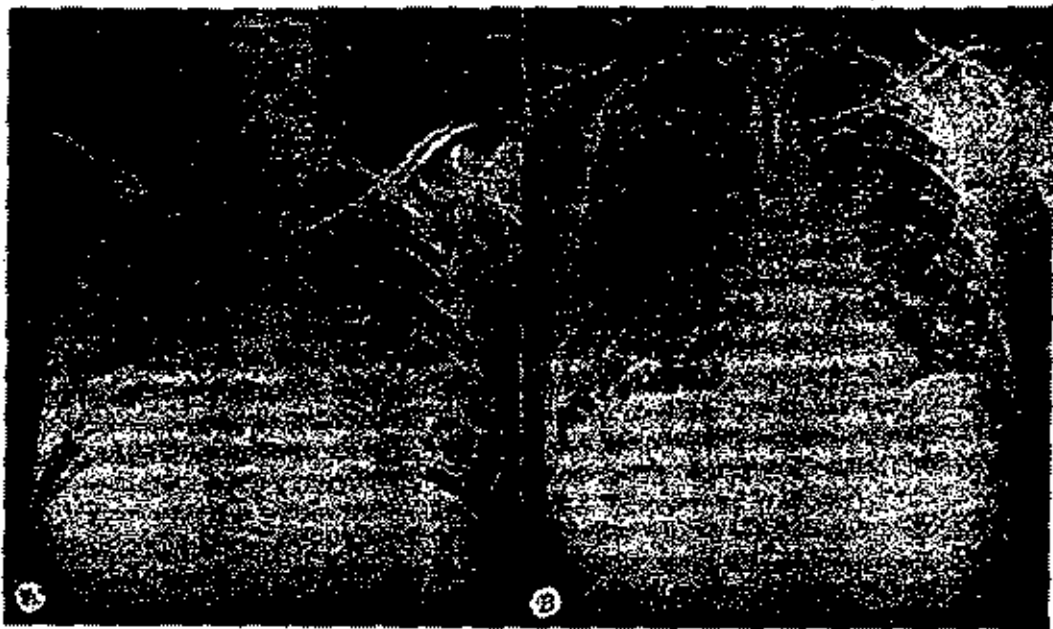


Fig. 3.—A, Patient J. J., 1941, marked basal infiltrations are noted. B, Patient J. J., 1954, progressive infiltration extending to upper lobes is seen; there is a dilated heart; clinical picture is one of cor pulmonale.

pulmonale. The pulmonary arteries and branches are prominent in a number of the chest x-rays. When comparisons are made with the roentgenograms taken in 1941, it is of interest to note that, although variable progression occurred in the majority of the patients (Fig. 3A and B), the most outstanding revelation is that what in retrospect had appeared to be severe pulmonary involvement in the original series cannot be so considered in the light of a 14-year interval. Furthermore, the hilar adenopathy which is seen in six of the present series in retrospect was also present in three of the x-rays in

No correlation between symptomatology and x-ray findings is noted, and this has been observed by others.⁸ Although the series is small, there appears, nevertheless, a trend between the degree of clubbing and chest x-ray involvement; those with severer clubbing show more extensive pulmonary involvement.

Six out of 11 show abnormal electrocardiographic configurations, such as (a) pattern of right ventricular hypertrophy (2); (b) pattern of left ventricular hypertrophy (2);

⁸References 6 and 8.

TALC PNEUMOCONIOSIS

(c) abnormal rhythm (1), and (d) non-specific T-wave alterations (1). There is a suggestive trend between clubbing and abnormal electrocardiographic findings. In five, whose electrocardiograms are normal, only one shows clubbing, and this to a minimal degree; in the six with abnormal electrocardiograms, clubbing varies from a moderate to a marked degree, being severest in the two with the right ventricular hypertrophy pattern. It is noteworthy that in the latter two, the clinical picture is characteristic of cor pulmonale. The incidence of the latter in tremolite pneumoconiosis is unknown; however, histologic evidence reported by several investigators⁸ confirms an etiological relationship. Jaques and Benirschke⁹ have reported not only generalized thickening of all the pulmonary arteries, with cardiac enlargement associated with progressive pulmonary talcosis, but also a granulomatous involvement of myocardium *per se*. In view of the paucity of the available pathological data on human pulmonary talcosis, the mechanism underlying the development of cor pulmonale is not clearly defined.

The peripheral blood findings are not remarkable and indicate that the peripheral blood does not reflect the physiopathologic changes associated with talc pneumoconiosis.

The workers presently observed are well developed and well nourished, in contrast to the observations made by Siegal and associates,⁶ and no reason can be offered to explain this apparent difference.

The results of the present study confirm the findings of other investigators that talc *per se* does produce a distinct fibrosing pneumoconiosis, and it has been suggested that this slowly developing fibrogenic disorder may be allied to asbestosis.¹⁰ According to McLaughlin, the evidence favors that talc pneumoconiosis is caused only by the fibrous varieties of talc. The asbestine variety of the talc found in our study may therefore explain the close resemblance of the x-ray picture to that of asbestosis. It is significant that asbestos bodies, first emphasized in talcosis by Gardner, are almost invariably present in cases of talcosis in which talc fi-

bers are of an appreciable length.¹⁰ This has been observed histologically by several investigators⁸ and by ourselves.^{||} In essence, this pneumoconiosis consists of a dense fibrosis which is particularly prevalent peribronchially and perivascularly and occurs in sheets, occasionally assuming a nodular configuration; the latter finding has been suggested as representing a reaction to the quartz content of the talc. The hilar lymph nodes are generally described as showing no enlargement or fibrosis, and on microscopic examination they are reported to contain talc-laden macrophages and the talc content to be of considerable magnitude.

It is appreciated that some of the workers may have been exposed to a relatively high concentration of quartz at some phase of their operation, but it appears highly unlikely that this was uniformly present for all the workers, particularly in view of the consistent finding of low free silica content in both the mills and the mines. Furthermore, evidence has been presented by recent investigators^{||} that moderately advanced pneumoconiosis is caused by talc in the absence of any silica in the talc mixture or in the atmosphere. It is not unlikely that some of the commercial preparations of talc which have different mineralogic and chemical characteristics, as pointed out by Hogue and Mallette,¹¹ may require a long exposure before chest x-ray evidence or symptoms appear. From observations of Siegal and associates,⁶ 10 years are required between exposure and onset of symptoms.

What the specific factors are in the causation of talc pneumoconiosis are not known. There is need for more epidemiologic studies where environmental conditions are well controlled and the life course of the worker is closely followed. This would permit a better statistical analysis of data than is now possible. There is also a need for further experimental and biochemical research in this field, and it is more than likely that the utilization of all three approaches will lead to the estab-

^{||} Kleinfeld, M.: Unpublished data from personal observation.

[¶] References 9 and 10.

lishment of better defined criteria and a clearer understanding of the mechanism and pathogenesis of talc pneumoconiosis.

SUMMARY AND CONCLUSIONS

The health status of a group of 32 talc workers, whose roentgenograms and histories were available after 14 years, were restudied, and the following data were obtained.

1. Nineteen of this group had died; their ages at death varied between 48 and 84 years. In four, whose death was believed due to pulmonary failure associated with talc pneumoconiosis, the ages varied between 60 and 79 years. Of the living, six are gainfully employed.

2. The outstanding clinical features involve the pulmonary and cardiovascular systems. Dyspnea and cough are frequent. Emphysema, basal rales, diminished chest expansion, and clubbing are the striking physical findings.

3. The characteristic chest x-ray is that of a diffuse infiltration of the basal and midlung fields, with occasional nodularities seen. Emphysematous bullae, hilar adenopathy, and cor pulmonale are not infrequent. Talc plaques, located in the region of the diaphragm, pericardium, and extending over a large part of the lung field, are consistently observed but do not reflect the degree of pulmonary involvement. Likewise, no correlation between symptomatology and x-ray findings is observed.

4. Abnormal electrocardiograms are seen in six and include patterns of right ventricular hypertrophy (two) and left ventricular hypertrophy (two); abnormal rhythm (one), and nonspecific T-wave alterations (one). The two persons demonstrating a right ventricular hypertrophy pattern had other features suggestive of cor pulmonale. There is a suggestive trend between degree of clubbing and abnormal electrocardiographic findings.

5. The peripheral blood findings are not remarkable and do not reflect the changes in the pathophysiology of this disorder.

6. In general, the workers appear well developed and well nourished in contrast to observations reported in 1941.

Although progression was observed in all, the clinical course is relatively slow, and in spite of the presence of moderate infiltration and pulmonary dysfunction, six of the workers are still actively employed.

The marked improvement in engineering methods is reflected in an appreciable decrease in the dust exposure. The pathological picture, however, did not retrogress with improvement of the industrial environment or upon retirement.

Assistance was rendered in the present study by Dr. Jesse R. Patton, of Ogdensburg, N. Y., by Mr. John Kean, Superintendent, and Miss J. Bishop, of the X-Ray Department of Edward Noble Hospital, Gouverneur, N. Y., and by our Industrial Hygiene Engineering Unit.

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Pneumoconiosis on the Kolar Gold Field, South India

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INTRODUCTION

Pneumoconiosis has been a compensable condition in the Kolar Gold Field* since 1940 and continues to be a potential hazard only because up to now, although there may be considerable dust retention within the lungs of underground workers after a period of 10 to 15 years, little disability is encountered. It does not primarily manifest itself as a clinical disease in the true sense of the word but rather as a radiological condition. The potential danger is the association with tuberculosis, which will be discussed later.

The type of mining carried out on the Kolar Gold Field requires the drilling and working of quartz. The quartz occurs in reefs, varying from a few inches to 6 ft. in width, which dip at a sharp angle. Over a considerable length of time—70 years—great depths, down to 9900 ft. have been reached and are being worked. At these depths the dry- and wet-bulb temperatures are high, and the use of water in dust prevention is excluded.† The quartz reef is encased in varying widths of lode matter formed from the

adjacent hornblende schist, and these lodes and hornblende schists are composed of silicates of Al, Mg, Fe, Ca, Na, and K (Ray and associates,¹ 1952).

The average underground workman is of Dravidian stock. Most of the workers came originally from the North Arcot District of the Madras State. Many of them are second- or third-generation born on the Field. They work in the mines throughout the year, except for short vacations, and usually complete 30 to 35 years of service before retiring. It is not exceptional to find men who have worked underground for 50 years. The usual age of beginning work is between 18 and 25.

DEFINITION

The Mysore Silicois Rules allow any man to retire with compensation if he has simple pneumoconiosis or to continue at work if he wishes. If he elects to do the latter, he forfeits present or future compensation should he later develop tuberculosis. If, on the other hand, he develops the infective type in the beginning, then he must retire, and he receives a greatly increased compensation. Pneumoconiosis is defined in three stages: (1) anteprimary—radiological evidence only,

† The rock temperature at a vertical depth of 9129 ft. is 143 F, and the geothermal gradient is 1 F per 110 ft. of depth in deep levels. Due to the autocompression of the air on account of the rise in barometric pressure from 27 in. at surface to 36 in. at a depth of 9000 ft., there is not only a reduction in volume but also a rise of temperature of 1 F per 190 ft. in depth. In order to improve the ventilation, the downcast air is dehumidified and cooled, and the volume supplied varies from 100,000 to 200,000 cu. ft. per minute. Consequently the dust is constantly stirred and kept air-borne. Extractor units at the rock face are used, and attempts are made continually to remove the dust hazard.

Recorded for publication April 7, 1955.

Formerly Senior Assistant Medical Officer,
Kolar Gold Field.

* The Kolar Gold Field is situated on the eastern border of Mysore State, South India, in latitude 12° 57' N. and 76° 18' E., at a height of 2893 ft. above sea level.

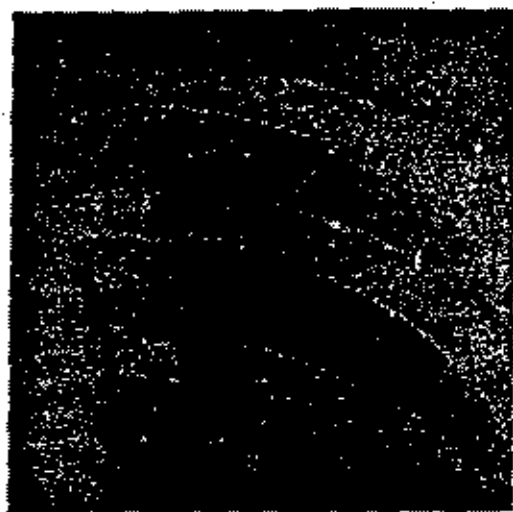


Fig. 1.—Right midzone of lung of machine man of eight years' underground service. The vague annular shadows can be seen in the third and fourth intercostal spaces, measuring from 2 to 5 mm. This is the preprimary stage.

without disability; (2) primary—radiological evidence, with symptoms causing incomplete disability; (3) secondary—radiological evidence of pneumoconiosis, with clinical and radiological findings of active tuberculosis and/or complete disability.

One stage is deemed to have developed into the next if chest pain, limitation of expansion, and dyspnea supervene, but this is an infrequent occurrence during the average working life unless tuberculous infection supervenes.

The first comprehensive study of pneumoconiosis on the Kolar Gold Field was made by Caplan and Burdon* (1947). Since then, other workers have used their classifications and findings and modified them in the light of subsequent studies until the following clinical, radiological, and pathological criteria have been adopted, which are in accord with the original Mysore Silicosis Rules.

CLINICAL DIAGNOSIS

There are usually no complaints or clinical findings in the antepimary stage, which occurs in between 64% and 93% of those

classified as pneumoconiotics.† In the primary stage the following may be found:

1. Cough and mild degree of shortness of breath occur on exertion. In all those cases with marked symptoms, emphysema or bronchitis is present. In cases with mild symptoms, great aggravation occurs following secondary respiratory infection, and bronchospasm may develop.

2. Pain in the chest, retrosternal, unilateral, or bilateral, is often complained of, but its significance is not understood.

3. Physical signs are limited to those with emphysema, bronchitis, or tuberculosis; in the latter case the condition is, *ipso facto*, in the secondary stage.

4. Chest expansion below 1 in. is considered evidence of diminished function but is surprisingly rare even with advanced radiological changes and occurs only with advanced emphysema or infection.

5. Exercise tolerance is again diminished only in the presence of emphysema and/or infection.

The assessment of disability in these subjects is often difficult, due to the unreliability of their symptoms and difficulty in carrying out even the simple tests required; the significance of modern tests for pulmonary function would probably be equivocal. It is

* 1948-1951 and 1953 Oorgaum Mine figures, respectively.

Fig. 2.—Right midzone of lung of machine man of eight years' underground service. Smaller fine and punctate shadows are well seen in the third and fourth spaces and are quite discrete. The linear markings of the lung parenchyma are still well seen. This is antepimary pneumoconiosis, moderately advanced.



PNEUMOCONIOSIS ON KOLAR GOLD FIELD

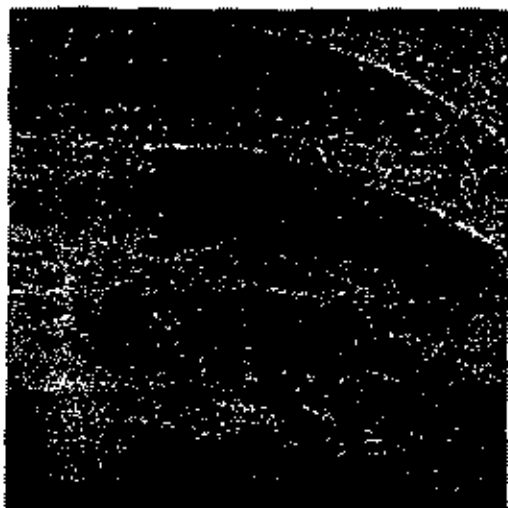


Fig. 3.—Right midzone of lung of machine man with 24 years' underground service. This is the typical picture of the fully developed antepneumonic stage, with fine mottling, annular shadows, and haziness obscuring the lung markings.

possible that some men even exaggerate their symptoms in order to obtain enhanced compensation.

RADIOLOGICAL DIAGNOSIS

Prepneumonic Stage.—A fine reticulation first appears in the right midzone, with small ring-like shadows from 2 to 5 mm. in

Fig. 4.—Heavily dust-laden lung with focal emphysema; the dust aggregates are seen in relation to the blood vessels. Left upper lobe.

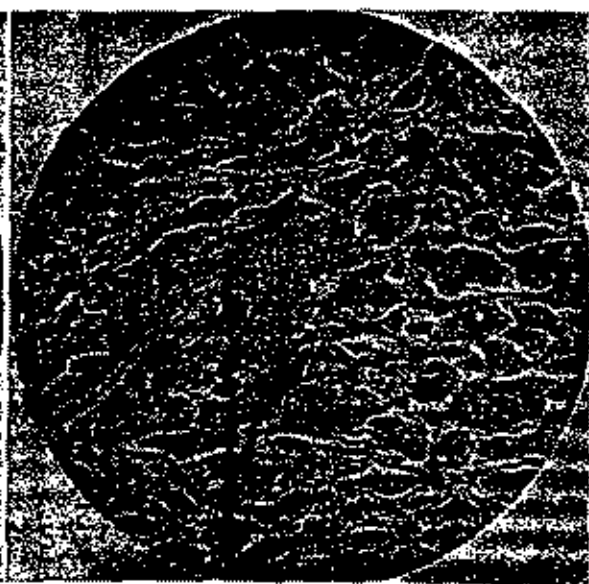


diameter, at first vague in outline but later more discrete and smaller (Fig. 1). The underlying reticulation may give the appearance of haziness unless carefully examined. This stage does not denote a sufficient degree of dust reaction to categorize as pneumoconiosis, but it is rather an alteration in the fine appearances of the lung through dust retention. The finding of increased hilar shadowing and radiating lung markings is not consistent, though these are present oftener than not; it is therefore not of value in arriving at a diagnosis.

Fine Nodulation or Mottling.—The fine reticulation is followed by the appearance of very small, discrete, annular, and punctate shadows, 1 to 3 mm. in diameter and even smaller if examined with a lens; the annular shadows predominate. They begin in the right midzone, later in the left midzone, and spread to peripheries, bases, and apices in that order, but the latter are affected only after many years' exposure (Figs. 2 and 3).

In both the above stages, the linear markings of the lung parenchyma continue to be seen, together with the specific changes, and this is regarded as fundamental when assessing the degree of pneumoconiosis.

Fig. 5.—Very heavy peribronchial and perivascular dust aggregates in a man who died of lobar pneumonia after 25 years' underground service as a machine man. Right lower lobe.



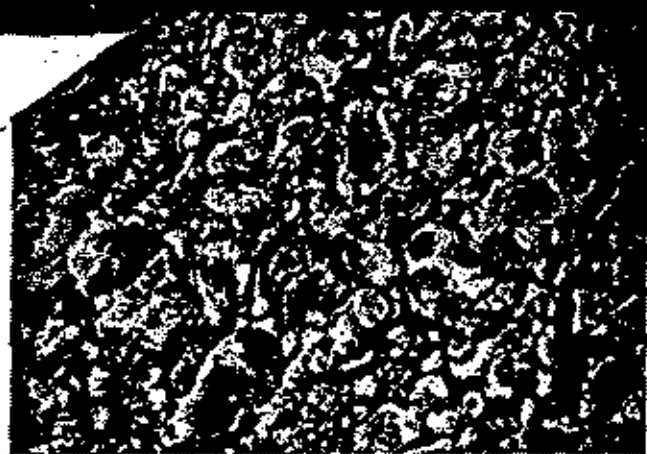


Fig. 6.—Grade 1 fibrosis; the fine reticulin framework is supporting the dust particles. Silver impregnation; $\times 1000$.

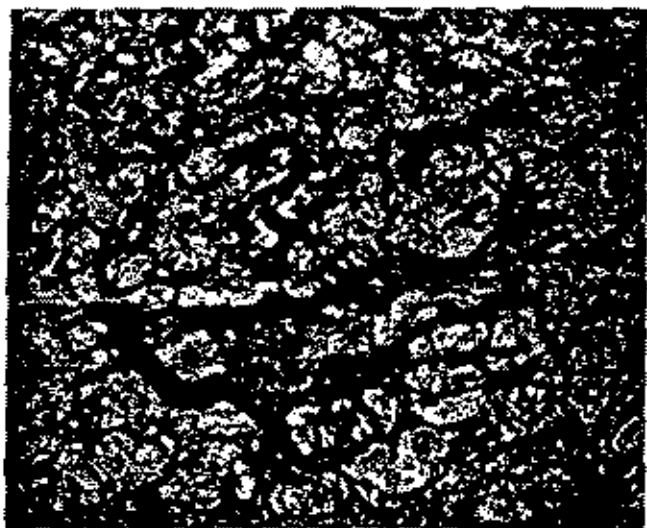


Fig. 7.—Grade 2 fibrosis; the reticulin is here more compact and coarser. Silver impregnation; $\times 1000$.

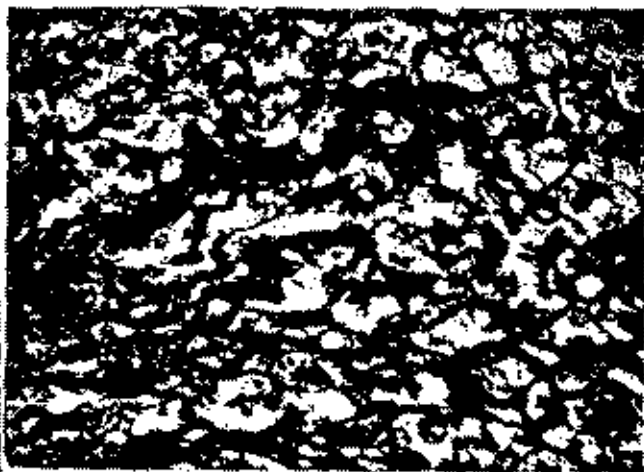


Fig. 8.—Grade 2 fibrosis; the reticulin is compact, with early collagen formation. Silver impregnation; $\times 1000$.

Discrete Mottling Affecting the Whole Lung Fields.—The shadows are more numerous and slightly larger, but now only the heaviest lung markings are seen, and the picture suggests a very fine, ground-glass appearance.

Diffuse Consolidated Shadows.—These shadows are indicative of active tuberculous infection which may obscure the underlying pneumoconiosis.

When assessing these films, the following technique was strictly followed to gain uniformity. The projection was posteroanterior, and the distance 72 in. The density of the film was such that the ribs and outline of the vertebral column could just be seen through the heart shadow, but not the intervertebral spaces. The contrast approaches black and white as far as possible. This is in accord with the suggestions put forward at the Third International Conference on Pneumoconiosis, at Sydney, in 1950. By these means the normal lung markings are standardized, and it is found impossible to detect the early fine specific changes (Stages 1 and 2) in a film that does not reach this standard. Between 1950 and 1953 approximately 30,000 films were examined and the above criteria were used.

PATHOLOGICAL DIAGNOSIS

Under the Mysore Silicosis Rules, autopsy must be performed in all cases where relatives of the deceased have applied for pneumoconiosis compensation. The Labour Associations have advised the relatives to do this in almost every case of death in an underground worker where there has been no recent chest x-ray. As a result, the material available for examination over the past 12 years has been considerable, and adequate criteria for histological diagnosis have been developed.

Caplan and Burdon* (1947) have laid down the basic picture as follows:

The characteristic lesion is the development and growth in size and number of dust-cell aggregates wherein there is a minimal tissue cell reaction. The histology remains almost unchanged even when the condition has reached an advanced stage, until a tuberculous infection is super-imposed, when

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cellular, infiltration, fibrosis and caseation become prominent features.

The dust is deposited in the perivascular and peribronchial areas (Figs. 4 and 5) and in the noninfective cases is not associated with any significant degree of fibrosis by ordinary staining methods, and one should not confuse the mass of dust-cell aggregates with the typical silicotic nodule. With the use of silver staining (Gordon and Sweets,² 1936) a fine reticulin framework supporting the dust particles at the aggregations is seen; in the absence of infection this does not progress to a significant degree. The assessment of pneumoconiosis in relation to the stages of progression of the fibrotic process introduced by Ray and associates,³ (1952) has been

dust accumulations and is not associated with interstitial fibrosis.

Since 1951 large tissue sections have been prepared in Professor Gough's laboratory in Cardiff from Kolar Gold Field lungs, and it has been possible to see very clearly the distribution of the dust in the uncomplicated cases, as well as the focal emphysema described above (Fig. 9). A comparison of the large tissue section with the x-ray film can be made and a clear relation defined.

INCIDENCE OF PNEUMOCONIOSIS ON THE KOLAR GOLD FIELD

Figures have been very difficult to collect, because under the Mysore Silicosis Rules workers engaged prior to 1940 were exam-

TABLE 1.—Incidence of Pneumoconiosis: 1948-1951
All Mines on the Kolar Gold Field

Year	Total Mines Examined, No.	Normal		Anteprimary Pneumoconiosis		Primary Pneumoconiosis		Secondary Pneumoconiosis		Total Pneumoconiosis	
		No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
1948	2,797	2,586	92.7%	27	2.347	18	0.650	21	0.607	122	4.364
1949	2,673	2,505	93.7%	23	1.515	12	0.450	28	0.600	70	2.619
1950	4,782	4,628	97.1%	24	1.471	18	0.375	22	0.461	134	2.816
1951	2,871	2,804	97.6%	21	2.000	17	0.592	19	0.662	57	2.334
Total	13,123	12,523	95.4%	105	1.805	65	0.495	90	0.678	382	2.817

used during the past year and has aided in getting a clearer picture. These authors describe five grades:

- Grade 1—loose reticulin fibrils with no collagen
- Grade 2—compact reticulin with or without some collagen
- Grade 3—somewhat cellular but made up mostly of collagen
- Grade 4—wholly composed of collagen fibers and completely acellular
- Grade 5—acellular, confluent, and collagenous

Pneumoconiosis on the Kolar Gold Field never progresses beyond Grade 2 (Figs. 6, 7, and 8), unless there is superadded infection, when Grade 5 may be seen.

An additional feature which has been noted is the ballooning out of alveoli on the periphery of large deposits, similar to the picture described by Gough and associates⁴ (1949) in the pneumoconiosis of South Wales coal miners as "focal emphysema." This, again, occurs only in cases with heavy

inhalation only if they so wished. Large numbers of workers of the older age group did not avail themselves of this privilege.

A tentative figure for the whole Field had been arrived at from a study of the men who received compensation between 1948 and 1951 (Table 1). Of 14,000 men, 2.8% received compensation following clinical and radiological examination; from mine records, the 14,000 corresponded to two-thirds of the average yearly underground strength, but, at the same time, one-third of the total underground labor force had not been examined under the Rules, and the majority of these had over 25 years' service with presumably a significant degree of dust retention.⁵ However, in 1953 Oorgaum Mine ceased operations after 70 years, and all personnel were required to be examined, the total underground workers being 2245. It has been possible to

⁵ Of 423 such men examined prior to retiring in 1952, 44% had compensable pneumoconiosis.



Fig. 9.—1.
The distribution of dust in tissue section of lung of blaster, aged 35, with 17 years' underground service.
of dust can be clearly seen. Anteprimary stage.

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arrive, therefore, at an incidence of the condition among a group of workers who, up to the time of the closure of the mine, constituted nearly one-fifth of the underground labor force on the Field and were in every way a representative group. This incidence was found to be 625 cases of all degrees of pneumoconiosis among 2245 workers (27.8%). Of these, 584 cases (25.5%) were in the anteprietary stage; 32 cases (1.4%), in the primary stage, and 9 cases (0.4%), in the secondary stage. These figures are probably more accurate than the totals so far given for the whole Kolar Field, because even up to the present time many of the underground labor force have not been examined under the Rules, mainly because they were long-service men who suspected they might have pneumoconiosis and, as they were employed prior to 1940, were exempt from compulsory examination.

EXPERIMENTAL STUDIES

Caplan and Burdon² (1947) found that the SiO_2 content of lungs varied from 0.7% in lungs with very few dust-cell aggregates to 7% when definite pneumoconiosis was present. The minimal fibrosis in relation to the heavy dust-cell aggregates indicates that the dust is relatively innocuous, a conclusion that is supported by the finding of a low disability rate (0.43% of 14,000 workers). It seems likely, therefore, that there is some factor present in the dust reducing the pathogenicity of the quartz component. This problem was studied by Ray and associates³ (1952), who analyzed the air-borne dusts (Table 2) and conducted experiments on rats by intratracheal injection of dust suspensions in order to assess its pathogenic effects. They found that, while the clear and the dark quartz, both of high solubility, produced silicotic nodules in 120 days, the hornblende schist, mostly silicate and of low silica solubility, did not produce any lesion greater than a Grade 1 fibrosis over a period of one year, and a similar result was obtained from the air-borne dusts of the different mines. It will be seen from Table 2 that the total silica varies from 44% to 52% and Al_2O_3

from 10% to 11%. The presence of the high aluminum oxide content may be of great significance, because these authors have previously shown that the presence of aluminous minerals is inhibitory to the silicosis-producing effects of quartz. They have concluded that on the Kolar Gold Field the aluminum oxide component is probably exerting an antidotal effect on the quartz.

It would appear from these studies that, if the quantity and percentage of hornblende schist in the air-borne dust is at any time reduced by change in rock formation or mining methods, a higher quartz content might result, leaving a greater proportion of silica which is not neutralized by the aluminum oxide, so that true silicosis may ensue.

RELATIONSHIP WITH TUBERCULOSIS

The danger of pneumoconiosis on the Field is in the association with tuberculosis. It is for legal purposes designated the infective type of secondary silicosis under the Mysore Silicosis Rules. The marked fibrotic reaction that occurs leads to interference with pulmonary function in those cases which do not succumb immediately to the tuberculous infection, and it is only in this type that the expectation of life is significantly shortened.

Like all the inhabitants of Southeast Asia, the miners are very susceptible to tuberculosis. It has not been possible to obtain true figures of incidence, because many cases are as yet undiagnosed, and there is no process of official notification and treatment either on the Field or elsewhere in South India. However, the incidence of radiologically apparent tuberculosis among 2460 surface and underground workers in Oorgaum Mine in 1953 was 9 cases of secondary silicosis and 9 cases of pulmonary tuberculosis without pneumoconiosis—a total of 18 cases, or 7 per 1,000.

It has been the impression over several years now that the presence of a significant degree of pneumoconiosis does increase the susceptibility to tuberculosis and may increase the incidence of breakdown of the quiescent disease. There is no evidence as

TABLE 2.—Analysis and Particle-Size Distribution of Mene and Mineral Dusts Used in Animal Experiments
After Ray and Associates¹

Size, Microns and Less	Mene			Mene Paste (Particulate, Per Cent)			Mineral Dusts (Particulate, Per Cent)			Horsham Dust ² SchAC		
	Champion Reef			Nundyaloo			Clear Quartz (Coarse)			Dark Quartz (Fine)		
	By No.	By Mass	By No.	By Mass	By No.	By Mass	By No.	By Mass	By No.	By Mass	By No.	By Mass
0.5	21.3	0.03	9.9	0.06	9.9	0.06	11.9	0.02	9.3	0.01	25.4	0.75
1.0	41.8	0.13	24.3	1.7	20.3	1.7	63.0	0.5	43.5	0.4	63.2	0.4
2.0	51.8	0.31	71.5	8.4	70.6	8.2	78.0	2.5	77.9	2.7	84.0	2.0
3.0	73.3	1.04	84.3	23.3	86.9	20.9	87.0	5.7	86.3	6.3	91.2	3.0
4.0	83.6	1.62	91.0	30.3	94.2	31.6	95.0	8.4	91.5	8.0	96.0	3.0
5.0	88.5	2.7	97.3	33.3	98.3	34.4	98.9	10.1	94.7	11.2	98.4	3.0
6.3	92.5	4.1	97.3	36.3	98.5	36.3	99.3	12.3	97.3	12.3	98.7	3.0
7.5	94.0	4.3	98.0	38.3	98.5	34.4	97.0	13.0	97.7	13.3	98.5	3.0
10.0	97.3	10.4	99.3	43.3	99.3	38.3	98.0	21.3	98.1	21.7	98.5	3.0
12.5	98.3	20.3	100.0	100.0	99.0	43.3	98.0	43.3	98.3	43.3	98.5	3.0
25+ ³	100.0	100.0	...	...	...	...	99.2	99.3	100.0	100.0	100.0	100.0
Analysis												
As ₂ O ₃	Per Cent	94.1	Per Cent	96.5	Per Cent	92.3	Per Cent	...	Per Cent	...	Per Cent	...
SiO ₂	48.8	62.3	47.3	62.3	47.3	47.3	...	...	...	...	...	...
Al ₂ O ₃	9.9	11.4	20.4	11.4	20.4	20.4	...	...	...	...	...	...
SiO ₂ solubility, mg. SiO ₂ /100 ml. H ₂ O at 100°C. for 7.6	...	...	1.4	...	1.4	1.4	...	...	...	...	...	...
Specific surface, cm. ² /gm. ²	...	...	...	...	...	...	...	...	...	...	...	...
							6,770	4,000	6,400	5,400	6,200	6,200

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to how this happens, and it is difficult to see how the tuberculous infection could be influenced, as in true silicosis, when the effect of silicon dioxide has already been modified in some way, possibly by the aluminum oxide of the mixed dust; on the other hand, it is possible that the tuberculous infection enables the silica to be released and so act as a fibrosing agent, either alone or in conjunction with some specific factor developed in the course of the tuberculous infection.

The suggestion put forward by Robson and associates⁴ (1934) that infections other than tuberculosis may influence development of silicosis would not appear to be borne out on the Kolar Gold Field, where the underground workers have an incidence of 18 per 1000 of primary pneumococcal lobar pneumonia alone (Firench,⁵ 1953) without the subsequent development of fibrosis. Robson and associates showed by animal experiments that exposure to the irritant action of gases from explosives and sulfide-containing rocks, combined with dust exposure, did produce silicotic lesions, whereas dust alone did not. It is interesting that such cases do not occur on the Kolar Gold Field, owing to the different methods of mining and types of rock.

COMMENT

To describe pneumoconiosis on the Kolar Gold Field as a severe health problem would be overstating the case. It is primarily a radiological condition but at any time might assume more serious proportions. Since it was described by Caplan and Burdon⁶ (1947), it has received increasing attention, and it must not be confused with the pneumoconioses that occur elsewhere in India, particularly the silicosis in the mica mines in Bihar, in the steel industry in Mysore, and in pottery and other works. The extent of pneumoconiosis in India is only just being uncovered, and with the dual types of industry—mining or factory on a large scale and family mining and village crafts, it will be difficult to arrive at true estimates.

The inference to be drawn from the work of Ray and associates³ (1952) on the chemi-

cal aspect of mine dust is beyond the scope of this paper, but it touches on the aluminum factor in the prevention of silicosis.

Not until the indigenous peoples of India become less susceptible to tuberculosis will pneumoconiosis on the Kolar Field cease to be a financial burden to the authorities.

The compensation received for all types of pneumoconiosis is considerable. The amount paid by the companies in 1952 was \$82,311, and in 1953 it was \$168,601; hence any methods that will reduce the dust hazard will pay off. The total number of cases compensated was 251 in 1952 and 860 in 1953; this latter figure is high because of the closure of Oorgaum Mine in 1953.

The Mysore Silicosis Rules were framed only in 1940 to cover all industrial processes giving rise to dust disease of the lung though it had already been realized in 1934 that a radiologically apparent pneumoconiosis existed. The Rules were drafted from those which existed on the Witwatersrand in South Africa before it was realized that disability was not always associated. By following too closely the South African legislation, the Mysore Rules came to be silicosis rules, which implies that classical silicosis predominates on the Field. This is not so, but nevertheless in the official courts the name stands.

SUMMARY

The type of pneumoconiosis occurring on the Kolar Gold Field is described, together with the clinical, radiological, and pathological criteria for diagnosis.

Experimental studies of Kolar Gold Field dusts by other workers have indicated that the relatively high aluminum oxide content of the air-borne dust may account for the relative harmlessness of the condition.

The relation to tuberculous infection is stressed. It is only when the two conditions occur together that life expectancy is shortened.

Dr. A. R. Riddell, of the Department of Industrial Hygiene, Province of Ontario, and Dr. J. C. Jeffrey, Chief Medical Officer, Kolar Gold Field, offered valuable criticisms in the preparation of

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The Dust Diseases in Great Britain

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The story of dust diseases in Great Britain goes back a long way. E. L. Collis, in his classical Milroy Lectures of 1915, quoted Herbert Spencer as saying that the starting point of human progress was the "localization of industries." There was such a localization in prehistoric factories for the making of flint implements at Grime's Graves, near Brandon in Suffolk, where the flint knappers still use tools like the deer-horn picks of their prehistoric ancestors. In 1914, Collis showed that these workers have a high mortality from silicosis. He said that it is probable that "the starting point of human progress" was associated with at least one form of pneumoconiosis. It has been long known that the dust of flint, which is nearly pure SiO_2 , is dangerous to health. Over 200 years ago, Thomas Benson, of Newcastle under Lyme, was granted a patent for grinding flints by a wet method. At that time it was said that a man who ground the flints dry could not live longer than two years.

Our greatest localization of industries took place during the Industrial Revolution, and this was really the starting point of our intensive knowledge about the effects of dust on the lung.

The first notable contribution was that of Pearson (1813), who, after many autopsies, decided that the black pigment in the bronchial nodes and the lungs was due to the inhalation of small particles resulting from the burning of coal, wood, and other inflammable materials. The German pathologists, on the other hand, thought that the pigment came from inside the body. Meiklejohn (1951) has described the hitherto little-known and re-

markable contributions of the Scottish physicians of the 1800's on the connection between disease of the lungs and coal dust; he also tells how the incidence of anthracosis diminished with improved ventilation of the mines. The Scottish physicians decided that simple coal dust was comparatively harmless and that stone dust was the really noxious factor.

Charles Turner Thackrah, a physician in Leeds, played a major part in the study of occupational diseases (including the dust diseases) in Great Britain. In his book "The Effects of Arts, Trades, and Professions," the second edition of which was published in 1832, he crystallized the idea that the inhalation of large quantities of dusts of any kind can damage the lungs but that some dusts are more harmful than others. His conclusions were based on first-hand observations of workers in hospitals, in their homes, and in the factories.

Two other great Englishmen in the history of pneumoconiosis about the middle of the 19th century were T. B. Peacock and E. H. Greenhow. Peacock first established miners' disease as an entity and distinguished it clinically from pulmonary tuberculosis before little was known about bacteriology and nothing about x-rays. Greenhow carried out the first large field investigations into the dusty industries of England and Wales, including the heavy-metal industries, the potteries, coal, copper, and lead mining, and even agriculture. In the *Transactions of the Pathological Society of London* (1860-1866) there are to be found excellent descriptions by both of these physicians of the disease, which was later to be called silicosis by Visconti, in 1870. They even found the dust of free silica in the lungs and examined it under polarized light.

For a long time after this excellent work nothing much was done about the dust diseases, but about the beginning of the 20th

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century a new interest began to be taken in the problem not only in England but also in other parts of the world. About the same time the tempo of life in general began to increase, and there was an urge for increased speed of production—an urge which has gradually gathered momentum. With the replacement of hand labor by the machine, dusty processes have become more dusty and methods of dust control have lagged behind output. The result has been a remarkable increase of the incidence of the dust diseases.

A noteworthy contribution in 1892 was Arlidge's book on the occupational diseases, which was only the second to be published in England.

In 1904, J. S. Haldane and his colleagues ascribed the high mortality among tin miners to the inhalation of rock dust. A little earlier, dust phthisis among slate workers was shown to be related to the dust of slate, particularly when it had a high quartz content.

E. L. Collis (1915) pinpointed the dust of free silica as the main cause of most of the dust diseases. He also drew attention to the role that dust inhalation plays in determining the mortality from lung diseases experienced by the general population. Long ago he showed the influence of air pollution on the mortality from lung diseases in general. Though Collis did this work 40 years ago, he is always up-to-date. He had, and still has, an uncanny knack of seeing to the heart of any problem. Just now in England there is controversy about chronic bronchitis and emphysema and whether they can be held to be caused by the inhalation of dust. It is true that the incidence of chronic bronchitis and emphysema is high among the general population, and the possible causes are legion. It is difficult to decide (in Arlidge's words) how much of the malady is "town-made" or "trade-made." But as Collis showed years ago, an agent which irritates the lung parenchyma can also irritate the bronchial mucous membrane. At present there is one industrial pulmonary disease of which the diagnosis is made largely on the presence of chronic bronchitis and emphysema, and that is byssinosis.

In the last 50 years in Great Britain (as elsewhere), there has been intensive research into all aspects of the dust diseases, such as causation, pathology, incidence in various industries, and prevention. For the first 25 years or so, much of the impetus came from H. M. Medical Inspectors of Factories, and prominent in the study of the chest diseases were Collis, Middleton, and Merewether. It might be said that they played almost a lone hand, with meager facilities for investigation. However, they were helped greatly by hospital physicians, general practitioners, radiologists, and pathologists, notably Hall, Robertshaw, Kettle, Gloyne, and Cooke. During this period much attention was paid to silicosis, and it, with tuberculosis, was established as being the cause of disability and death in most of the industries where there is exposure to the dust of free silica. *Pari passu*, regulations laying down dust-control measures were issued by the Factory Department for most of the major industries. Notable contributions were Collis's work, already mentioned, on the role of free silica and Middleton's field investigation (with E. L. Macklin) into the grinding industry in 1923. In the late '20's, a series of brilliant observations by Cooke, Gloyne, Burton Wood, Stuart McDonald, and M. J. Stewart on the clinical, radiological, and pathological features of a new disease, which Cooke named asbestosis, led to field investigations by Merewether and Price (1930). These firmly established that the dust of asbestos was dangerous to health, and it was the first time that the dust of combined silica, as opposed to free silica, was found to damage the lungs. The condition, as Legge points out, was first seen in 1906 by Murray at Charing Cross Hospital, but little or no notice of it was taken at that time.

An important landmark was the passing of the Workmen's Compensation (Silicosis) Act of 1918, which came into force in 1919. For the first time compensation for disablement or death was given in respect of an industrial pulmonary disease. The Act provided initial and periodical medical examination of all workers in the refractories industry

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and suspension from the industry on a diagnosis of simple silicosis as well as silicosis with tuberculosis. The medical officers responsible for the examinations were the Tuberculosis Officers of the Local Authority administering sanatorium benefit under the National Health Insurance Act. The scheme was revised in 1925, and again in 1931, to provide for examinations by a medical board. This was the beginning of the whole-time Silicosis and Asbestosis Medical Board under its first (and only) Chief Medical Officer, C. L. Sutherland.

A close association began between the Medical Inspectorate of Factories and the Silicosis and Asbestosis Medical Board, both groups working under the Home Office. In general, the Medical Inspectorate made the field investigations which established the risk of silicosis (or asbestosis) in an industry or process and which led to the establishment of the various compensation schemes. But the members of the Board (stationed at Sheffield, Manchester, Stoke on Trent, and Cardiff) also carried out field investigations into various industries, such as sandstone (Sutherland and Bryson, 1929), granite (Sutherland and Bryson, 1929), and potteries (Meiklejohn, 1949). But perhaps the most significant result of the formation of the Board was that there was begun a systematic and valuable collection of case histories with x-ray films, together with occupational details and post-mortem findings.

At first the Board was limited to a few industries, but gradually its scope has increased and more and more dusty industries have come under examination. Workers in the refractories industry first came under a compensation scheme in 1925, metal grinders in 1927, and sandstone workers in 1929. In 1928, the Various Industries Scheme included the processes of mining, quarrying, drilling, and blasting in silica rock, the crushing and grinding of siliceous materials, and also isolated processes in steel foundries (not iron foundries) and metal works, in potteries, and in tin mines. In 1934 the Various Industries Scheme was amended to include coal miners

with silicosis; in 1935 hematite ore miners were included, and in 1939 slate miners. Workers with asbestosis were first compensated in 1931; compensation for byssinosis was introduced in 1941 and was dealt with by a specially constituted board. Pneumoconiosis, as opposed to classical silicosis, in coal miners was brought under the compensation schemes in 1943 and in coal trimmers in 1946. The Various Industries Scheme was again amended in 1946 to include molders of iron castings who used siliceous parting powders and also blasters of any type of metal castings to free them from adherent sand, even if the blasting abrasive was nonsiliceous. The National Insurance (Industrial Injuries) Act was passed in 1946 and altered the whole basis of compensation in that it became the responsibility of the Government but with contributions from employers and workers. Beryllium "poisoning" became compensable in 1949. In 1954 all foundry workers (iron, steel, and nonferrous) became entitled to compensation under the Industrial Injuries Act. A fuller account of the development of compensation in Great Britain has recently been written by Meiklejohn (1954). The Silicosis and Asbestosis Medical Board was transferred from the Home Office in 1946 to the Ministry of National Insurance (later combined with the Ministry of Pensions). The Board was divided into a series of Pneumoconiosis Panels, but they work in much the same way as the Board did, except that there is now no Chief Medical Officer.

The various compensation schemes mentioned above reflect the evolution of the study of the industrial lung diseases in Great Britain. There are comparable legal enactments and regulations designed to control the risks in each industry, but they are too numerous to mention in detail.

To "flash back" a little, in 1936 Middleton, in his Milroy Lectures, reviewed the position of the dust diseases in Great Britain. He covered all the dusty trades, including coal mining, but at that time only cases of silicosis in coal miners were recognized as being eligible for compensation. Most of the miners,

such as hardheaders, drifters, or rippers, had been exposed to stone dust, but Middleton also showed that there was a high incidence of a lung disease among coal miners, particularly in South Wales, which was not classical silicosis. Much of his evidence was drawn from the findings of the Silicosis and Asbestosis Medical Board. Following his paper, there began a series of intensive investigations by the Medical Research Council into the health risks of coal mining, which covered all aspects, such as clinical, radiographic, and environmental. (Medical Research Council Special Reports I [1943], II [1943], and III [1945]). The important fact emerging from this work was that coal dust by itself could cause pneumoconiosis, and this was followed, as previously mentioned, by the extension of compensation to coal miners and coal trimmers. In 1945, the Pneumoconiosis Research Unit of the Medical Research Council was set up in Cardiff, and an impressive body of work has emerged on various aspects of coal miners' pneumoconiosis. This work is well known, and I propose, therefore, to limit my remaining observations mainly to the dust diseases resulting from work in places which come under the Factories Acts, with only incidental references to coal mining.

SILICOSIS

Silicosis has been found to be a cause of disability in the following broad groups of industries as well as in coal mining and other forms of mining, such as tin, hematite, copper, barites, and fire clay.

1. Refractories industry. This group includes the making of silica bricks, furnace dismantling and rebuilding, and retort setting and repairing.

2. Pottery industry. Workers in this group have been engaged in the manufacture of both earthenware and china with their various subdivisions and as flint millers and polishers. The substitution of ground flint by alumina for the placing of biscuit ware has resulted in a diminution of deaths from silicosis among workers in that process.

3. Stone quarrying, crushing, and dressing. This group includes workers with sandstone, millstone, gritstone, slate, granite, and other igneous rocks. The risk varies with the amount of free silica in the rock and, of course, with the protective measures adopted. Recently some limestone quarrymen have contracted silicosis, but the limestone contained a fairly high proportion of free silica.* In this group could be included rock tunnelers, in whom the onset of silicosis may be very rapid. As regards slate workers, a billiard-table maker has recently received compensation for silicosis.

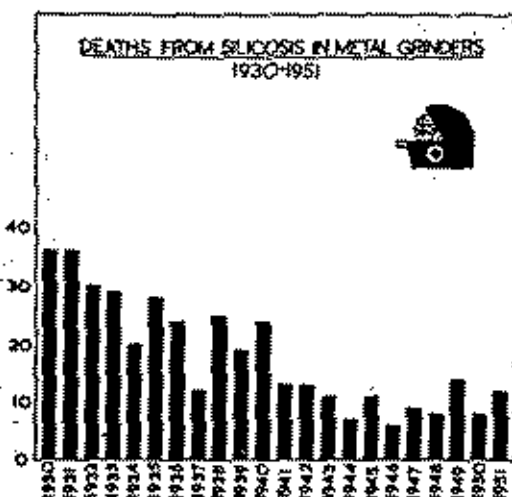


Fig. 1.—Chart showing diminishing numbers of deaths among metal grinders during the period 1930-1951, inclusive.

4. Metal grinding. The silicosis risk in the grinding of metals has greatly diminished, owing to the replacement of the sandstone grinding wheels with artificial ones composed of Carborundum, alumina, or emery. Apart from the lower "toxicity" of the dusts from these substances, the wheels are much harder than sandstone, and less dust is created. But the grinders of castings (iron, steel, and non-ferrous) are still exposed to a silicosis risk on account of the presence of burned-on sand on the castings. The diminishing number of deaths among grinders is shown in the chart (Fig. 1).

* Doig, A. T.: Unpublished data.

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5. Sandblasting. This job, as Merewether (1936) showed, had a high silicosis risk. The position has altered materially after sand began to be replaced by other nonsiliceous abrasives, such as steel shot, and since the use of sand as an abrasive was prohibited in 1949 by the *Blasting of Castings (and other Articles) Regulations*. The process of wet sandblasting of ships' hulls does not come under the Regulations (because legally a ship is not an article), but it is thought that there is also a risk of silicosis in the job. Sandblasting is still used in the open air on works of engineering construction, e. g., in order to prepare large metal surfaces for the application of paint.

6. Manufacture of abrasive soap. Middleton showed in 1936 that the manufacture of abrasive soaps carried with it a risk of acute or subacute silicosis, accompanied by tuberculosis. There was a disastrous experience at one factory in London between 1921 and 1928, when there were 13 deaths among 81 workers. This experience led to rigorous dust control in the processes, but between 1941 and 1952 there were nine deaths from silicosis among this type of worker. It is not possible to state the incidence of disease and disability, because there is a rapid turnover of labor (mostly young women) in the job. Silica flour is still being used as an abrasive, though efforts are being made to find a less harmful substitute which will be acceptable to the manufacturers and the users. There were no new cases of silicosis in this trade in 1953.

7. Foundry industry. The iron and steel foundry industry has been investigated in great detail during the past 10 years or so, and the results were published in 1950 in book form by McLaughlin and others ("Industrial Lung Diseases of Iron and Steel Foundry Workers"). Pathological studies of 64 cases, as well as clinical and x-ray examinations of some 3000 workers, showed that there was a varying risk of silicosis and mixed dust pneumoconiosis (to which reference is made below) in the various categories of foundry workers.

Steel fettlers (dressers or castings cleaners) had a severe risk, largely owing to the

fact that the dust from the pneumatic hammer is not controlled. The main pathological lesion was classical silicosis, with or without tuberculosis. Among iron fettlers, the risk was not so great as among steel fettlers, and the main pathological lesion found was mixed dust pneumoconiosis, though classical silicosis did occur. Steel molders were less affected by disease and disability than iron molders, though statistically the incidence of x-ray abnormalities was greater among steel workers. More deaths occurred among iron molders, and this fact appeared to be related to the use of siliceous parting powders. The use of siliceous parting powders has now been prohibited by the *Foundries (Parting Materials) Regulations, 1950*. Silicosis still occurs among shot blasters of both iron and steel castings, but the risk is controlled by ventilation and personal protective devices, and the numbers of cases and deaths, in contrast with the experience among steel fettlers, are not increasing. Other categories of iron and steel foundry workers are subject to much less risk than the above groups of workers. New and stringent regulations (*Iron and Steel Foundry Regulations*) were issued in 1953. They require strict dust control in the dusty processes.

The question of pneumoconiosis among nonferrous foundry workers is now being examined in detail. Isolated cases of silicosis and mixed dust pneumoconiosis have occurred among both casters and dressers of nonferrous metals, but an extensive survey has not yet been carried out. Harding and McLaughlin† have described the pathological, clinical, radiological, and environmental details of six fatal cases.

Table I shows the number of new cases of pneumoconiosis (i. e., silicosis and mixed dust pneumoconiosis) in foundry workers diagnosed by the Pneumoconiosis Panels in 1953.

These figures can be regarded as an understatement of the real position. More than half

† Harding, H. E., and McLaughlin, A. I. G.: To be published.

TABLE 1.—*New Cases of Pneumoconiosis—1953*
Foundries

Occupation	Total
Iron molding.....	87
Iron dressing.....	21
Iron foundry knockouts.....	1
Steel molding.....	4
Steel dressing.....	46
Nonferrous dressing.....	2
Welders and burners (in castings cleaning shops).....	70
General foundry work.....	22*
Total.....	192

* Twenty-seven of these workers had also been exposed to coal dust for varying periods.

of the cases in iron molders came from one area where there had been an x-ray survey of three foundries. If more iron foundries had been similarly surveyed, more cases would have been found. In certain steel foundries the dressers (chippers or castings cleaners) are x-rayed each year, but a complete picture of the true position will not be obtained until all workers undergo periodical medical examination. This statement also applies to other dusty industries.

In Table 2 details are given of fatal cases of silicosis and asbestosis investigated fully by the Medical Inspectorate of Factories between 1930 and 1953. The average ages at death and the length of employment in the dusty industries are also given.

It is seen that as regards silicosis the manufacture of scouring powders and sandblasting were the most dangerous industries, with the lowest average age at death and the shortest average period of employment. Another interesting point is that tuberculosis occurred in about half of the cases of silicosis, whereas it was found in only about two-fifths of the cases of asbestosis. The average age at death and the length of exposure in the cases of asbestosis were much lower than in the silicotic group as a whole but more on the level of sandblasters and makers of scouring powders.

The connection between asbestosis and cancer of the lung is becoming clearer, and in one series of 100 autopsies on asbestosis cases there were 25 cases of cancer of the lung. Wyers (1949) has pointed out that the x-ray

TABLE 2.—*Fatal Cases of Silicosis and Asbestosis Investigated by Factory Department, 1930-1953*

	Deaths, No.	Average Age at Death, Yr.	Duration of Employment		
			Longest, Yr.	Shortest, Yr.	Average, Yr.
Silicosis					
Pottery					
Silicosis.....	700	61.7	67.0	2.8	36.4
Silicosis with tuberculosis.....	601	58.2	67.0	8.0	34.7
Sandstone					
Silicosis.....	267	60.9	62.0	9.0	39.8
Silicosis with tuberculosis.....	209	57.5	59.0	8.0	37.4
Grinding of Metals					
Silicosis.....	128	60.5	61.0	14.0	35.9
Silicosis with tuberculosis.....	211	54.9	66.9	2.8	33.0
Sandblasting					
Silicosis.....	75	50.4	43.0	1.7	18.4
Silicosis with tuberculosis.....	99	46.2	40.0	2.0	18.1
Manufacture of scouring powders					
Silicosis.....	10	40.5	37.0	2.3	8.3
Silicosis with tuberculosis.....	6	40.5	11.2	2.0	7.0
Miscellaneous					
Silicosis.....	283	55.4	67.0	1.5	34.3
Silicosis with tuberculosis.....	166	51.8	60.0	0.7	34.6
Total					
Silicosis.....	1,314	59.4	67.0	1.5	34.1
Silicosis with tuberculosis.....	1,294	56.4	67.0	0.7	31.2
Asbestosis					
Asbestosis.....	780	49.5	48.0	0.5	16.0
Asbestosis with tuberculosis.....	87	40.2	33.0	0.5	11.4

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appearances of asbestosis are undergoing some change in that nodular as opposed to ground-glass shadows are beginning to appear. He thinks it probable that this is because of the lessened exposure to dust over a longer period, owing to the rigorous application of exhaust ventilation to the dusty processes and the use of personal protective devices. Cases of asbestosis, however, are now appearing in workers who do asbestos lagging of pipes and boilers. In this process, particularly if asbestos is being sprayed, it is difficult to apply adequate protective measures, more especially because the workers are usually peripatetic.

PRESENT POSITION

How many cases of pneumoconiosis (silicosis, asbestosis, coal miners' pneumoconiosis,

In all industries there were 8789 deaths from occupational fibrosis of the lung in the 12-year period, and it will be seen that the total yearly figures are going up. Over the same period there were 6907 deaths from non-occupational fibrosis of the lungs. About two-thirds of the total number of deaths in the occupational group occurred in coal miners, who form the largest group (about 700,000) exposed to dust inhalation. The figures rose steeply from 232 in 1940 to 937 in 1951 (in 1952 the figure dropped slightly, to 912). It may well be that part of the increase is due to more accurate diagnosis, or at least to greater interest in the pneumoconiosis problem, among coal miners. In Figure 2 is shown a comparison, based on the crude figures of Table 3, between the coal miners and factory

TABLE 3.—Deaths from All Types of Pneumoconiosis in England and Wales, 1940-1951

Industry	1940	1941	1942	1943	1944	1945	1946	1947	1948	1949	1950	1951	Total
Potteries	53	65	47	41	82	63	69	54	48	63	73	62	806
Sandstone	109	82	54	77	57	64	51	46	68	51	29	71	779
Grinding of metals, etc.	41	26	25	21	24	22	22	27	26	27	22	21	225
Refractories	15	12	7	7	6	9	4	10	12	13	8	8	111
Miscellaneous	7	4	7	5	13	19	14	20	27	25	70	129	347
Coal mining	232	196	230	276	311	387	421	377	639	746	940	637	5,806
Other mining	64	60	46	43	30	40	31	60	49	54	42	31	679
Asbestos	11	17	11	8	10	11	16	15	15	17	12	18	161
Cotton (byssinosis)	..	..	6	7	1	10	3	4	8	7	11	9	66
Total	533	423	484	485	485	604	645	518	809	1,023	1,113	1,306	8,789
Nonoccupational	250	481	643	493	531	620	569	616	651	654	679	732	6,907

etc.) occur in Great Britain? It should be mentioned that at the present time it is impossible to give accurate figures of the populations at risk in the various trades and processes. Both the Registrar-General and the Ministry of Labour classify occupations in groups too broad to give specific figures of the populations in the dusty industries, and those in the possession of employers' associations and trades unions are not complete. It may be possible in several years' time to give more accurate information. All that can be done now is to state the numbers of deaths reported to the Registrar-General and to give the figures for one year of the new cases diagnosed by the Pneumoconiosis Panels.

The deaths from all forms of pneumoconiosis between 1940 and 1951, inclusive, in England and Wales are given in Table 3.

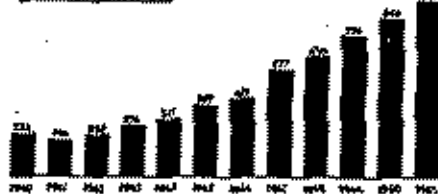
workers. In the factory processes, the yearly number of deaths was going down until 1943, but there has been a slight rise in the later years.

In both groups, it should be emphasized that the deaths in each year are related to conditions which obtained in mines and factories some years previously, possibly 10 to 20 years or even longer.

New Cases in Factory Occupations.—The following Table 4 gives the numbers of new cases of pneumoconiosis diagnosed by the Pneumoconiosis Panels in 1953. These figures have been kindly supplied by the Ministry of Pensions and National Insurance, but it should be noted that they differ slightly as regards the numbers in each occupation from the figures originally supplied. The Ministry usually classifies the cases as falling into the

DEATHS FROM ALL TYPES OF PNEUMOCONIOSIS

1940-1953, inclusive

CALCULATED
BASED ON 1.0% DEATH RATE

FACTORY OCCUPATIONS



Fig. 2.—Chart showing trends of deaths from fibrosis of the lungs among coal miners and factory workers during the period 1940-1953, inclusive.

category of the last jobs done by the workers, whereas Dr. G. O. Williams, of the Factory Department, has reclassified some of the cases on the basis of all occupations done by each worker in order to determine the most likely cause of the pneumoconiosis.

There were 896 cases of pneumoconiosis diagnosed, and this figure includes 54 cases of byssinosis. The cases with an uncomplicated occupational history numbered 665, and in the

remainder there was exposure for varying periods to other dusts, mainly coal dust. Additional exposure to coal dust occurred mainly in those industries situated in coal-mining areas, such as refractories, stone (sandstone and granite), pottery, slate, and foundry industries. The pottery industry contributed the greatest number of cases (353, mainly silicosis), and the foundry industry came next with 190 cases. There are roughly 25,000 pottery and about 220,000 foundry workers (iron, steel, and nonferrous); so it is probable that the pottery industry has a higher pneumoconiosis risk than foundries. Such general statements are not of much value, because the risk varies from process to process within the same industry. The substitution of ground flint by calcined alumina has reduced the silicosis risk among placers of biscuit ware in potteries, whereas the fettling of steel castings is still a dangerous job.

New Cases in Mining.—Table 5 gives the numbers of new cases of pneumoconiosis occurring in all mining operations in 1953.

These figures show clearly the tremendous problem which faces the coal-mining industry. There is no space to give in detail the varying degrees of severity of pneumoconiosis found in the 4048 cases, but the figures are given in the "Digest of Pneumoconiosis Statistics

TABLE 4.—New Cases of Pneumoconiosis—1953
Factory Occupations

Industry	No Other Dust Exposure	Other Dust Exposure		Total
		Coal	Other	
(1) Refractories	15	30	..	25
(2) Stone workers (sandstone, granite)	55	30	1	86
(3) Pottery	254	95	13	353
(4) Slate workers (quarrying and splitting)	82	89	..	101
(5) Foundries	154	27	9	190
(6) Metal grinding (other than foundries)	5	2	..	7
(7) Sandblasting	5	4	..	9
(8) Shot blasting	2	..	..	2
(9) Furnace dismantling, etc.	17	7	..	24
(10) Boiler scaling	4	2	..	6
(11) Abrasive wheel manufacture	8	..	..	8
(12) Asbestos	14	5	3	22
(13) Abrasive soap powders	..	..	..	..
(14) Graphite and carbon electrodes	..	..	..	..
(15) Tin smelting	1	..	..	1
(16) Cotton (gymnastics)	40	14	..	54
(17) Coal trimming	10	..	..	10
(18) Miscellaneous	24	..	..	24
Total	665	205	26	896

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TABLE 5.—*New Cases of Pneumoconiosis—1953*
Mining *

Industry	Cases, No.
(1) Coal mining.....	1,245
(2) Tin mining.....	2
(3) Barite mining.....	1
(4) Fire clay mining.....	16
(5) Other clay mining.....	2
(6) Hematite mining.....	4
(7) Lead mining.....	2
(8) Tunneling.....	2
Total.....	1,275

* No cases in chert, oil shale, or stratified ironstone mining.

† Fourteen fire clay miners were also exposed to coal dust.

for 1953," issued by the Ministry of Fuel and Power (1954). It can be said, however, that more than 50% of the cases had only slight disability, and only about 3% were totally disabled.

The number of cases in hematite mining is diminishing, but the small numbers found in tunneling are usually instances of rapid and severe silicosis.

DUSTS OTHER THAN SILICA, ASBESTOS, AND COAL

About the middle 1930's the Factory Department began to turn its attention to other dusts. Middleton, in his 1936 review, referred to dusts, such as tripoli, sillimanite, kieselguhr, talc, china clay, and fullers' earth. In the same year Doig and McLaughlin published a paper on the x-ray appearances of the lungs of electric-arc welders. From this has arisen a world-wide study of the inert and radiopaque dusts, and notable American contributors have been Sander, Enzer, Pendergrass, Vorwald, and Hamlin. Perhaps the most interesting outcome of this study has been the alteration of the approach to the interpretation of x-ray films of the chest, because the x-ray features of siderosis, baritosis, and stannosis, in the absence of occupational histories and clinical examinations, can be mistaken for fibrotic changes in the lungs. In fact, an alarming x-ray picture is often found in a worker who has little or no disability. The study of siderosis was helped by the excellent work of Stewart and Faulds (1934) and later Craw (1937) on the hema-

tite miners, in which group the lesion was found to be siderosilicosis, often accompanied by tuberculosis. Craw's later work (1947) in eliminating tuberculosis from the hematite mines and in improved dust control methods is of major importance.

Other occupations and dusts which have been studied include those of boiler scalers, graphite workers, grain dockers, and workers exposed to beryllium and its oxides, to the dust of leather mixed with other dusts, and to bagasse. Attention has also been given to exposures to the dusts of aluminum, manganese, and vanadium and to asthma occurring in workers exposed to the double salts of platinum and also to various wood dusts, such as western red cedar.

Pathology.—A great deal of work has been done on the pathology (gross, histological, and experimental) of coal miners' lungs by Gough, Harding, King, Heppleston, Wright, Gloyne, Nagelschmidt, and others. I might, however, state some conclusions about pathology which Harding and I (with our late colleague, S. Roodhouse Gloyne) have arrived at after studying the lungs of workers in many diverse industries.

Until about 10 years ago, the pathology of the dust diseases was dominated by the classical silicotic nodule (Fig. 3). In the same way, before a diagnosis could be made, the patient had to have x-ray nodulation, or the classical "snowstorm" effect. Classical silicosis usually occurs after the worker has been exposed to dust containing a high proportion of free silica. It is becoming increasingly clear, in our opinion, that even small proportions of free silica in a dust can cause a fibrosis which is composed of nodules not of the classical type (Fig. 4). The arrangement of the fibers is linear and radial, and the outline of the whole nodule is stellate. It looks like a black star. Harding, Gloyne, and I have applied the term mixed dust pneumoconiosis, or mixed dust fibrosis, to this nodule. It has been found in foundry workers, especially in cleaners of iron castings, in persons exposed to the dust of graphite containing about 10% free silica, and in boiler scalers who are ex-

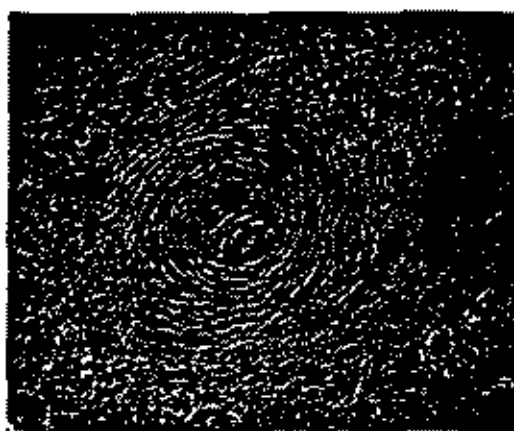
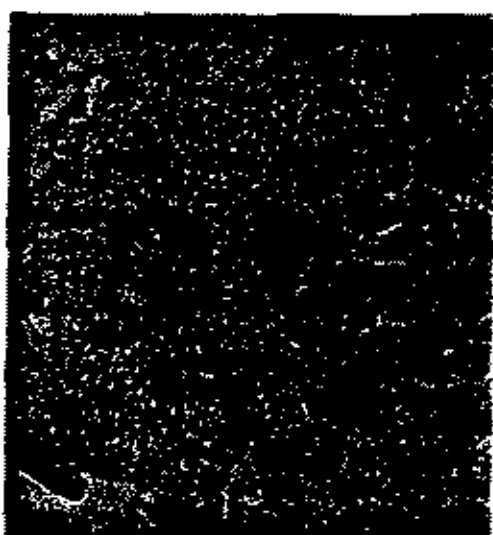


Fig. 3.—Classical silicotic nodule from lung of a gold miner (30 years old); hematoxylin and eosin; $\times 24$.

posed to a mixed dust with a low proportion of SiO_2 . The coal nodule of coal miners' pneumoconiosis has much the same appearance as our mixed dust pneumoconiosis nodule. Coal contains varying proportions of free silica. In any case, the common denominator in those cases and occupations in which this type of nodule is found appears to be the presence of a small proportion of free silica in the dust. Where there is a high proportion, as stated above, the classical silicotic nodule is found. But in the same case, there may be both the classical nodule and the

Fig. 4.—Mixed dust pneumoconiosis nodule from a steel fitter's lung; hematoxylin and eosin; $\times 24$.



mixed dust pneumoconiosis nodule. Indeed, there are also nodules which show a transition stage between the mixed dust nodule and the classical one (Fig. 5). It should be mentioned that the x-ray appearances of the lungs of a worker with mixed dust pneumoconiosis differ little, if at all, from those of one with silicosis, and the disease is just as disabling and as fatal.

Boiler Scalers' Pneumoconiosis.—Experience of pulmonary diseases in ships' boiler scalers illustrates well the etiology of mixed dust pneumoconiosis. These men are exposed to a mixed dust which varies according to the type of fuel used to heat the boilers and also according to the source of the water used.

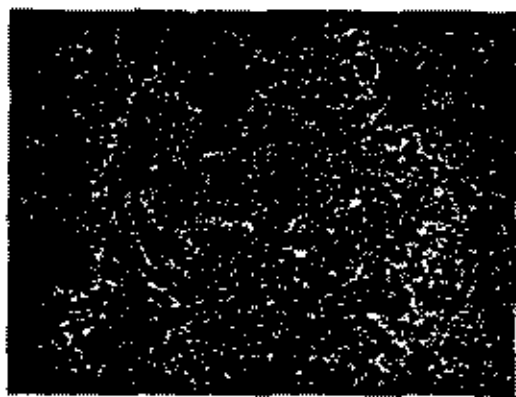


Fig. 5.—Transition nodule, from mixed dust pneumoconiosis nodule to silicotic nodule in an iron dresser's lung; hematoxylin and eosin; $\times 24$.

in them. It contains carbonates, silicates, iron, and carbon. There is usually under 5% of free silica, but there is often a high proportion of iron and its oxides. Flue dust contains more iron than does the scale on the water tubes, sometimes as much as 48%.

In the first case of boiler scalers' pneumoconiosis the worker had been scaling boilers for over 40 years (Harding, Tod, and McLaughlin, 1944). In 1938 an x-ray film of his chest showed nodulation in the upper and outer lung fields, and in the lower zones reticulation (or micronodulation). At that time we made a tentative diagnosis of silicosis in the upper zones, with siderosis in the lower zones. Seven years later the patient

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died of cancer of the lung, and histological examination of the lungs showed (apart from the cancer) the presence of classical silicotic nodules in the upper and outer zones, and in the lower zones (where there was x-ray reticulation) there were mainly deposits of carbon and iron dust in the lungs, with no fibrosis. In all other parts of the lung there were nodules of mixed dust pneumoconiosis. Up to the present time we have had autopsies on nine boiler scalers, and all showed this type of fibrosis. Only one scaler had classical silicotic nodules in addition. But five of them also died of cancer of the lung, and this may well have been partly caused by carcinogenic substances present in the soot.

The change from coal to oil as a fuel for ships' boilers has brought with it another problem. The dust from oil-fired boilers causes symptoms of bronchospasm or asthma in a high proportion of cases, and it is likely that this is due to the presence of vanadium in the oil soot. Williams (1952) has published an interesting series of cases illustrating this point. My colleagues and I are at present examining (with clinical, radiographic, and environmental details) the boiler scalers (some 300 of them) in the port of Southampton, where the boilers of ocean-going and large passenger liners are cleaned. The investigation has not been completed, but up to the present we have not found as much lung damage as was shown in a previous inquiry in the port of Hull, where the boilers of fishing trawlers are mainly scaled. So far we have found three cases of compensable pneumoconiosis among 50 workers and one case of cancer of the lung, together with a proportion of cases with lower degrees of pneumoconiosis and disability.

Talc Pneumoconiosis.—A great deal of work on talc pneumoconiosis has been done in the United States and Canada (Dreessen, 1933; Dreessen and Dalla Valle, 1935; Riddell, 1940; Siegal, Smith, and Greenburg, 1943, etc.). Merewether (1933-1934), in England, studied the x-ray and clinical features of rubber workers exposed to talc dust. But it was not until 1949 that we were

able to study the histological appearances of a proved case of talc pneumoconiosis (McLaughlin, Rogers, and Dunham, 1949). A man, 51 years of age, had worked for 37 years in a rubber-tire factory, where he had been exposed to a fairly high concentration of talc dust. Moderately advanced pneumoconiosis of both lungs was found at autopsy (in addition to incompetence of the aortic valve). Throughout the lung substance were scattered small gray nodules, more numerous in the lower lobes. In some areas the nodules had coalesced to form small masses. The fibers appeared to be arranged concentrically around small vessels, giving the impression of whorling, but not like the appearance of silicosis. There were, in addition, many "curious" or talc bodies, resembling, but easily distinguishable from, asbestos bodies. Much dust, which proved to be talc, appeared in the sections, and it was thought at the time that the particles were all fibers. More recent work on the lung by Nagelschmidt ‡ has shown that the bulk of the dust is in the form of plates with only a few fibers.

At least three other autopsies on cases of talc pneumoconiosis (all from rubber works) have been made, and they show similar features to the first published case. Small surveys have been made on workers exposed to talc dust in various industries, but larger ones have been planned to take place shortly. It is clear that talc dust, though fibrogenic, is not so active as asbestos in damaging the lungs.

Leather Dressers' Pneumoconiosis.—Co-operation between the directors of chest clinics, the mass radiography units, and the Medical Inspectorate of Factories has been instrumental in bringing to light hitherto unsuspected causes of pneumoconiosis. Since the mass radiography campaign was begun in 1948 for the early detection of cases of pulmonary tuberculosis, some 13,000,000 persons have undergone examination. Many factory populations have been surveyed, and

‡ Nagelschmidt, G.: Personal communication to the author.

included among them have been factories where there is a dust risk. The workers at one leather factory were examined by Dr. Hugh Ramsay, of the Wanstead Mass Radiography Unit. He drew our attention to the fact that in one department a high proportion of the workers showed abnormal x-ray changes, whereas in other departments, where there was no dust, no abnormalities were seen. In the department with the high proportion of x-ray abnormalities, skins loaded with china clay and calcium carbonate are dressed on rapidly revolving felt wheels covered with a layer of fine Carborundum powder. The job is very dusty, though it is done under exhaust ventilation. The dust is composed of much fine leather dust, with smaller proportions of china clay (kaolin), calcium carbonate, and Carborundum. It was found that the dust contained about 5% of free silica. The x-ray films showed all stages of abnormality, varying from early reticulation (micronodulation) through nodulation to massive shadows. In a few cases there was clinical evidence of disability. One man with an x-ray film showing massive shadows had died from "asthma and pneumonia" a year before the investigation began, and there was no autopsy. In spite of the fact that up to the present time no pathological evidence has been available, it is likely that the condition will fall into the group of the mixed dust pneumoconioses. The dust of china clay, which for years has been thought to be comparatively harmless, is becoming more and more suspect. Even apart from china clay, the presence of a small proportion of free silica is *prima facie* evidence that the dressing of such skins is a hazardous occupation.

Beryllium Pneumonitis and Granulomatosis.—It is remarkable that British experience of beryllium pneumonitis and granulomatosis is not as extensive as that in the United States, though many workers have been exposed to the dust of fluorescent lamp powders containing beryllium oxide and also the dust and fumes from the alloys. Only one death has occurred, and the Factory Department has collected clinical, x-ray, and environ-

mental details of five nonfatal cases, one of whom is now very ill. The other four cases are either recovering, or their condition is stationary. It is also remarkable that five out of six affected workers were chemists engaged in the development of the beryllium lamp powders. At the factory where the fatal case of beryllium granulomatosis occurred, 150 of the other workers were examined clinically and radiographically and no more cases were found, though there had been considerable exposure to the dust of the lamp powders in the early days. It is undeniable that beryllium oxide is toxic, but examination of the histology of the lungs of the one fatal case has led me to hold the unorthodox view that beryllium was not the sole cause of the condition. There were two types of lesion: one of a granulomatous type, in which there were giant and epithelioid cells, and the other in which were many fibrotic nodules indistinguishable from silicosis. Under polarized light many doubly refractile particles were seen in the nodules, and an eminent crystallographer stated that these were cristobalite, one of the most active forms of free silica. This is not surprising, because one of the ingredients of the lamp powder is silica gel (25%), which in the preparation of the powder is heated up to about 1100 C. The changed methods of preparing the lamp powder have eliminated both the beryllium oxide and the free silica, so that the risks both of beryllium granulomatosis and of silicosis have also been eliminated.

"Pneumoconiosis" from Vegetable Dusts.—Apart from cotton, not a great deal of work has been done on the vegetable dusts. The illnesses noted among cotton workers include mill fever, a transitory illness which affects nearly all new workers in cotton, flax, and hemp mills and also in malt houses; "Monday fever" (or feeling); weavers' cough, and byssinosis.

Byssinosis develops after about 20 years as a natural progression from "Monday fever" and in its final stage has the characteristics of chronic bronchitis and emphysema. As Schilling (1954) says, though it was de-

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scribed by Greenhow nearly 100 years ago, its etiology is still obscure. It presents an odd but characteristic history of chest tightness and breathlessness on Mondays, which gradually extends to other working days as the disease progresses. "In its later stages these symptoms are very distressing, but usually remain worse on Monday than on any other day. It causes no specific x-ray changes in the lung fields." In the main, the workers in the cotton card and blowing rooms suffer most from the disease. Strippers and grinders who clean the carding engines are especially affected. As mentioned previously, workers with byssinosis are compensated under a special scheme.

Bagassosis.—Only one factory in the country handles bagasse (or sugar cane without the sugar), and bagassosis has occurred mainly in those workers who were grinding bagasse in a dry state. The condition is an acute bronchiolitis, with high temperature, severe dyspnea, and x-ray picture of the lungs showing generalized military shadows. Fifteen cases of this acute disease have come to the notice of the Factory Department; some of these have been described by Castleden and Hamilton-Paterson (1942), Gillison and Taylor (1942), and Hunter and Perry (1946). The last case occurred in 1948. Since we got the firm to grind the bagasse under water, there have been no further cases.

Farmers Lung.—Farmers', or threshers', lung was first described by Campbell (1932), and after that Fawcitt (1936 and 1938) did a great deal of work on the condition. It has features similar to bagassosis, but, since it occurs mainly among workers who have been handling moldy hay during a wet summer, it is regarded as being caused by a fungus. Fawcitt was firmly of this opinion. Single cases of the condition are described from time to time by physicians in the agricultural districts.

Pneumoconiosis in Grain Dockers.—Dunner, Hermon, and Bagnall described in 1946 the clinical features and abnormal x-ray appearances in a group of 55 grain dockers.

Thirty of these men had pulmonary tuberculosis, but 11 others had x-ray changes suggestive of the presence of pneumoconiosis. Fourteen had normal x-ray films. Analysis of the dusts from various grains showed small percentages of free silica; oat dust, for instance, had 5%. No autopsies have been carried out, but it seems that a case has been made out for an extended investigation of larger groups of grain dockers.

Graphite Pneumoconiosis.—It has been found by some observers in England (Dunner, 1945, 1948, and 1949; Gloyne, Marshall, and Hoyle, 1949, and Harding and Oliver, 1949) that workers exposed to the dust of natural graphite develop radiographic changes in the lungs and disability. The range of x-ray abnormalities closely resembles that seen in coal miners. Pathological and experimental studies (Gloyne and others, 1949, Harding and Oliver, 1949) show that the condition falls into the group of the mixed dust fibroses, the fibrotic nodules having a linear and radial pattern as opposed to the whorled fibrosis of the classical silicotic nodule. Natural graphite contains small percentages (of the order of 5%-10%) of free silica. There is as yet no evidence that pure graphite will produce a similar condition.

Manganese Pneumonitis.—A few cases of manganese poisoning affecting the nervous system occurred in the middle 1930's in workers grinding manganese dioxide for use in lamp batteries. In 1946, Lloyd Davies reported a high incidence of pneumonia in a group of workers exposed to manganese dioxide dust in the manufacture of potassium permanganate. Animal experiments by Lloyd Davies and Harding (1949) confirmed that manganese dioxide irritated the lung tissue and caused intense infiltration of the alveolar walls and alveoli. Later granulomatous changes developed in some instances. These results are in line with those described by workers in other countries.

Vanadium Pneumonitis.—Wyers (1946) recorded his observations on workers exposed to vanadium pentoxide dust, and his results

are similar to those described by Sjöberg (1949) in Sweden. The effects are a combination of systemic poisoning and irritation of the pulmonary tissue, leading in some cases to bronchospasm and pneumonia. Doig § and Williams (1952) have described the marked bronchospasm occurring in workers exposed to the soot of oil fuel, which is thought to be caused by the high percentage of vanadium in the soot.

SUMMARY

The position as regards the dust diseases in Great Britain may be summarized as follows:

1. During the past 50 years, the risk of silicosis in most of the major industries has been firmly established. Until the late 1920's, free silica was the only dust which was thought to damage the lungs. Asbestosis, caused by the dust of a combined silica mineral, came into prominence about that time. In the middle 1930's, attention was given to the effects of other dusts on the lungs, such as iron and its oxides, and of radiopaque dusts, china clay, sillimanite, kieselguhr, talc, and mixed dusts containing free silica.

During the middle 1930's also, the effects of coal dusts on the lungs were given increasing attention, and extensive surveys were carried out, culminating in the formation of the Pneumoconiosis Research Unit of the Medical Research Council in 1945. The coal miners numerically constitute the greatest problem of dust disease in Great Britain.

2. Despite the combined efforts of inspectors of factories and mines, physicians, chemists, engineers, and research workers, the deaths from pneumoconiosis have continued to rise yearly. The reasons for this increase may be found in more accurate diagnosis of the condition and in the publicity given to occupational diseases of the lungs, leading to more frequent mention of pneumoconiosis by physicians on death certificates. But a more likely cause is the urge for increased speed of production, and the introduction of machines

which make a dusty process more dusty and cause a lag in dust-control methods.

3. Compensation for industrial pulmonary disease began soon after 1918, and gradually most of the processes and industries which damage the lungs are being brought under the provisions of the various Acts of Parliament. The Industrial Injuries Act of 1946 removed the responsibility for compensation from employers and insurance companies to the Government. Since then cases taken under Common Law against the employers have increased rapidly.

4. Numerous legal provisions, contained both in Acts of Parliament and in Regulations, have been brought into force. Routine inspection by inspectors of factories and mines has been instrumental in limiting the numbers of cases of disability and death brought about by inhalation of the dangerous dusts.

5. It is expected that more accurate information about the incidence of the dust diseases will be obtained in the near future, when statistical studies of the information obtained by the Pneumoconiosis Panels have been carried out, and when the report of the Registrar-General about the occupational incidence of disease at the time of the 1951 Census becomes available. At the present time no reliable information exists about the populations at risk in each industry and process.

6. Surveys of the population by mass radiography to detect early tuberculosis are bringing to light information about the effects of dust in some hitherto unsuspected occupations.

7. Many problems about dusts and the lungs are still unsolved, and some would say that we have only just begun to attack the fringes of the problem. Nevertheless, a great deal has already been accomplished.

Assistance in compiling the information contained in this paper was rendered by Dr. P. K. Walker and the members of the Pneumoconiosis Panels of the Ministry of Pensions and National Insurance; Drs. E. R. A. Merewether, A. T. Doig, and G. O. Williams, of the Factory Department,

§ Doig, A. T.: Unpublished data.

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Ministry of Labour and National Service; Dr. H. E. Harding, lately of Sheffield University, and Dr. G. Nagelschmidt, of the Safety in Mines Research Laboratories, Sheffield.

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Clearance of Radioactive Dust from the Human Lung

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One of the important potential health hazards associated with the atomic energy industry is that of air-borne radioactive dust. This is not a new problem, since radium and uranium mines have always had radioactive dust and radon gas. Indeed, the only practical experience with this hazard originated in the European uranium mines, where there was an extremely high incidence of lung cancer.¹

The control of radioactive dust is in one sense an economic matter, because the greater the expenditure for ventilation equipment the less the degree of personnel exposure. The problem then has been to establish reasonable levels of exposure which would insure safety of the workers without being overly conservative and therefore too expensive. Two approaches to this problem have been made. The known average concentration of radon (3×10^{-4} curies/liter) in the Schneeberg and Joachimstal mines has been used as the basis for a recommended maximum permissible concentration of 10^{-21} curies/liter.² In practice, however, 10^{-10} curies/liter has been used to a considerable extent. The other approach to the problem of establishing safe working concentrations is based on a maximum permissible radiation dosage rate to the lung of 300 millirem/week.³ An estimate is made of the air concentration of the particular dust in question which if inhaled over the period of a working week would deliver this radiation

dosage to the lung. It is pertinent to note that the value of 300 millirem/week is also used for whole-body exposure to penetrating radiation and is derived from estimates of the dose which would not be damaging to the blood-forming organs.⁴ Whether it is reasonable to utilize the same permissible dosage for both the lung and the blood is not answerable at the present time.

It is of interest to compare the dose rate of 300 millirem/week with that calculated for the maximum permissible exposure to radon. Harley⁵ has calculated that exposure to 10^{-10} curies/liter, assuming 50% retention of the radon daughter products on the bronchial epithelium, would deliver 50 rem/week. This is 150 times higher than the 300 millirem/week permissible value. This calculation must be tempered by the lack of information on the actual fraction of inhaled radon daughter products deposited on the bronchial mucosa and the question of whether the radon or thoron daughters, in fact, remain in the lung or become rapidly dissipated in the blood stream. This latter point, that of the effective half-life of the daughters of radioactive gases, forms the subject of some experiments to be reported here.

Although the dosages from the current maximum permissible concentration of radon and the maximum permissible exposure rate to the lung of 300 millirem/week do not compare very closely, it is well to point out that the use of the more conservative value involves a number of assumptions which are, at best, crude approximations. For example, one must assume that a certain fraction of the inhaled dust is retained and that this retained dust has a biological half-life of a certain magnitude. These factors, together

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with the radiological half-life and the effective energy of the emitted radiation, enable one to calculate the permissible air-borne concentrations. There may be a major fallacy in this approach, since most of the lung cancers observed in the European uranium mines, and these presumably were due to radiation, occurred in the epithelium of major bronchi. The walls of such bronchi are sufficiently thick to prevent the penetration of the alpha and beta radiations (which are the important ones so far as lung damage is concerned) from the outside of the bronchial wall through to the inner lining, which is the target organ in question. Consequently, radiation to the bronchial mucosa must originate largely from the particles which are initially deposited in the bronchi or which are swept out over them by the ciliary mechanism. From this point of view, the radioactive particles which are rapidly removed from the lung constitute the real hazard. The estimates for the maximum permissible air concentration are, however, based on the fraction which remains behind in the lung, and, for all we know, this material deposited in the alveoli may be rendered harmless by the comparative radioresistance of the alveolar structures. This, in one sense, would be analogous to the situation in which lead is detoxified by being deposited in the skeleton and its damaging effects occur while in transit to and from the bone. If this, in fact, is the truer picture of the situation, the better estimate of the hazard would involve information on the fraction of inhaled radioactive particles which are deposited on the bronchial mucosa and the rate at which they are removed. It is this point, namely, the speed with which radioactive particles are removed by ciliary action, that constitutes the subject of the second group of experiments to be reported here.

EFFECTIVE BIOLOGICAL HALF-LIFE OF THORON DAUGHTERS

As indicated in Figure 1, the daughters of thoron gas are more suitable than those of radon for the estimation of the effective half-life in the lung, because they have a radiologi-

cal half-life of about 10½ hours, compared with 30 minutes for radon daughters. In addition, ThC and ThC' have gamma radiations of greater than 1,000,000 electron volts, which make their detection from the outside surface of the chest feasible.

In these studies, thoron gas was dispersed into a 1000 cu. ft. chamber by bubbling air vigorously through a 2 mc. solution of ThX. At the same time a cloud of kaolin (aluminum silicate, $H_4Al_2Si_2O_6$, density 2.1) dust was maintained in the same chamber. After the thoron supply to the room is shut off,

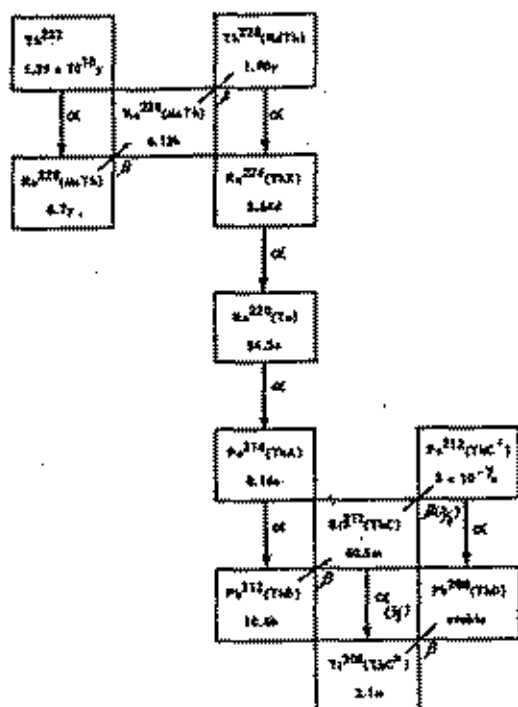


Fig. 1.—Thorium decay series.

ThA, with a half-life of 0.16 second, decays almost immediately and the remaining activity is governed by ThB, with a half-life of 10.6 hours. The thoron daughters are produced in atomic form or in very small aggregates, and they adsorb onto the surfaces of suspended dust and are deposited in the lung with the carrier dust. Since they are attached to the dust in a tenuous fashion, we were interested in determining whether the daughters were quickly washed off and carried away from the lung by the blood.

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A concentration of 10^6 curies/liter of ThB was maintained throughout the experiments, of which six were performed on four healthy subjects. The dust was inhaled for approximately one hour through a face mask attached by a short length of rubber hosing to a port in the dust chamber. Cascade-impactor samples were taken during the early and latter parts of the breathing period. When the subject completed the dust inhalation, he washed his face and removed any dust from the pharynx and mouth by gargling. He then seated himself before a scin-

The results of these studies are presented in Figure 2, where the experiments were divided into two groups on the basis of the initial count rate recorded from the surface of the chest. It can be seen that the effective half-life, as determined from both curves, was about nine hours. This value is very close to the radiological half-life of 10.6 hours, indicating that the biological half-life is in the order of 60 hours. This study indicates that, once deposited, the thoron daughter products, and by analogy radon daughter products (because their chemical forms are

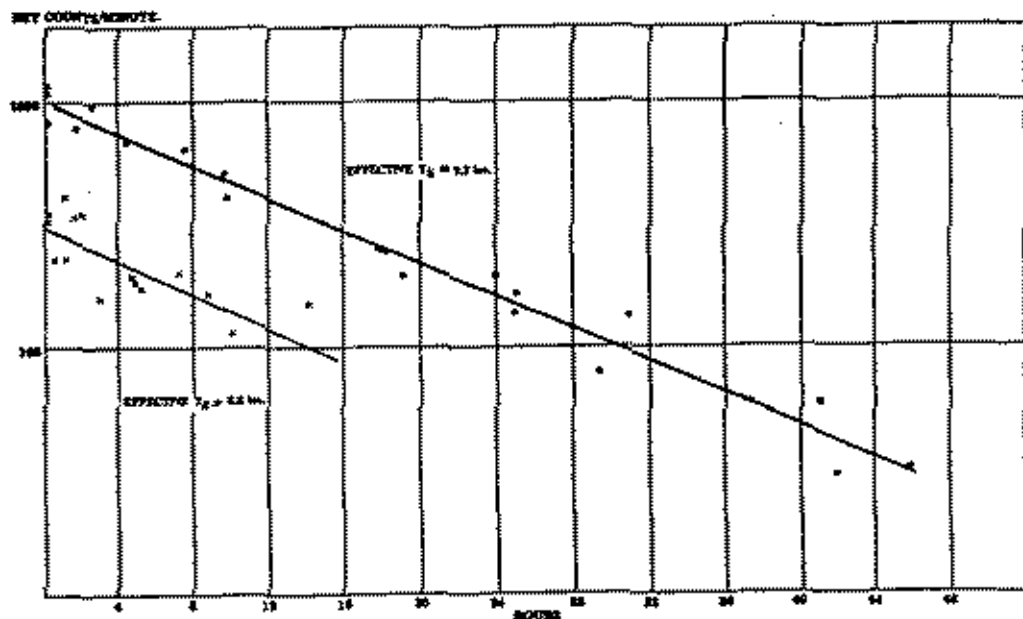


Fig. 2.—Net gamma count rate from the surface of the chest following inhalation of thoron daughters.

tillation counter which utilized a cylindrical sodium iodide crystal, 2 in. in diameter and $1\frac{1}{2}$ in. thick. This crystal was mounted in a lead shield in such a manner that the front of the crystal could be pressed against the subject's chest. During all experiments the crystal was positioned on the anterior surface of the thorax on the midline at the level of the second rib. The crystal received the gamma radiations emitted by ThC and ThC'. The particle-size distribution of the kaolin dust was quite uniform and ranged in all the experiments from 1.1μ to 1.3μ mass-median diameter.

almost identical), are removed slowly enough so that the effective half-life is not significantly different from the rate of radiological decay.

CLEARANCE RATE OF DUST BY THE CILIARY MECHANISM

As indicated previously, the hazard of inhaled radioactive insoluble dust may come from those particles which are removed by ciliary action rather than from the ones remaining behind, and it was of interest to determine the rate of this removal in humans. Animal studies have indicated that the linear

velocity of particles carried on the bronchial mucosa is quite high, about 1 to 3 cm. per minute, depending on the portion of the respiratory tract.⁸ In addition, it is common experience of radiologists that iodized oil (Lipiodol) used for bronchography is frequently removed within one day. Animal studies utilizing radioactive dusts also indicate that the bronchial mucosa is cleared in a matter of hours.⁹

For these studies, metallic iron powder was used, which had been irradiated with

Blendor was turned on for three seconds, and at the end of this interval the subject was instructed to take a breath; at the same time a cascade-impactor sample was obtained. The Blendor was turned off, and the subject rinsed his mouth and pharynx by gargling with water and then went quickly to the scintillation counter, as described before.

In the experiments to be reported here, eight studies were performed, four with par-

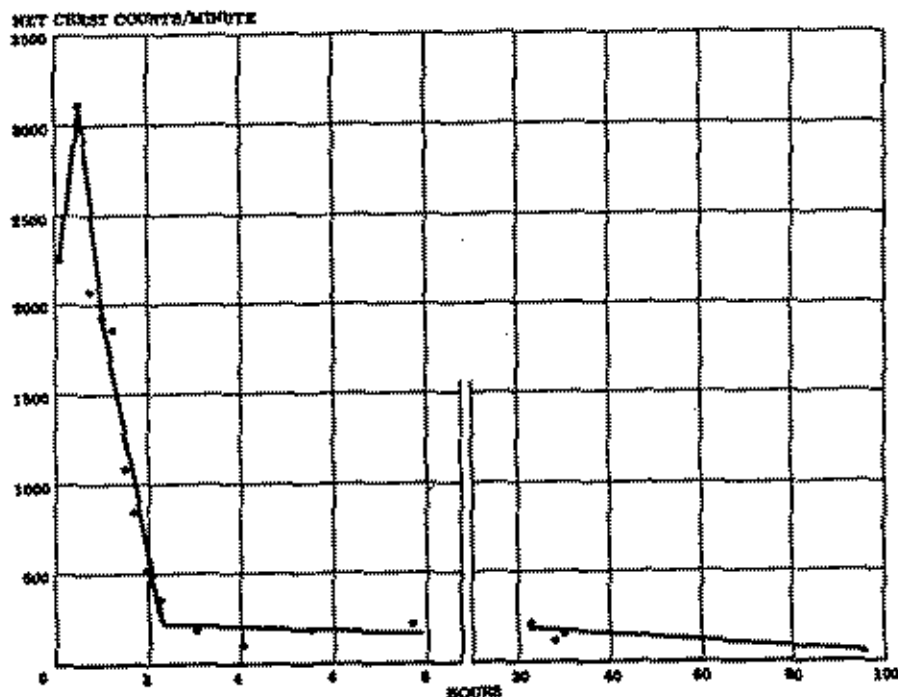


Fig. 3.—Net gamma count rate from the surface of the chest following inhalation of radioactive iron dust in Subject A. B.

neutrons in an atomic pile to produce a radioactivity level of $100\mu\text{c}$ of Fe^{59} per gram of iron. This iron isotope has a strong gamma component and consequently is also suitable for detection from the surface of the chest. The radioactive iron powder was placed in a Waring Blendor which was fitted with a tight cover. The cover had an opening for a short breathing pipe and a port for the inlet of a cascade impactor. At the beginning of the experiment, the subject placed his mouth around the breathing pipe. The

particle sizes of $3.4\mu\text{--}4.3\mu$ and four with particle sizes of $1.4\mu\text{--}2.3\mu$ mass-median diameter.

Three of the four studies with the larger particle sizes were remarkably similar. Figure 3 illustrates an experiment in which the count rate from the surface of the chest started at about 2000 counts per minute, rose rapidly several hundred counts more, and fell precipitously to about 5% of the initial activity in two hours. Figure 4 presents a similar response in another subject. During the course of this run, it occurred to us that the activity which was lost from the chest

CLEARANCE OF RADIOACTIVE DUST FROM LUNG

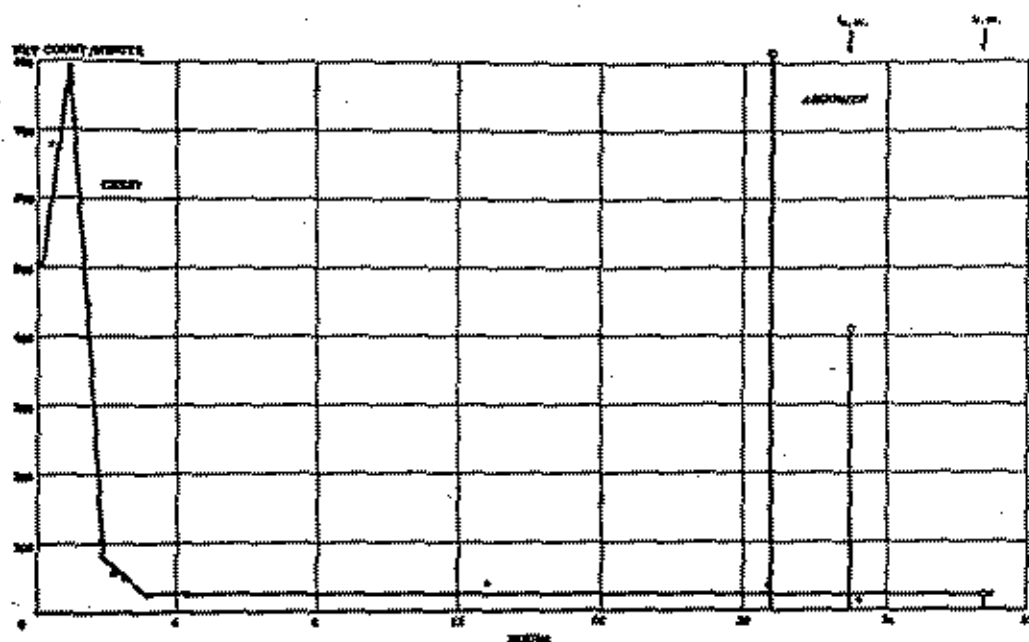
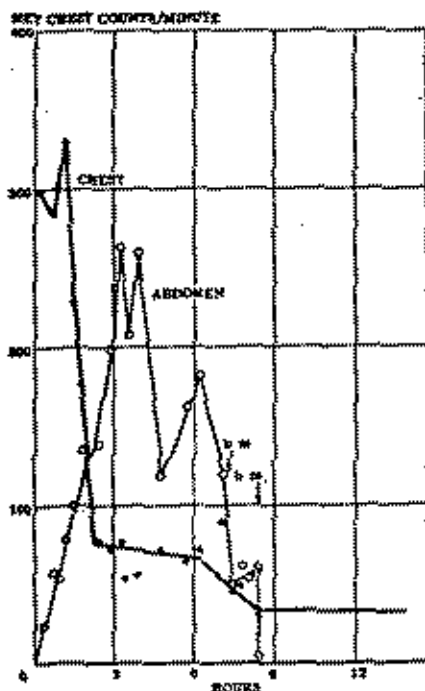


Fig. 4.—Net gamma count rate from the surface of the chest following inhalation of radioactive iron dust in Subject R. A.

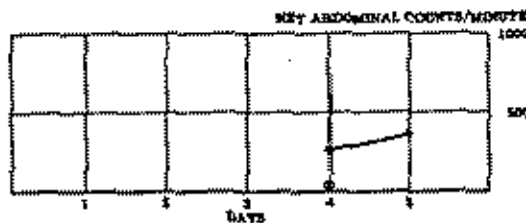
should appear in the abdomen, because particles raised by ciliary activity are swallowed. When the subject placed his abdomen against the crystal at about the level of the umbilicus,

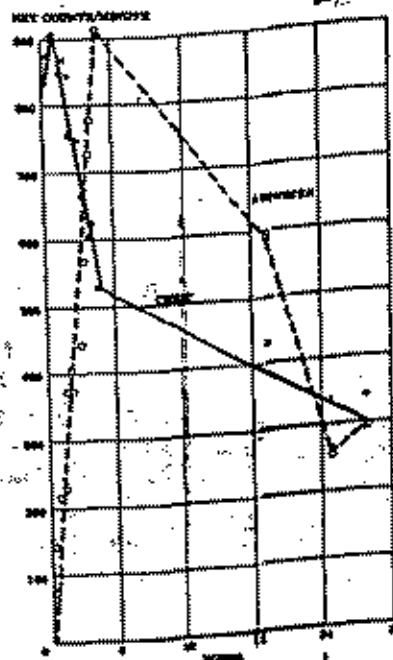
the indicated high count rate was observed. A saline cathartic was administered, after two defecations the count fell to very low levels. Blood samples taken during the period of rapid clearance from the chest indicated no detectable radioactivity.



The next subject (Fig. 5) was unusual. Whereas the other subjects achieved a high chest count with one respiration, this subject had to inhale about four times in order to reach a counting rate of only 300 per minute. In retrospect, the subject recalled that while breathing he had kept his tongue close to the hard palate. It is possible that because of the narrowing of the breathing passage through the mouth, the velocity of the air

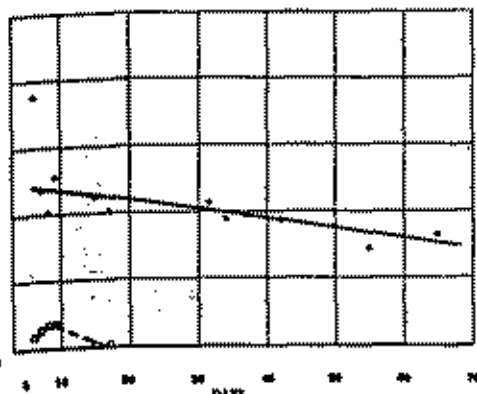
Fig. 5.—Net gamma count rate from the surface of the chest following inhalation of radioactive iron dust in Subject L. A.





activity and then dropped more slowly to a level of about 12% in eight hours. In this experiment, serial abdominal counts indicated that the activity in the abdomen followed the chest activity inversely, and, as in the previous run, the activity returned to

Fig. 6.—Net gamma count rate from the surface of the chest following inhalation of radioactive iron dust in Subject M. W.



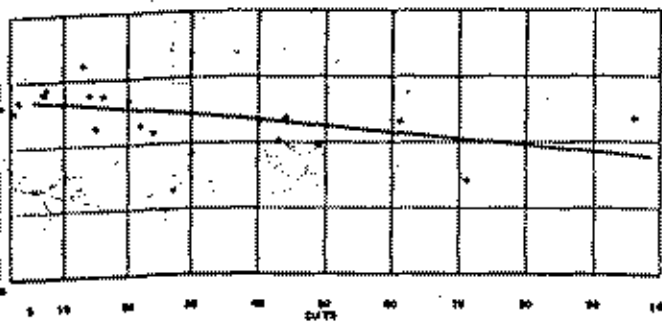
became high enough to impact more particles in the pharynx so that fewer reached the lung, and of those that did there was a greater predominance of smaller particles. In any event, this subject again showed the initial rapid drop in count rate, but this time the fall stopped at about 25% of the initial

background levels only after several bowel evacuations.

The response to the smaller particles is illustrated by Figure 6. Here we see that there is again a rapid initial fall, in this case in 4 hours to about 60% of the initial activity, and then a slower fall over the course of 30 hours to a level which is thereafter sustained for the remainder of the observation period of 70 days. It is worth noting (Fig. 7) that in two subjects receiving the smaller particles the secondary 30-hour clearance period appeared to consist of two parts, with



Fig. 7.—Net gamma count rate from the surface of the chest following inhalation of radioactive iron dust in Subject E. H.



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a more rapid initial phase which resembled the secondary clearance in subjects receiving the larger particles (Figs. 4 and 5).

In summarizing the data in Figure 8, the average time for completion of the first decay curve in the four experiments with the larger particle sizes, was 2.1 hours, with a range of 1.9 to 2.3 hours, and the average percentage of the material cleared from the lung after this period was 87%, with a range of 75% to 95%. In two of these subjects, there was a second clearance period, lasting 3.2

COMMENT

The technique of measuring the clearance of radioactive particles from the lung, as used in these studies, is sensitive to changes in geometrical distribution of radioactivity within the chest, but the interpretations of the data, as reported here, would not be seriously affected by this factor.

The results obtained with the thoron daughter experiments are probably more representative of particles deposited mainly in the alveoli, and consequently it is still

	PARTICLE SIZE		FIRST DECAY PERIOD (hours)	% CLEARED	SECOND DECAY PERIOD (hours)	% CLEARED
	MM	OSD				
A. B.	3.5	1.75	2.3	91	---	---
F. A.	3.5	2.13	1.9	88	3.2	95
W. D.	3.5	1.72	2.3	95	---	---
L. A.	4.3	1.72	2.0	75	6.5	88
AVE.			2.1	87		

M. W.	2.3	1.70	4.0	36	31	69
M. E.	2.2	1.64	1.6	47	36	62
H. G.	1.4	1.70	2.4	53	33	75
E. H.	1.9	1.67	2.0	52	32	64
AVE.			2.4	47	33	68

Fig. 8.—Summary data on inhalation of radioactive iron dust.

and 6.5 hours, which reduced the retention about another 10%.

In the four experiments where the subjects inhaled the smaller particle sizes, the average time for completion of the first clearance period was 2.4 hours, with a range of 1.6 to 4.0 hours, and the average activity cleared from the chest after this period was 47%, with a range of 36% to 53%. All these subjects exhibited a second, shallower clearance slope which ended in an average of 33 hours, with a range of 31 to 36 hours. This second clearance period increased the lung clearance from an average of 47% to 68%.

moot whether radon or thoron daughters would be cleared by the ciliary mechanism. It is worth noting that, because the radioactive daughters are fixed onto the surfaces of particles, their distribution in a dust cloud will tend toward the smaller particles, where the surface area is greatest, and these are the ones which would tend to be deposited in the alveoli. This is to be contrasted with the radioactive iron particles, in which the amount of radioactivity is a function of mass rather than of surface area.

There is little doubt that the initial rapid removal of the radioactive iron from the

lung represented ciliary clearance. Metallic iron is an insoluble material, and the translocation of the radioactivity to the intestine and the lack of appearance in the blood were convincing evidence that the iron was not solubilized to any extent and thus removed from the lung. The speed with which the ciliary mechanism cleanses the bronchial mucosa would appear to make this a very effective means of minimizing radiation damage to the bronchial epithelium. The technique by which this has been demonstrated in humans could no doubt be extended to provide further information on the relationship of particle size to bronchial deposition.

SUMMARY

The effective half-life of thoron daughters in the lung following deposition, together with kaolin particles of mass-median diameter $1.1\mu-1.3\mu$, is about nine hours. This indicates that the pulmonary clearance of radon and thoron daughters under these conditions will not materially reduce the radiation hazard following inhalation.

The early bronchial clearance of radioactive iron particles appears to have two phases: The first clearance period ends in 2 to 4 hours and the second in about 30

hours. The larger the average inhaled particle size, the greater the fraction removed in two to four hours.

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The Antagonistic Biological Action of Quartz and Potassium Carbonate

An Experimental Study on Guinea Pigs

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and

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One of the major catastrophies of the silica industry was first recorded 25 years ago, when Koch¹ reported an acute silicosis resulting from the inhalation of fine quartz dust mixed with alkalis. Since that date a spate of similar occurrences have been reported from all over the industrial world.* In the majority of instances, the incriminating exposures were experienced in connection with the manufacture of scouring powders, and one of us (G. W. H. S.) has seen several instances in South Africa. In most of these cases, the silicosis was of an aberrant type and characterized by the rapid appearance of massive confluent fibrocellular lesions and marked hilar periadenitis. The disease proved fatal in less than two years in a large proportion of cases, and in some instances the victims died within a matter of weeks.² Abnormal susceptibility did not appear to play a part in provoking this malignant reaction. In Rössing's³⁰ series, for instance, all employees were affected within a space of seven years. The terminal complication in the majority of reported cases appeared to be cor pulmonale or tuberculosis, but it is

remarkable that tuberculosis played no role in the early pathogenesis of the disease. Owing to the often rapidly spreading nature of the radiographic shadow, the attendant malaise and toxemia, the frequent appearance of miliary shadowing, and, in some instances, dissemination of the process to extrathoracic organs, such as the liver or spleen,³ tuberculosis was frequently diagnosed in error until autopsy provided the final answer.

In some cases the quartz flour was mixed with diatomite and kaolin,³⁰ thus confusing the issue. However, in the majority of cases, the combination of quartz flour with an alkali (in the form of soda) was the only factor to contend with. The alkali content ranged from 2%³⁰ to 25%.³ Soon the theory that the alkali had increased the solubility of the quartz became widely accepted. Kettle³¹ opposed this concept on chemical grounds, and Lochtkemper and Telcky³² drew attention to the fact that in their clinical experience with a sandpaper industry the addition of varying quantities of alkali produced no significant additional danger over that which could result from comparable exposures to pure quartz dust generated in a quartz mill. The suggestion would seem to be, therefore, that it is the fineness and purity of the quartz flour, together with massive exposures, rather than the addition of the alkali, which provoked the overwhelming pulmonary reaction. It is clear that this type of problem would be settled only by the experimental method. There is no record of any systematic investigation in this direc-

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Director (Dr. Schepers) and Research Associate (Mr. Delahant), The Saranac Laboratory.

* References 2-11.

tion, though The Saranac Laboratory did experiment with one of the soap powders and failed to obtain any fibrotic response.

It is with considerable interest, therefore, that among the uncompleted labors of the late Dr. L. U. Gardner a brief relevant experiment, in which one of us (A. B. D.) participated, could be found.

In this study a mixture of quartz dust, potassium carbonate, and carbon in the following proportions

Quartz (1 μ -3 μ)	61.0%
K ₂ CO ₃	38.5%
Charcoal (3 μ and less)	0.5%

was introduced intratracheally into the guinea pig lungs and intraperitoneally. The mixture was injected into the trachea in nine animals in two doses of 0.5 cc. of a 10% suspension at weekly intervals. Thus a total dose of 100 mg. per animal was administered. For the intraperitoneal injections, pairs of guinea pigs each received 2 cc. of a suspension of the mixture. The strength of the suspension, which was different for each pair of animals, was 10%, 7%, 5%, 2%, and 0.5%.

OBSERVATIONS

In Tables 1 and 2 the results of these experiments are summarized. It will be seen that five of the nine animals in the intratracheal experiment died of pneumonia. Whether or not this was due to an intercurrent infection was not established. The occurrence of the first three deaths within the first six weeks suggests a causal relation between the deaths and the acute tissue response to the injected mixture. However, animals succumbing to toxic factors in an injected dust usually do so within a shorter period, and the deaths may possibly be coincidental. To substantiate this postulate reference to the records of The Saranac Laboratory at the time of inception of the present experiment revealed that an epizootic was rampant at that time.

The initial conspicuous lesions produced in the lungs of these animals are quite in conformity with the results to be expected on the introduction of moderately irritative

TABLE 1.—Pulmonary Effects of Intratracheal Injections of a 3:2 Mixture of Quartz Dust and Potassium Carbonate

Guinea Pig No.	Days after Injection	Died* or Killed	Gross Pulmonary Reaction
19	32	D	Consolidation left caudal lobe
4	38	D	Single large gray conglomerate lesion, with pleural adhesion
6	41	D	Congestion with consolidation of right cephalic lobe; large firm conglomerate lesion, with overlying adhesion
1	40	K	Large conglomerate lesion, with heavy pleural pigmentation and obliterative pleuritis
2	120	K	Large conglomerate lesion, with overlying adhesion
20	179	D	Voluminous lungs, with a conglomerate mass in left caudal lobe; metastatic gray subcapsular hepatic and splenic foci of dust reaction
8	258	D	Spontaneous rupture and pleural effusion, with large conglomerate lesion
5	400	K	Large pale green conglomerate lesion, with obliterative pleuritis
21	575	K	Two large black soft conglomerate lesions

* All spontaneous deaths were due to pneumonia.

foreign matter. The point of greatest relevance concerns the fact that the masses provoked did not increase in size, become indurated, or undergo necrosis even after 575 days. The response to an equal dose of quartz alone would, at a commensurate stage, have been an unequivocally progressive sclerotic affair.

The peritoneal reaction parallels this pulmonary response (Table 2). The deaths from the 10% and 7% suspensions in the early phases of the experiment were undoubtedly due to the toxic action of the injected SiO₂ plus K₂CO₃ mixture. The lesions were instances of classical chemical peritonitis. Guinea Pig 55, however, shows that this peritonitis was not invariably fatal, leading to partial recovery. The lesions found in the remaining animals may all be classified as benign in comparison with those ordinarily to be expected from quartz alone in an equivalent dosage.

The analysis of the pulmonary histopathology elucidated the whole problem. The immediate effect of the introduction of this blend of quartz and potassium carbonate was

ANTAGONISTIC ACTION OF QUARTZ AND POTASSIUM CARBONATE

TABLE 2.—Effect of Intraperitoneal Injections of a 3:2 Mixture of Quartz and Potassium Carbonate

Concentration of Suspension, %	Guinea Pig	Survival Days, No.	Died or Killed	Observations
10	37	1	D	Serosanguineous effusion with intense injection; no necrosis; distended bowel
	46	1	D	
	57	15	D	
	60	18	D	
7	55	30	K	Pleural peritonitis with small masses Small soft peritoneal plaques; slight thickening of omentum Small soft peritoneal plaques; external fecal adhesions with fatal obstruction. Matted adhesions of ileum and omentum; died from rodent typhoid
	56	120	K	
	59	140	D	
	58	180	D	
5	63	30	K	Peritoneal and omental plaques Fecal adhesions; multiple omental soft dust deposits
	64	120	K	
2	65	30	K	Single small soft peritoneal plaques and isolated multiple small omental dust deposits
	67	120	K	
0.5	61	30	K	Isolated multiple omental dust deposits
	62	120	K	

to produce marked and universal cytological reaction.

By the end of three days very little pigment was preserved within the lungs and all of it was found intracellularly. Some of the dust had also been transferred to the hilar lymph nodes.

The characteristic lesion consisted of a diffuse alveolar wall thickening caused by capillary distention, proliferation of septal or mural cells, and infiltration of these walls by numerous macrophages and fibroblasts, many of the former being pigment-laden.

Lying free within the alveoli there were numerous macrophages and multinucleated giant cells. These cells were charged with dust particles and tended to be in contact with the alveolar walls. Some of the giants were so large as to occupy some alveoli completely.

The abundance of macrophages and fibroblasts was particularly marked around the smaller blood vessels and bronchioles. The epithelium of the respiratory passages showed some swelling and regional superficial necrosis, which became a more constant feature in the smaller ramifications, where copious desquamatory matter occurred in the lumina. The smaller blood vessels likewise were found ensheathed in prominent cellular cuffs, and their muscular layers showed hypertrophy even within the lymph nodes (Fig. 1).

At the end of 400 days, the essential lesion still persisted as a cellular hyperplasia of all components of the lung tissue. Regionally the infiltration of the alveolar walls was so abundant that confluence might be simulated, especially where numerous macrophages were present within the alveoli (Fig. 2A). This effect was enhanced in some areas and simulated at others through marked regional atrophy of alveolar spaces in which dust-filled macrophages and giant cells tended to collect (Fig. 2B). These atelectatic parts of the lung may be topographically related to foci of bronchitis and obliterative bronchiolitis, which were observed at separate points.

Atrophic vesicular emphysema was apparent throughout both lung fields (Fig. 2). There was a distinct decrease in the vascularity of the parenchyma because of the partial obstruction of smaller blood vessels by the proliferated cells around them or composing their walls.

In some of the animals killed after 575 days, condensations of the dust were found at isolated foci (Fig. 3A). These areas consisted of pigment-filled atrophic alveoli, and there was no significant cellular reaction in relation to these areas and no fibrosis. These conglomerate masses of pigment with supporting stroma comprised of the residua of alveolar walls were contained in giant macrophages.

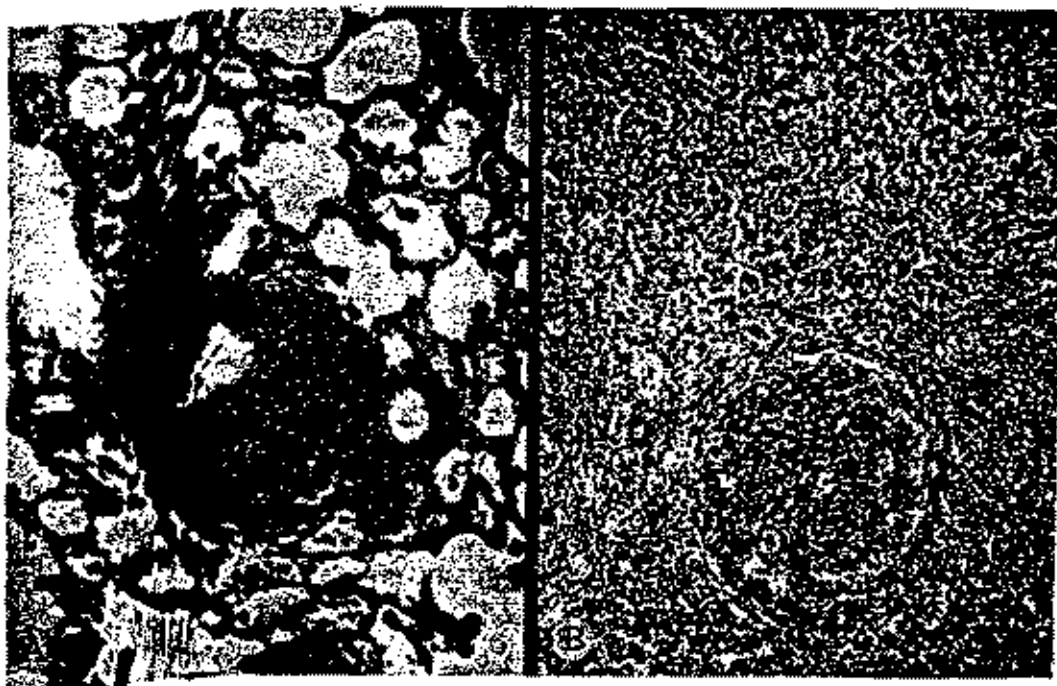
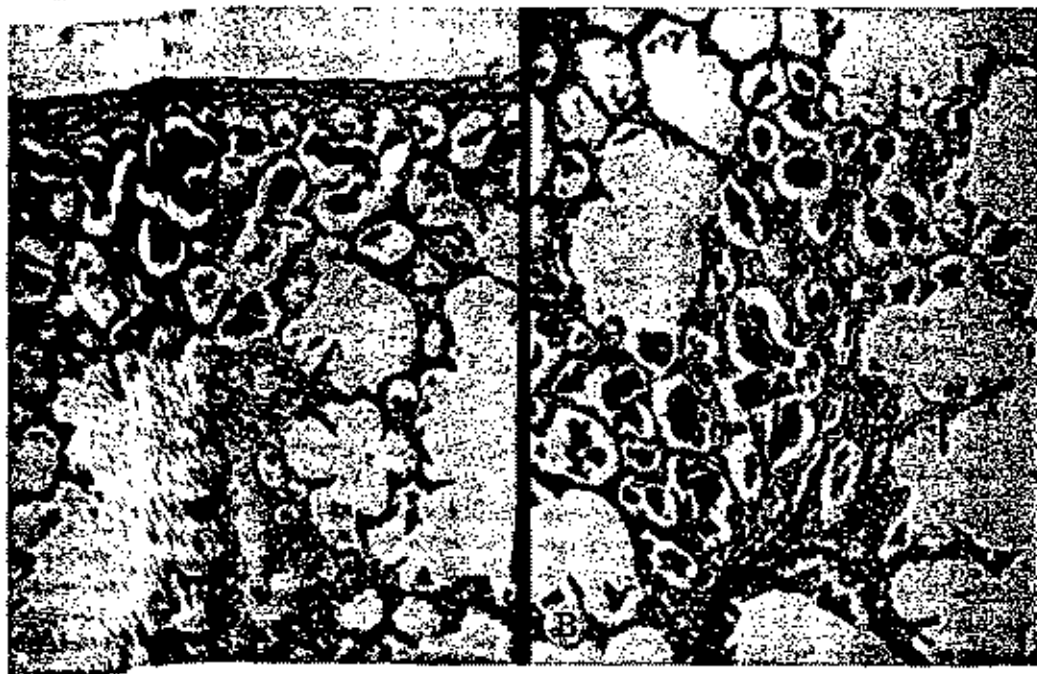


Fig. 1. Inhibitory action of potassium carbonate on quartz: guinea pig, 32-day result. *A*, lung tissue: illustrates marked cellular proliferation, with macrophage catarrh and alveolar wall thickening; no necrosis. *B*, lymph node: macrophage infiltration of medulla, without necrosis or sclerosis.

Fig. 2. Delayed combined effect of quartz and potassium carbonate: guinea pig, 400-day result. *A*, subpleural region with dust-laden macrophages and giant cells trapped in cortical alveoli; note atrophic emphysema. *B*, atelectatic parabronchial zone, with retained intracellular dust in alveoli.



ANTAGONISTIC ACTION OF QUARTZ AND POTASSIUM CARBONATE

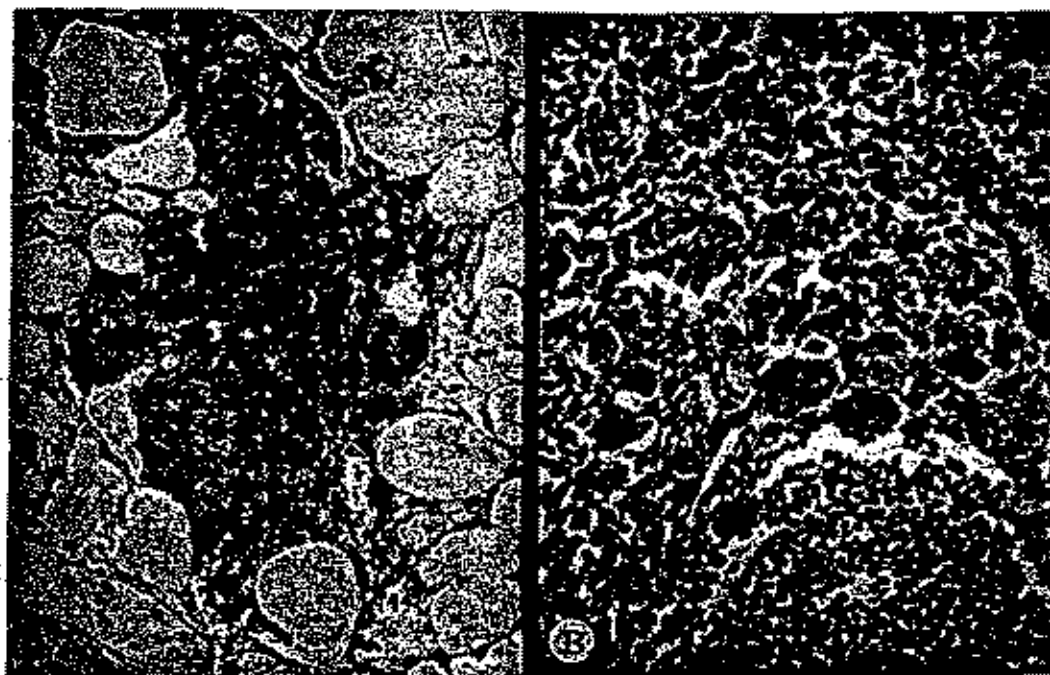


Fig. 3.—Residual lesions resulting from the intratracheal injection of quartz and potassium carbonate in a 3:2 ratio: guinea pig, 575-day result. *A*, lung: parenchymal focus with dust trapped within atrophic alveoli; no residual, regional, cellular, or fibrotic reaction. *B*, lymph node: persisting dust-laden macrophages in medulla, without associated fibrogenesis.

The lymph nodes still showed marked macrophage and giant cell infiltration into the medulla at this stage. Whole islands of such cells were found within distended lymph sinuses (Fig. 3*B*).

Signs of fibrosis could first be discerned in the lungs of this last group of guinea pigs. It was sparsely laid down and mainly perivascular in distribution. Some of the alveolar walls were fibrotic and avascular, and the atrophic emphysema had advanced a little further in some areas. On the whole, however, there were fewer konoiphores in the alveoli.

In the lymph nodes, too, the macrophages had more or less disappeared, leaving behind central collections of opaque pigment.

From these microscopic features it is clear, therefore, that the combination of potassium carbonate with quartz in a 3 to 2 ratio, with a trace of charcoal added, nullified to a large extent the fibrogenic propensity of the quartz and no silicotic nodules

developed, though some diffuse minimal alveolar wall and vascular damage, bronchiolitis, and emphysema persisted.

The peritoneal histological features were in complete conformity with the reaction to transiently irritating foreign substances. In these animals that died of a chemical peritonitis as a result of the introduction of the 10% suspension, the inflammatory reaction was subacute in degree, without any necrosis. The subperitoneal masses which formed in the animals receiving the 7% suspension were unlike those associated with quartz dust, being limited to monocytic and isolated giant cell infiltrations and occasional initial minimal leucocytosis. This benign cellular reaction persisted to the end of the 160th day. The reactions to the 5%, 2%, and 0.5% suspensions of the quartz-potassium carbonate mixture were limited to monocytic infiltration, without giant cell formation or necrosis. These lesions showed no significant regression after 120 days but also gave no indication of aggravation or fibrosis.

COMMENT

While the tissue reaction to this mixture of dusts cannot be classified as completely inert, there is no doubt that the quartz had been inhibited in respect of its most characteristic propensity, i. e., the capacity to provoke fibrosis. To be precise, some fibroblasts were detectable within the cellular lesions at the end of the first month, and fibrosis of a limited degree was discernible in animals at the end of 575 days; but this reaction was no more than what could be found in the presence of so-called inert dust lesions and by no means comparable to the marked sclerosis induced by pure quartz.

The faculty of quartz to bring about focal necrosis was in equal measure suppressed. It is not yet certain whether the fibrogenic propensity of quartz is not perhaps linked to its faculty to bring about cellular death, though a recent study by one of us²¹ suggests that quartz has triple independent cytobiological action, viz., to denature or precipitate tissue ground substance protein, to attract and destroy eosinophile leucocytes, and to attract and cause histiocytes and fibroblasts to proliferate. In the case of the present quartz-potassium carbonate mixture the capacity to attract eosinophile cells was apparently also suppressed, as none were found in the lesions examined.

In designing this experiment Dr. Gardner merely had in mind duplicating an industrial hazard which he had under observation at the time. His surprise at the result was candidly expressed in some of the correspondence on file at the Laboratory. It became immediately apparent to Gardner that the results of the experiment challenged very fundamentally the solubility theory of silicosis and that it possibly favored his own colloidal silica pathogenic concept.

To test out these hypotheses, Gardner proceeded as follows †: A 10% mixture of the various components was suspended in isotonic saline, arnoldized, and then stored in

a Pyrex flask in the icebox for four days. "Soluble" silica was then determined colorimetrically by the phosphomolybdic acid method. The results were as follows:

Component	pH	"Soluble" Silica, Ppm
Complete blend	...	279.1
Quartz 61% and K ₂ CO ₃ 39.1%	1.8	281.1
Quartz 61%	1.4	27.7
K ₂ CO ₃ 39.1%	10.2	51.2

The value of 51.2 for the K₂CO₃ alone probably represents the amount of SiO₂ dissolved from the glass. Subtracting this value from that for the complete blend yields a net "soluble" silica for the latter of 227.9 ppm.

From these results Gardner concluded that the soluble silica theory of silicosis had received a further refutation. From the fact that no fibrosis resulted even after 575 days and the low pH of the mixture, it seemed evident that the quartz and potassium carbonate underwent a more or less permanent combination.

Gardner did not attribute undue importance to the presence of the small amount of charcoal in the mixture in bringing about the inhibitory action. *In vitro* tests had already shown that carbon does not adsorb colloidal silica, the two substances having the same electrical charges.

Gardner also detected that the apparent protection against the action of quartz exerted by the potassium carbonate appeared to be more complete than that produced by aluminum in at least one respect. "In the case of aluminum inhibition, for reasons as yet unexplained, quartz that is transported outside the primary organ of localization seems to leave its inhibitor behind and is free to produce silicosis in the metastatic foci." In the case of the potassium carbonate-quartz mixture, no fibrosis of any consequence developed in either the lungs or the root nodes. However, in one instance (Guinea Pig 20, Table 1) metastatic foci of reaction appeared under the capsule of the liver and spleen. They were remarkably like tuberculosis in their histological features but were obviously caused by the dust. Their occur-

† Gardner, L. U.: Private correspondence, Saranac Laboratory Archives, 1945.

rence reminds one of the hepatic and splenic dissemination described by Ritterhoff* in an abrasive-soap-manufacturing employee.

The results of this experiment shed no further conclusive light on silicotic fibrogenesis in terms of either the surface adsorption theory or the silicic acid polymer concept sponsored by Holt and Yates.¹⁵ However, the persisting low pH obtained in vitro in spite of the admixture of the alkaline potassium carbonate does not negate the possibilities in favor of the polymer theory.

The lack of cellular necrosis revealed by this study may, more than perhaps any other factor, account for the rapid spread and aberrant character of the silicotic reaction in victims of abrasive-soap industrial exposures. If the macrophages laden with quartz and the soda ash in these cases fail to die before being transported to far-distant points, an opportunity is left for subsequent extensive silicotic fibrosis once the chemical factor blocking the biotoxic capacity of the quartz is overcome.

SUMMARY

The problem of the diffuse, sclerosing reaction and the high fatality rate in persons excessively exposed to quartz flour mixed with alkalis is reviewed.

An intratracheal and intraperitoneal injection experiment with a mixture of quartz dust and potassium carbonate in a 3 to 2 ratio is described.

The potassium carbonate effectively inhibited the necrotizing and fibrogenic properties of the quartz.

This result is apparently not brought about by increased solubility of the SiO_2 which is promoted by the K_2CO_3 .

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An Experimental Study of the Effects of Rare Metals on Animal Lungs

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In this paper the results of a series of experiments which I conducted under the direction of the late Leroy U. Gardner, M.D., during 1943 will be reported. The report will be limited to a review of the method and the macroscopically observable results. The analyses of the histopathological reactions are reported separately.*

In all, six metallic substances were studied. These comprise tantalum oxide, tungsten, tungsten carbide and carbon, cobalt, cobaltic oxide, and tungsten carbide and cobalt. As will be apparent, these are all substances which may gesture as potential environmental respiratory hazards in the cemented tungsten carbide industry. The purpose of the study as designed by Dr. Gardner was to establish which particulate metallic component, that may be inhaled in such an industry, could provoke pulmonary lesions.

TECHNIQUE

Dust was introduced into the lungs of the guinea pigs by the intratracheal route. This technique in our hands was performed without general anesthesia. Instead, a 5% solution of procaine hydrochloride (Novocaine) was applied locally by swab to the mucous membranes of the animal's throat. A nasal speculum, modified so that it might be used as a mouth gag, exposed the vocal cords to view. A special 20 gauge, 6 in. needle was passed between the cords and gently inserted

down the trachea to its bifurcation. The suspended dust was then slowly injected into the lungs. The average weight of the animals used was approximately 600 gm. The dosage and the number of injections varied with the dust employed. The injections were usually administered in three equal doses at weekly intervals. The toxic reaction that was manifest between injections usually gave indication as to the size of the dose that should be used. Certain disadvantages attended this method but did not outweigh the advantages. Dosages were, for instance, controlled to some degree and doubtless with greater precision than would have been obtainable with inhalation techniques. However, there was in a few cases some loss of injected material through subsequent coughing. There was also in some instances a tendency to produce localized accumulation of dust, so that even dispersion of the material was not accomplished as certainly as would have been expected had the substance been introduced by means of the inhalation technique. Some hazards also attended this technique. As no general anesthesia was used, it was not always possible to control struggling movements of the experimental animal. Rupture of the lung, with subsequent infection and even death, therefore, sometimes ensued. Of one thing one was always certain, however, namely, that the dust was effectively introduced into the lungs by this method.

RESULTS

In the case of tantalum oxide, tungsten, cobaltic oxide, and a mixture of tungsten as a mouth gag, exposed the vocal cords to view. A special 20 gauge, 6 in. needle was going technique. Unless the product was sup-

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Research Associate, The Saranac Laboratory.

* References 1 to 6.

EFFECTS OF RARE METALS ON ANIMAL LUNGS

plied in a sufficiently fine state of subdivision, attempts were made to obtain 3μ and under sizes by sedimentation in 95% alcohol. In some instances this did not prove possible, and the dusts were introduced as received. The dusts were suspended in isotonic saline in 10% suspension and sterilized by arnoldization (100 C) for one hour. The dosage in each case was 150 mg. administered in three equal quantities at weekly intervals.

Six guinea pigs were used in the study of each dust. An occasional animal died of inter-

TABLE 3.—Pulmonary Effects of Cobaltic Oxide Intratracheal Method

Guinea Pig No.	Days After Last Injection	Died or Killed	Gross Pulmonary Appearance
31	20	K	Large black diffuse firm areas of pigmentation
32	22	D	Pneumonitis with slightly firm, diffuse, or isolated dust areas
33	120	K	Slightly firm circumscribed lesions
34	140	K	Slightly firm circumscribed lesions with black pigmentation
35	260	K	Few large circumscribed and several small foci of dust pigmentation; all are soft

TABLE 1.—Pulmonary Effects of Tantalum Oxide Intratracheal Method

Guinea Pig No.	Days After Last Injection	Died or Killed	Gross Pulmonary Reaction
1	1	D	Congestion and heavy white dust pigmentation
2	4	K	Few soft white circumscribed dust lesions
3	8	K	Several large white soft areas of dust pigmentation
4	12	K	Large white circumscribed dust lesion, only slightly firm
5	16	D	Large white soft circumscribed dust lesion; intercurrent pneumonitis
6	200	K	No dust reaction discernible

current infection, and the remaining animals were killed at 1, 4, 8, and 12 months after the last injection. At autopsy (Tables 1 to 4) the lungs usually exhibited large circumscribed, soft to slightly firm, pigmented lesions. Occasional small discrete foci of pigmentation were widely distributed beneath the visceral

TABLE 2.—Pulmonary Effects of Tungsten Metal Dust Intratracheal Method

Guinea Pig No.	Days After Last Injection	Died or Killed	Gross Pulmonary Reaction
7	20	K	Dark gray, slightly firm circumscribed foci of dust pigmentation
8	120	K	One large soft circumscribed focus of dust reaction
9	140	K	No gross dust lesion present
10	160	K	No gross dust lesion present
11	200	K	Small area of puckering; no pigmentation
12	200	K	Small area of puckering; no pigmentation

pleura. No appreciable temporal change in the gross character of the lesions was noted in these successively killed animals. On the whole, therefore, these four dusts proved to be relatively benign in their biological effects on lung tissue.

In the case of cobalt metal, all attempts to obtain a 3μ and under product by sedimentation in 95% alcohol failed. The dust was, therefore, used as received. The particle size

TABLE 4.—Pulmonary Effects of Tungsten Carbide and Carbon Intratracheal Method—Tungsten Carbide: Carbon Ratio—94:6

Guinea Pig No.	Days After Last Injection	Died or Killed	Gross Pulmonary Reaction
13	20	K	Moderately heavy black pigmentation of diffuse soft localized areas
14	120	K	Large areas of soft black pigmentation
15	140	K	Isolated diffuse areas of soft black pigmentation
16	200	K	Diffuse areas of soft black dust pigmentation
17	200	K	
18	200	K	

range was as follows: particles 5μ and under, 95%; particles 5μ to 10μ , 5%. A few granules measuring up to 30μ were also present. The dust was gradually suspended in isotonic saline by means of a rubber policeman and diluted to 10% suspension. Sterilization was effected by arnoldization (100 C) for one hour.

One dose of 50 mg. and another of 25 mg. were given, respectively, to each of two

TABLE 5.—Pulmonary Effects of Cobalt Metal Dust
Intratracheal Method

Guinea Pig No.	Quantity of Dust Injected, mg.	Injections, No.	Days After Last Injection	Died or Killed	Gross Pulmonary Reaction
20	50	1	1	D	Generally congested
25	50	1	1	D	Acute pneumonitis
28	50	1	1	D	Acute pneumonitis
26	50	1	240	K	No definite dust pigmentation
27	50	1	360	K	Few pleural adhesions; small firm circumscribed dust lesions
29	50	1	360	K	Obstructive pleuritis
27	25	1	2	D	Acute pneumonitis
28	25	1	2	D	
41	25	1	2	D	
40	25	1	19	D	
39	25	1	240	K	One circumscribed black dust lesion
42	25	1	360	K	No dust reaction perceptible
					Pleural adhesions; one moderately large circumscribed lesion and several small foci of dust pigmentation
46	10	2	4	D	Acute pneumonitis
47	10	2	4	D	
48	10	2	6	D	
45	10	2	6	D	
46	10	2	21	D	Acute and chronic pneumonitis
44	10	2	360	K	No gross reaction

series of six guinea pigs. Two doses of 5 mg. each were injected a week apart into a third series of six guinea pigs.

All animals (Table 5) became acutely ill within 24 hours after injection regardless of dosage. Of the first series, which received the 50 mg. dose, three died within 48 hours. Of the three survivors, one was killed eight months and the remaining two one year after the introduction of the cobalt.

Of the second series, which had received the 25 mg. dose, three also died within 48 hours; one died after 19 days. The two survivors were killed, respectively, eight months and one year after the introduction of the cobalt dust.

In the third series, which received two doses of 5 mg. each, all survived the initial dose, but after the second dose five animals died, between the 4th and 11th days. The lone survivor was killed at one year. All animals dying within a few days after injection exhibited an acute pneumonitis, usually extensive. Of the animals surviving this acute initial reaction, those killed at 8 and 12 months presented gross evidence of having

passed through the initial phase, such as pleural adhesions and sometimes obliterative pleuritis. Black pleural dust pigmentation was often visible in the unobscured portion.

The tungsten carbide and cobalt metal dust, which was present in a ratio of 91:9, was studied by means of both the intratracheal and the inhalation techniques. As received, the dust required very little preparation to reduce it to a size of 3μ and less. Sedimentation in 95% alcohol for five minutes was sufficient. The identical intratracheal technique used in the preceding experiments was applied, but three equal doses were administered at weekly intervals, resulting in a total dosage of 150 mg.

There were no intercurrent deaths (Table 6), and the six guinea pigs were killed as planned at 1-, 4-, 8-, and 12-month intervals after the last injection. Macroscopically, the lungs exhibited well-circumscribed linear and diffuse patterns of black pigmentation. All lungs were normally soft, and no appreciable successive change in the character of the lesions was discernible by naked eye during the 12-month period under study.

EFFECTS OF RARE METALS-ON ANIMAL LUNGS

TABLE 6.—Pulmonary Effects of a Mixture of Tungsten Carbide and Cobalt Metal Dust Intratracheal Method—Tungsten Carbide: Cobalt Ratio—91:9

Guinea Pig No.	Days After Last Injection	Died or Killed	Gross Pulmonary Reaction
12	30	K	Large soft circumscribed area of dust reaction
14	120	K	Soft lesions of both linear and diffuse dust pigmentation
15	140	K	Many small soft foci of black pigmentation
16	200	K	Soft foci of black pigmentation
17	200	K	
18	200	K	

For the inhalation experiment, the mixture used was quite different. On the basis of x-ray diffraction-line intensity, it was estimated that the material contained approximately 75% tungsten carbide and 25% cobalt metal. The guinea pigs were exposed to the dust by inhalation in a small dust box, measuring 4 by 2 by 2 ft. This box was equipped with an atomizer for dispensing dust in a dry form. The concentrations were somewhat irregular. During the first 20 days of exposure, moderately high concentrations were maintained, i. e., 250,000,000 to 300,000,000

particles per cubic foot of air, or approximately 8,800 to 10,600 particles per cubic centimeter. The particles were 0.5 μ to 2.0 μ in size. During the second exposure, of 15 days, the concentrations were appreciably reduced, to approximately 80,000,000 particles per cubic foot of air, i. e., approximately 2,800 particles per cubic centimeter.

Twenty guinea pigs were exposed to this dust by inhalation eight hours daily for five and one-half days a week. After approximately 20 days (Table 7), five of the animals had died, and dust exposure was discontinued on this 20th day. Three more animals died on the following two days. As the condition of the surviving 12 animals improved rapidly after cessation of the first dust exposure period, they were again exposed daily to the dust after five days in normal air but at appreciably lower concentrations. After 10 days of this second exposure, three more animals had died and a further two died on the 13th day. After 15 days, this second, the final, exposure was, therefore, terminated. Two animals died, however, one day later. The remaining four animals were killed as follows:

TABLE 7.—Pulmonary Effects of Tungsten Carbide and Cobalt Metal Inhalation Method—Tungsten Carbide: Cobalt Ratio—3:1

Guinea Pig No.	Days of 1st Exposure Period	Days in Normal Air After 1st Exposure Period	Days of 2d Exposure Period	Days in Normal Air After 2d Exposure Period	Died or Killed	Gross Pulmonary Lesions
12	20	1	15	1	D	Acute pneumonitis
13	20	1	15	1	D	
14	20	1	15	1	D	
15	20	1	15	1	D	
16	20	1	15	1	D	
17	20	1	15	1	D	Acute pneumonitis
18	20	1	15	1	D	
19	20	1	15	1	D	
20	20	1	15	1	D	
21	20	1	15	1	D	
22	20	1	15	1	D	Dust pigmentation and residual pneumonitis
23	20	1	15	1	D	
24	20	1	15	1	D	
25	20	1	15	1	D	
26	20	1	15	1	D	
27	20	1	15	1	D	Acute pneumonitis and faint dust pigmentation
28	20	1	15	1	D	
29	20	1	15	1	D	
30	20	1	15	1	D	
31	20	1	15	1	D	
32	20	1	15	1	D	Faint diffuse dust pigmentation
33	20	1	15	1	D	
34	20	1	15	1	D	
35	20	1	15	1	D	
36	20	1	15	1	D	
37	20	1	15	1	D	Dust pigmentation; pericarditis; pleural effusion
38	20	1	15	1	D	
39	20	1	15	1	D	
40	20	1	15	1	D	
41	20	1	15	1	D	
42	20	1	15	1	D	Hemorrhagic, firm, rubbery, faintly pigmented lesions
43	20	1	15	1	D	
44	20	1	15	1	D	
45	20	1	15	1	D	
46	20	1	15	1	D	

two at 181 days and two at 585 days after termination of the dust exposure.

All the animals which had died from natural causes showed acute pneumonitic pulmonary consolidation. Those guinea pigs which survived and were killed at 6 and 19 months, respectively, showed faint diffuse dust pigmentation.

COMMENT

Judging by the mortality rates and the nature of the gross pulmonary reactions, it is evident from this study that tantalum oxide, particulate tungsten metal, cobaltic oxide, and tungsten carbide and carbon are relatively inert when introduced intratracheally into guinea pigs. Cobalt metal, on the other hand, proved intensely irritating to pulmonary tissue, and when cobalt was combined with tungsten carbide, the toxic property of the cobaltic component predominated.

SUMMARY

Experiments are described in which six metallic substances, to which personnel may be exposed in the cemented tungsten carbide industry, were introduced intratracheally in guinea pigs.

Four of these components proved to be relatively inert (tantalum oxide, tungsten, tungsten carbide and carbon, cobaltic oxide).

Two of the components proved to be toxic (cobalt, tungsten carbide and cobalt).

These experiments were conceived and planned by the late Leroy U. Gardner, M.D. My thanks are due also to G. W. H. Schepers, M.D., D.Sc., Director of The Saranac Laboratory, who suggested the writing of this report and helped with its preparation.

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The Biological Action of Tantalum Oxide

Studies on Experimental Pulmonary Histopathology

G. W. H. SCHEPERS, M.D., D.Sc., Saranac Lake, N. Y.

The method followed in this study has been described by Delahant,¹ and the present account will be limited to a description of the microscopic changes associated with retention of the 3 μ and smaller tantalum oxide dust particles in the lung tissues of those guinea pigs which did not succumb to intercurrent infection. Whether the death of the latter group of animals was related to the introduction of the foreign agent into the lung tissue could not be excluded with certainty, but the over-all benignity of the reaction rather suggests that the pneumonic infection was purely coincidental.

ACUTE RESPONSE

Within one month, the intratracheal introduction of the 10% suspension of tantalum oxide dust (100 mg.) produced focal reactions whose severity apparently was quantitatively related to the topographic disposition of the metallic oxide. An almost universal minor tissue response was also discernible.

The least change observed comprised an acute to subacute bronchitis and bronchiolitis, manifesting itself primarily as epithelial proliferation and desquamation, mucosal hyperemia, and a peribronchitis (Fig. 1A). Pigment granules could be traced to the adventitial layers of the bronchi where plasma cell reaction to these granules was present at some sites.

In the lung parenchyma, the minimal reaction was found to consist of alveolar epithelial proliferation, with macrophage carters. Some of these cells were seen to

have engulfed the metallic particles, but most of the dust lay free in the alveoli. There was a tendency toward subpleural or cortical localization of the pigment and of the cellular reaction (Fig. 1B).

A minimal degree of vesicular atrophic emphysema and perivascular deposits of dust-filled macrophages occurred (Fig. 1C). The blood vessels generally were found to be markedly distended, and the alveolar capillaries were engorged. The lymphatic system seemed to escape almost entirely, but more generally there was some central pigment deposition and hyperemia in the hilar nodes.

From this type of minor response, reactions varied through all nuances of severity to a marked type of peripigmental interstitial cellular pneumonitis, with associated sanguineous alveolar exudate in some areas. Copious pigment collections were found trapped among the proliferated cells, which consisted for the greater part of endothelioid and plasma cells. Over relatively large areas the alveolar walls were therefore markedly thickened (Fig. 1D).

In isolated areas, the concentration of pigment was exceedingly dense, and there was some attempt at encapsulation and organization of such deposits. Only in sites such as these was any collagen found.

These were the changes which were to be seen within a month after direct exposure of pulmonary tissue to the metallic oxide.

RESIDUAL LESIONS

A year later the whole picture had changed, and there was almost complete recovery of the acute process, though residual sequelae persisted. At some sites some very minimal cellular reaction persisted, mostly in relation to the residual presence of macrophages containing phagocytosed metallic particles. The main cell types were plasma

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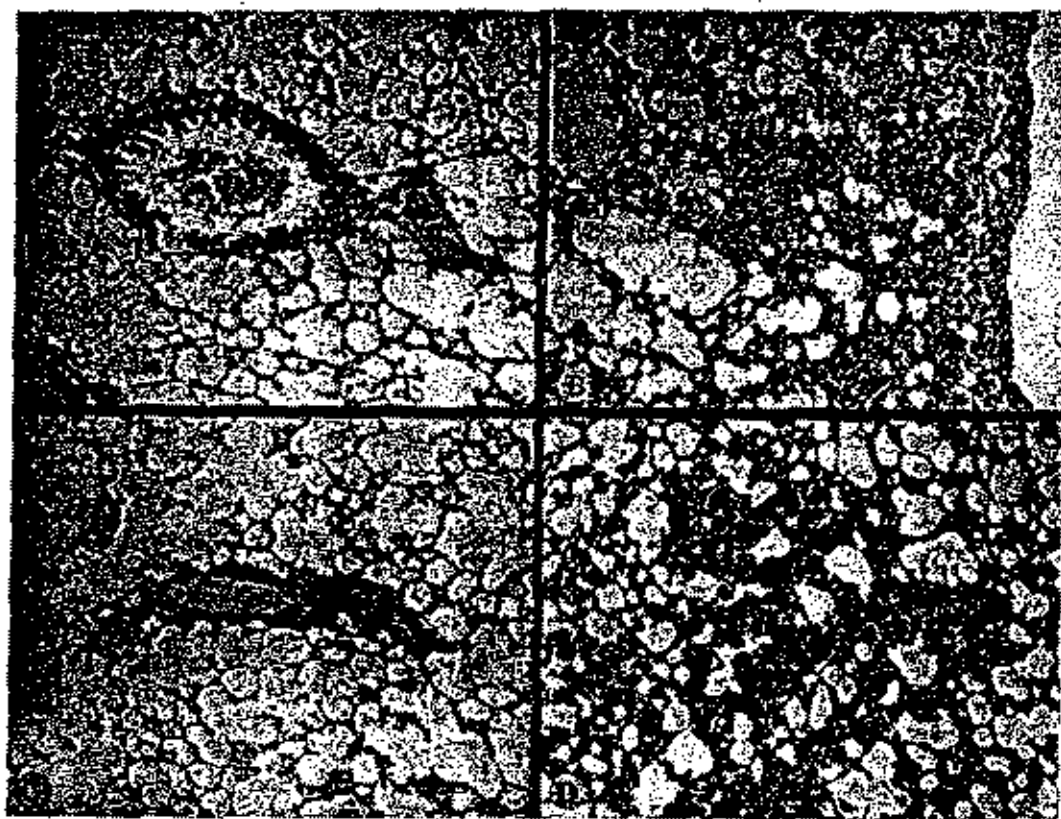


Fig. 1.—Pulmonary reaction to tantalum oxide—guinea pig lung: one month. *A*, bronchitis with epithelial desquamation and peribronchial cellular accumulations. *B*, subpleural pigmentation and interstitial pneumonitis. *C*, perivascular cellular accumulation and pigmentation. *D*, interstitial pneumonitis around trapped pigment in atelectatic alveoli.

cells, eosinophiles, and proliferated alveolar epithelial cells. No fibrocytes were seen.

Isolated small pleural plaques were discovered (Fig. 2*A*). These comprised focal accumulations of proliferated mesothelial cells with centrally trapped metallic particles.

The bronchi and bronchioles appeared to have undergone almost complete healing, but there was slight hyperplasia of the epithelium, even though the ciliated surface had been restored (Fig. 2*B*).

Perhaps in consequence of earlier sustained bronchial or bronchiolar damage, foci of hypertrophic emphysema were found (Fig. 2*C*), a feature which was superimposed upon the atrophic emphysema already apparent within a month.

Most of the pigment had been removed from the lung tissue by the end of the first year, and some of it could be found in the

lymph nodes. No reaction was discernible around it (Fig. 2*D*).

COMMENT

The pulmonary reaction to tantalum oxide dust introduced as a 10% suspension was found to be essentially benign, involving transient bronchitis, interstitial pneumonitis, and associated hyperemia. Residual sequelae of any consequence comprised focal hypertrophic emphysema and organizing pneumonitis around excessive metallic deposits.

The fact that there was so little residual effect after a year does not yet warrant classification of this dust as innocuous. It should be emphasized that the result of repeated introduction of the substance by inhalation may well prove to be considerably more pathogenic than would at first seem probable on the basis of the lack of a

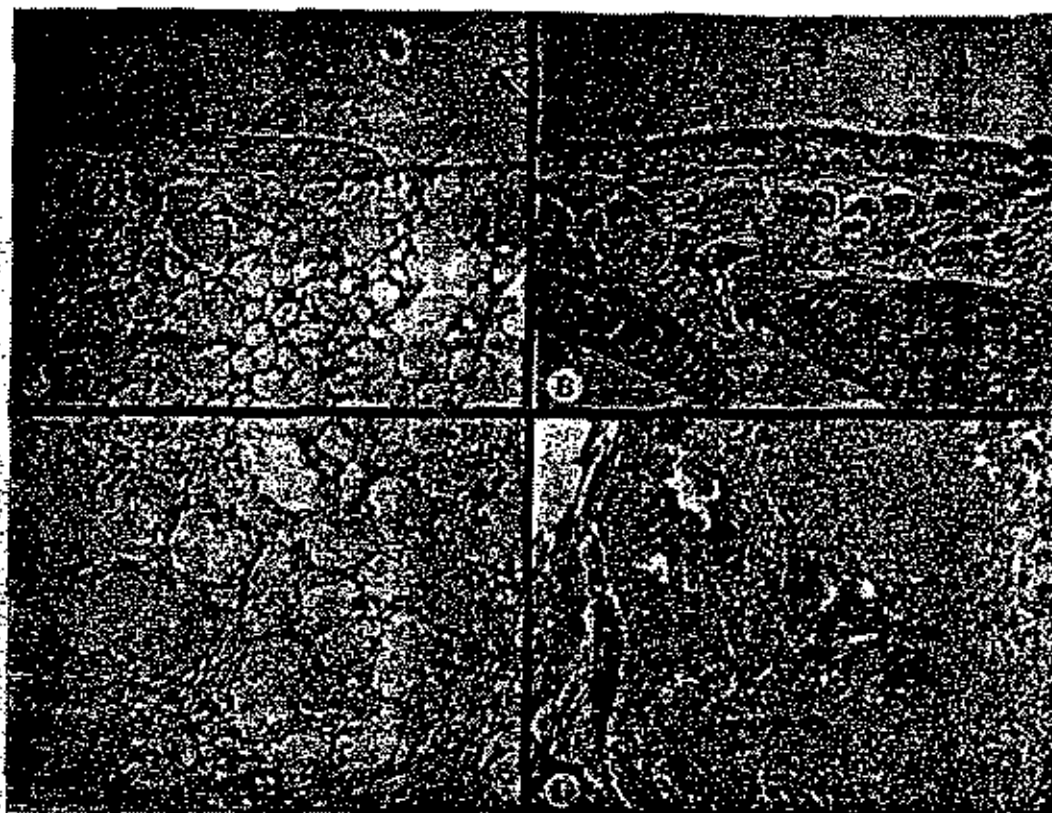


Fig. 2.—Pulmonary reaction to tantalum oxide—guinea pig lung: one year. A, epipleural fibrocellular plaque around collection of pigment. B, bronchial mucosa showing minimal residual submucosal and adventitial cellular infiltration and minimal basal cell epithelial hyperplasia. C, local hypertrophic emphysema due to overdistention of alveolar ducts. D, pigment accumulation in the cortex of a hilar lymph node without any significant cytological response around it.

chronic fibrotic response. The minor bronchial epithelial hyperplasia deserves further attention, and the occurrence of hypertrophic focal emphysema may be significant, as such a result is not commonly found in association with experimental pulmonary dust lesions.

The literature on the subject of tantalum as a noxious agent is refreshingly silent, perhaps because the metallic dust is truly inert but more probably because human exposures have been very limited. Indirect reference is made to tantalum by Miller, Davis, Goldman, and Wyatt² and by Sjöberg.³ Certainly, it seems likely that in industries where tantalum oxide may be encountered as an atmospheric pollutant there will still be for some time to come other associated environmental hazards of more material consequence.

SUMMARY

Tantalum oxide when introduced into the guinea pig lung by the intratracheal technique produces transient bronchitis, interstitial pneumonitis, and hyperemia with residual focal hypertrophic emphysema and organizing pneumonitis around metallic deposits. The dust is nonfibrogenic.

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The Biological Action of Cobaltic Oxide

Studies on Experimental Pulmonary Histopathology

G. W. H. SCHEPERS, M.D., D.Sc., Saranac Lake, N. Y.

As described by Delahant,¹ the cobaltic oxide dust was introduced in three weekly doses of 50 mg. as a 10% solution. Observations were made at 1-, 4-, 8-, and 12-month intervals after the last injection.

ACUTE REACTION

The effective introduction of this metallic oxide into the guinea pig lung provokes within a month a subacute peribronchial cellular proliferation and focal pneumonitis which is confined to the area of pigment deposition. Occasional bronchioles show epithelial damage, but for the most part the only change consists of mucosal plasma cell and eosinophile infiltration.

The parenchymal foci of reaction vary in character in accordance with the amount of dust deposited. In some areas, the cellular reaction is disproportionate to the amount of dust present (Fig. 1A). In others, the cobaltic oxide particles are massed together. At such sites (Fig. 1B), by far the greater proportion of these oxide particles are as yet extracellular. Rarely an alveolar macrophage may be observed to be in the process of engulfing such granules, and many particles are clearly lodged within the thickened alveolar walls. The dominant cell types appear to be plasma cells and macrophages with occasional eosinophiles. The alveolar walls are relatively broadened near the focal dust deposits but are quite normal elsewhere. Conspicuous perivascular cellular cuffs surround the smaller arterioles.

The pulmonary lymphoid tissue has undergone regional hyperplasia, with the extension

of columns of lymphocytes into the abutting alveolar walls. Eosinophile cells may be intermixed with these lymphocytes. The hilar nodes show diffuse hyperplasia but only scanty pigmentation.

CHRONIC RESPONSE

Twelve months after the introduction of the cobaltic oxide into the lung, the foregoing changes have been largely reversed. Oxide particles may still be aggregated together into focal intra-alveolar accumulations, but now they are entirely contained within clusters of large koinophores (Fig. 2A). There is now but insignificant residual tissue reaction to the presence of these foreign substances and no eosinophilia. Nonpigmented macrophages are scarce, and there are no giant multinucleated cells. At isolated sites, typical clusters of hyperinflated alveoli occur. This type of hypertrophic emphysema appears to be the only significant residual lesion provoked by the cobaltic oxide. The bronchial epithelium and mucosa are restored to almost complete normality, but slight adventitial cellular accumulations persist (Fig. 2B).

The lymphoid tissue, though still abundant, has reverted once more to circumscribed spherical nodes. The hilar nodes show abundant central pigment accumulations but no fibrosis or endothelial hyperplasia.

COMMENT

The essential point established by this study is that cobalt has an effect on animal tissue when introduced into lung tissue as a metal totally different from its effect when introduced as an oxide. Harding² has emphasized the relatively toxic effect of cobalt metal when introduced into animal lungs and has recorded symptoms and x-ray signs in men industrially exposed to cobalt pow-

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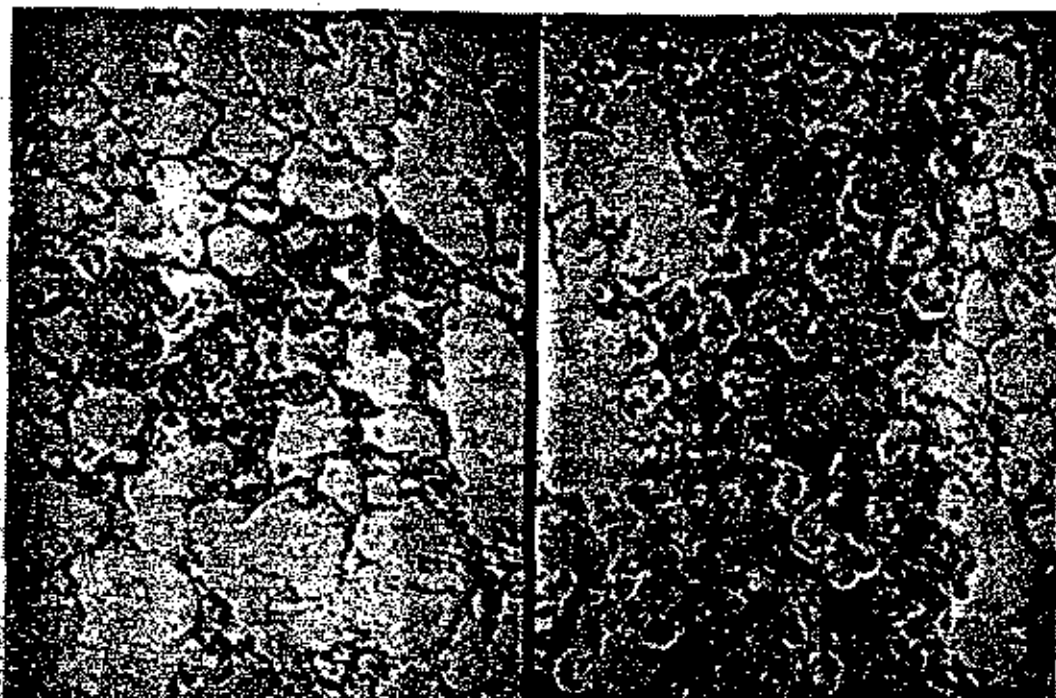
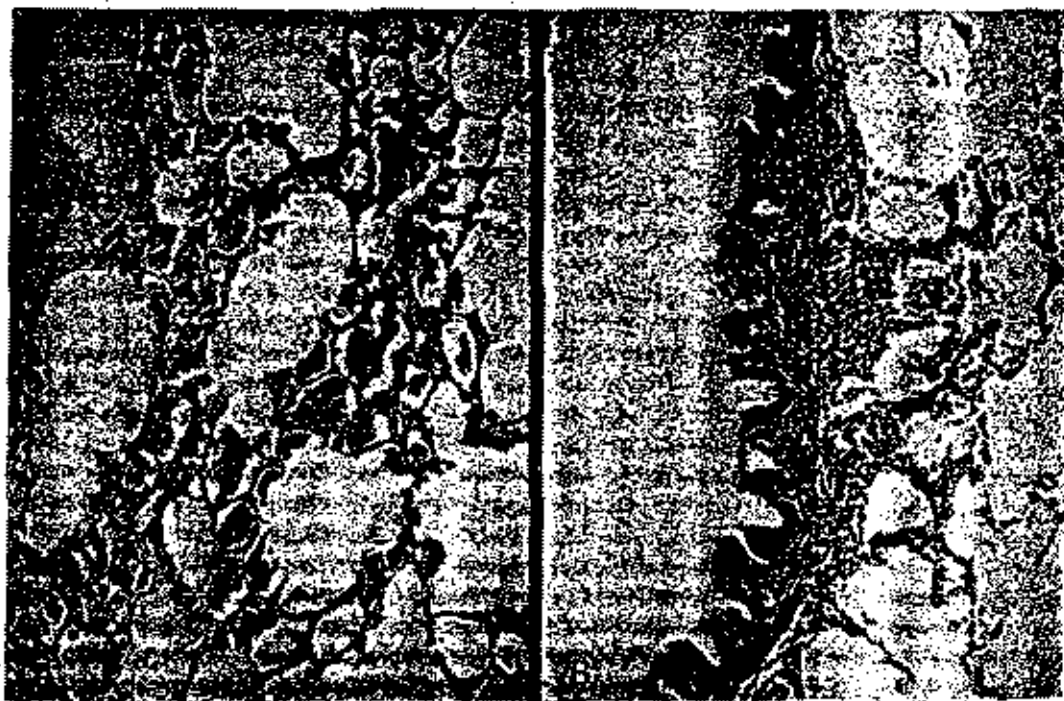


Fig. 1.—Reaction of pulmonary tissue to cobaltic oxide—guinea pig lung: one-month result. *A*, focus of alveolar wall cellular proliferation and macrophage catarrh, with minimal pigment deposition. *B*, maximal focal pigment aggregation, with incipient phagocytosis and parenchymal reaction.

Fig. 2.—Reaction of pulmonary tissue to cobaltic oxide—guinea pig lung: one-year result. *A*, residual focal metallic retention in pulmonary alveoli, without any associated alveolar wall reaction. *B*, bronchial wall, showing mild persistent epithelial hyperplasia and adventitial round-cell infiltration.



der. He has referred to the fact that, while cobalt has a low solubility in isotonic saline, its solubility in plasma is 500 times greater. Fairhall, Castberg, Carrozzo,³ and Brinton⁴ and Fairhall, Keenan, and Brinton⁴ have been unable to confirm the marked toxicity of either cobalt metal or the oxide, although they acknowledge the occurrence of upper respiratory tract symptoms in persons exposed to these substances. It is possible that cobalt metal may prove the more toxic substance because of the cobaltous ions which may be released when it comes into contact with body fluids, whereas cobaltic oxide is likely after introduction into the body to lead to the formation of hydroxyl groups.

This subject needs further study in view of the increasing use of cobalt as an industrial bonding agent and with particular reference to the Schneeberg problem in connection with which Weber,⁵ among others, has incriminated cobalt as a possibly significant factor in the high incidence of lung cancer. No evidence in favor of the latter theory has been produced by the present study on cobaltic oxide.

SUMMARY

Intratracheal introduction of 150 mg. of cobaltic oxide produces a focal and peribronchial, transient, subacute, inflammatory reaction which becomes virtually completely reversed within one year. On this evidence, cobaltic oxide may be classified as a doubtfully toxic respiratory hazard.

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The Biological Action of Particulate Cobalt Metal

Studies on Experimental Pulmonary Histopathology

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The primary purposes of this study were to confirm the acute toxicity of particulate cobalt metal and to determine what chronic lesions ensued in animals which survived the intratracheal introduction of the dust. The latter objective was partially interfered with because of the high initial mortality rate

described by Delahant.¹ However, sufficient animals survived the total experiment to warrant some observations on the acute as well as the subacute and chronic reactions. For descriptive purpose, a distinction will be drawn between the reactions to the 50 mg., 25 mg., and 10 mg. doses.

RESPONSE TO 50 MG. DOSE OF PARTICULATE COBALT METAL

The immediate response of the guinea pig lung to the intratracheal injection of 50 mg. of cobalt metal particles is the appearance of marked pulmonary edema, with moderate alveolar wall hyperemia (Fig. 1A). Very

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Fig. 1.—Acute pulmonary tissue reaction to 50 mg. dose of particulate cobalt metal—guinea pig: 24 hours. A, hemorrhagic pulmonary edema and capillary hyperemia. B, hilar lymph node showing some hyperemia and edema.



little of the foreign substance is to be seen in the pulmonary parenchyma, and most of it is to be found in the bronchi and bronchioles surrounded by cells and serum fibrin. The air passages show epithelial desquamation. Hyperemia and edema also affect the hilar lymph nodes (Fig. 1B).

The dominant feature of the residual sub-acute response after eight months is a perivascular diffuse cellular infiltration with marked prominence of eosinophile cells (Fig. 2A), which make their appearance in large numbers within the pulmonary alveoli, in close proximity to veins. Some measure of alveolar wall and perivascular infiltration is present, and isolated foci of subpleural eosinophile granuloma formation may be found (Fig. 2B). Regional obliterative bronchiolitis, with peribronchiolar fibrosis, and arteriolar spasm are present as alarming features (Figs. 2C and D). Small eosinophile granulomata may also be seen.

At 12 months the chronic residua have taken a quite new form. In relation to the sites of cobalt metal deposition, there now are areas of quite considerable fibrocellular infiltration. Where these lie in juxtaposition to bronchi, there may be regions of marked cystic dilatation of epithelialized alveolar spaces, and these foci amount to an adenomatosis (Fig. 3A). Isolated clusters of multinucleated giant cells may occur in relation to massed pigment deposits (Fig. 3B). The bronchial epithelium has partly recovered and is hyperplastic, but foci of chronic inflammatory infiltration of the mucosa may persist (Fig. 3C). No active pneumonitic areas were found at this stage, but there are foci of abundant koinophore infiltration of alveolar walls.

The lymphatic tissue shows no sign of reaction comparable with that in the lung. The hyperemia of the hilar lymph nodes previously noted has receded, and there is now slight diffuse central fibrosis (Fig. 3D).

RESPONSE TO 25 MG. DOSE OF PARTICULATE COBALT METAL

Halving the concentration of the cobalt appears to have some influence in reducing the degree of pulmonary edema which ensues

as an acute reaction; the edema does not occur in the same degree or so uniformly as with the 50 mg. dose (Fig. 4A). There is also less hyperemia. Macrophages commence to appear in the alveolar spaces and gather up some of the metal particles. Many such cells develop conspicuous vacuoles. Eosinophile cells already tend to make their appearance at this stage.

Simultaneously, there is considerable bronchial and bronchiolar catarrh, with extensive areas of epithelial desquamation (Fig. 4B). Foci of hypertrophic emphysema may also be present. There is plasma cell infiltration of the bronchial submucosa at such sites and some local hyperemia.

Eight months later, healing has proceeded further than was the case with the 50 mg. cobalt metal dose and a comparable lapse of time. The residual disturbances comprise a measure of proliferation of the lymphoid tissue, especially around smaller blood vessels, but with little tendency to extension of the reaction into the adjacent alveolar walls. There is also quite considerable eosinophile infiltration, but no tendency to giant cell formation. The bronchial mucosa and epithelium have been fairly successfully and universally restored to normality and may be somewhat hypertrophic at some points. Lymph nodes show slight central endothelioid hyperplasia.

RESPONSE TO 10 MG. DOSE OF PARTICULATE COBALT METAL

When the cobalt is introduced in two successive doses of 5 mg. each, the acute reaction of the pulmonary tissue is considerably less violent. Once more, however, the immediate response is an edema which is, however, less diffusely distributed and tends to predominate in the peribronchiolar regions. There is markedly less of the tendency to diffuse alveolar wall hyperemia seen with higher concentrations.

Within four days much of the exudate has commenced to disappear, and the alveoli are now overtaken by multiple dust-laden macrophages, with occasional multinucleated giant cells among them (Fig. 5A). At isolated

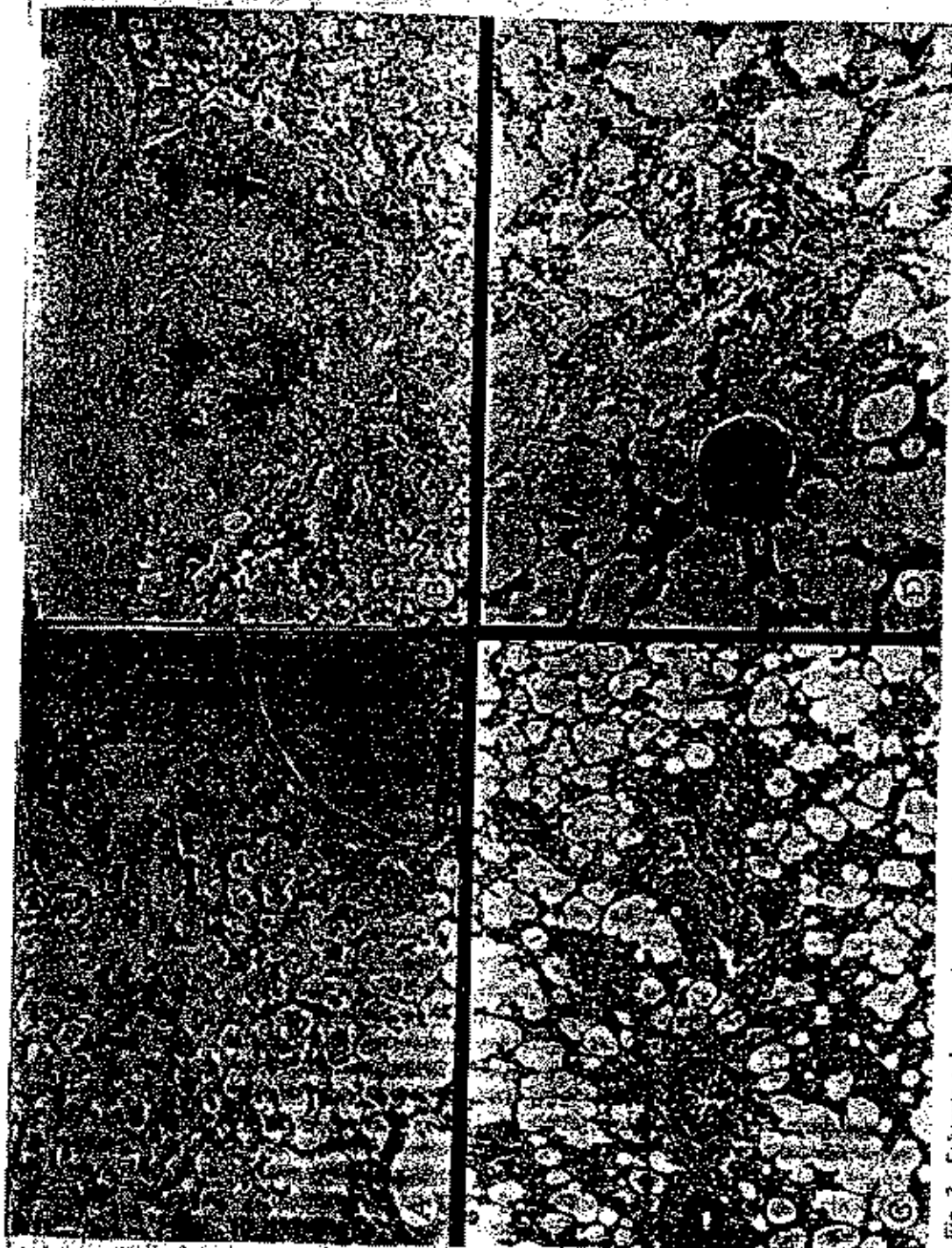


Fig. 2.—Subacute pulmonary tissue reactions to 50 mg. dose of particulate cobalt metal—guinea pig; eight months. *A*, eosinophilic catarrh of alveoli. *B*, subpleural eosinophilic granuloma. *C*, bronchiolitis obliterans and interstitial pneumonia. *D*, focal peribronchiolar fibrosis.

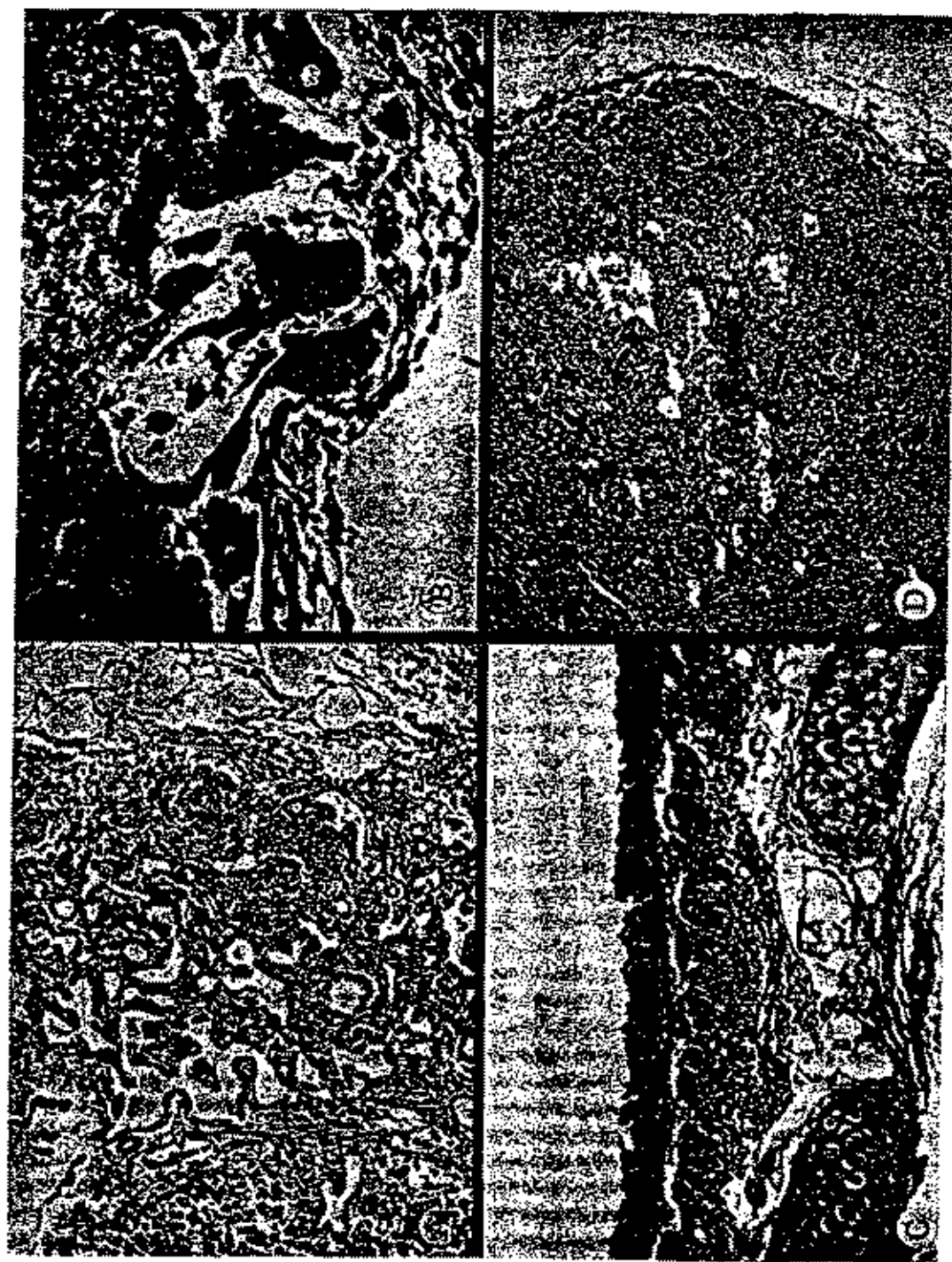
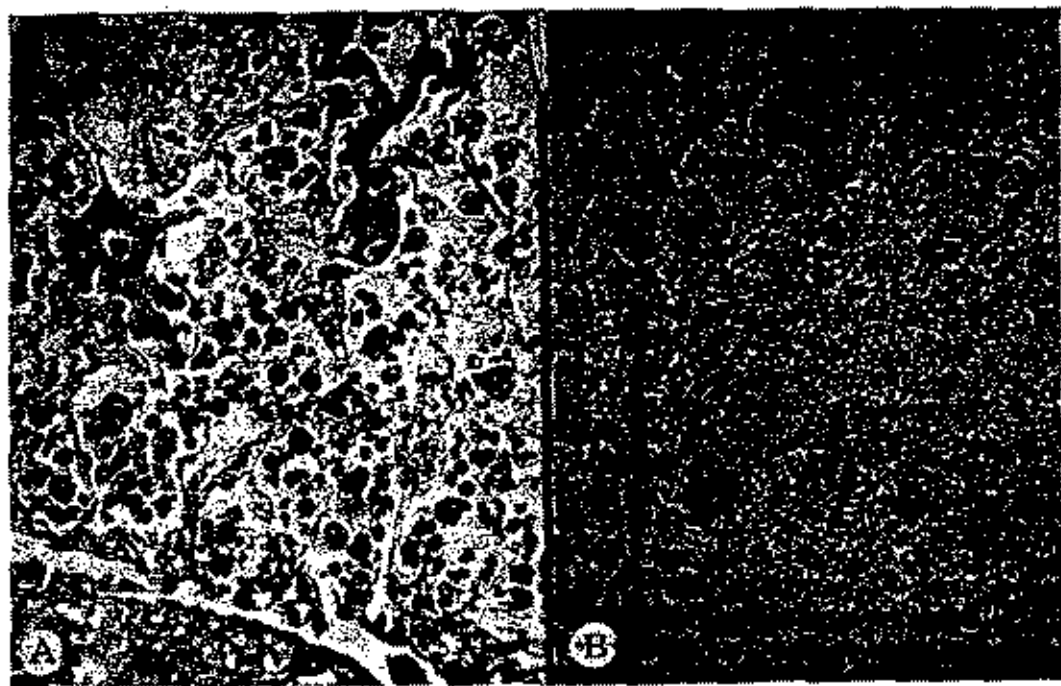


Fig. 3.—Chronic pulmonary tissue reaction to 50 mg. dose of particulate cobalt metal—guinea pig 12 months. *A*, adenomatous expansion of epithelialized alveoli with interstitial foci of cobalt metal. *B*, giant cell reaction in relation to massed accumulation of cobalt particles. *C*, bronchial mucosa showing regenerating epithelium, thickened basement membrane, plasma cell infiltration. *D*, lymph node with minimal medullary endotheloid hyperplasia.



Fig. 4.—Acute pulmonary tissue reaction to 25 mg. dose of particulate cobalt metal—guinea pig: 48 hours. *A*, hemorrhagic edema and focal hypertrophic emphysema. *B*, bronchiolitis with epithelial desquamation.

Fig. 5.—Acute pulmonary tissue reaction to 10 mg. dose of particulate cobalt metal—guinea pig: four days. *A*, macrophages mopping up residue of the exudate of the acute reactive phase. *B*, cellular focus with persisting exudate and incipient organization.



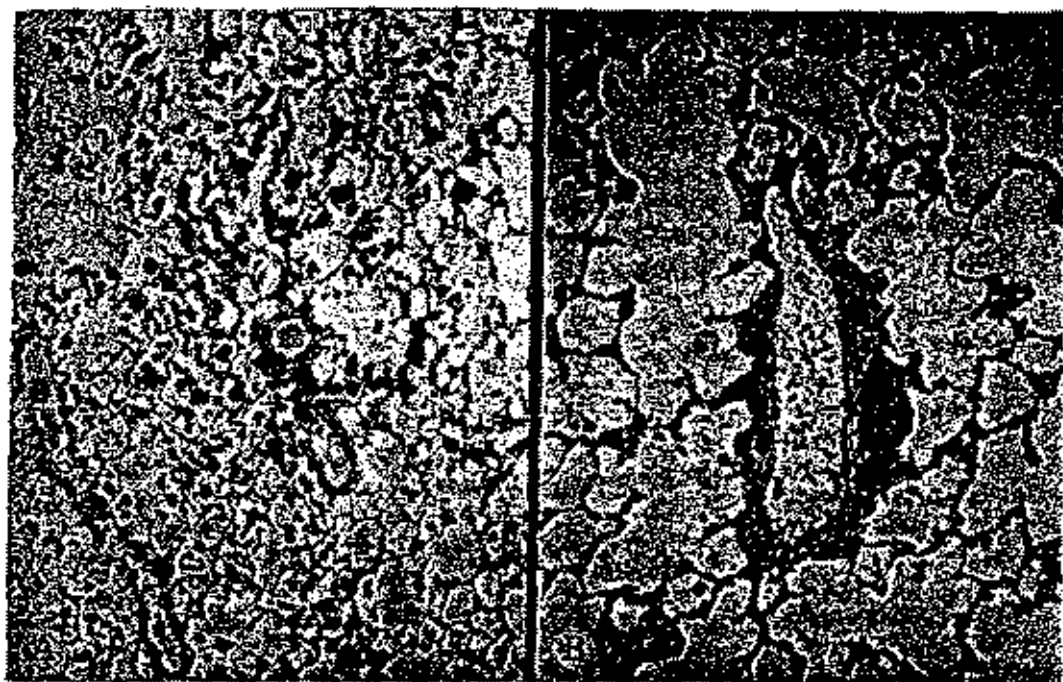


Fig. 6.—Chronic pulmonary tissue reaction to 10 mg. dose of particulate cobalt metal—guinea pig: 12 months. *A*, persisting masses of metallic particles within alveoli without significant tissue reaction around them. *B*, perivascular cellular cuff and atrophic emphysema.

foci the lymph nodes have proliferated, and polymorphonuclear cells invade the alveoli. Numerous distended capillary loops may occur within these inflammatory foci (Fig. 5*B*). The bronchial mucosa does not show any significant signs of injury.

The regional lymph nodes present a measure of hyperemia and lymphoid hyperplasia.

The lesions initially provoked by the 10 mg. dose of cobalt metal are no longer demonstrable in the guinea pig lung by the end of 12 months. At many sites masses of cobalt particles may be found within the alveolar spaces without any obvious tissue reaction in relation to them (Fig. 6*A*). At isolated points some residual focal cellular aggregation persists, and in some of these areas occasional multinucleated giant cells may be found. Some perivascular cellular aggregations may be seen, and a tendency toward diffuse alveolar membrane fibrosis is present. At various regions some atrophic vesicular emphysema may be observed (Fig. 6*B*).

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Around larger blood vessels there may be considerable fibrotic change. The bronchial mucosa is restored to normality or may be a little hypertrophic. The pulmonary lymphoid tissue is once more undisturbed, though perhaps a little more abundant than usual.

COMMENT

The chemical pneumonitis which occurs in response to the introduction of particulate cobalt metal into the lung tissue of the guinea pig is clearly shown by this brief study to be a function of dosage and possibly due to the release of cobaltous ions. The untoward reaction to the second intratracheal injection of 5 mg. of cobalt metal particles in animals which had survived a first dose of 5 mg. may have to be explained on an allergic basis, which is perhaps likely in view of the known propensity of cobalt to cause cutaneous sensitization and conjunctivitis (Fairhall and associates²).

The high predominance of eosinophile cells in the subacute lesion perhaps signifies a di-

BIOLOGICAL ACTION OF PARTICULATE COBALT METAL

rect chemotropism. The lack of an alveolar wall cellular reaction constitutes a further distinctive feature. The metal is nonfibrogenic and does not provoke a chronic lesion in the regional lymph nodes.

Tolerance to the presence of the cobalt metal appears to develop in animals surviving the least dose. This may reflect either a state of biological balance or may be due to stabilization of the physicochemical behavior of the metal particles after prolonged residence in body fluids. Possibly this cobalt has changed to cobalt oxide, which has already been shown to be inert as a pulmonary irritant (Schepers *).

Of all the chronic responses, the incipient adenoma formation appears to be the most spectacular, particularly if it is recalled that cobalt metal is an integral component of the atmospheric substances inhaled by the miners at Schneeberg, long well known as a center of occupational lung cancer production. However, there is already much epidemiological doubt concerning the role of cobalt in occupational pulmonary carcinogenesis, as high neoplasm rates have not been reported from other sites where cobalt is mined, such as Canada (Cobalt City), Belgian Congo (Katanga), Norway (Skuterud), France (Allemont), or Czechoslovakia (Dobschina).

Powdered cobalt metal has in recent years been extensively employed as a bonding material in the manufacture of hard cutting tools, and respiratory symptoms and abnormal radiograms have been reported among men exposed to such powder. Harding * has previously experimentally demonstrated the acute irritant action and hyperemia provoked by cobalt metal powder when introduced as a 5% suspension into the rat and hamster lung or peritoneum. The marked damage to capillaries has been ascribed to the great solubility of the cobalt metal in plasma, which is 500 times higher than its solubility in saline. Cobalt, along with tungsten and titanium, has

recently been incriminated as a cause of fatal interstitial fibrosis in a Swedish metal worker.*

It is possible, too, that cobalt may have a tissue-specific effect for the lung. It is known, for instance, that it is not orally unduly toxic, and its beneficial influence on erythropoiesis has been proved in numerous experiments, has been applied in the therapy of human anemia, and has been suspected as a cause of polycythemia vera in some instances. The outpouring of eosinophile cells may in a small measure reflect this capacity of cobalt to cause proliferation of the hematon system.

SUMMARY

Particulate cobalt metal is an acutely irritating substance when introduced into guinea pig lungs in 50 mg. and in 25 mg. doses.

A single 5 mg. dose is not lethal, but repetition of such a dose proves to be so.

Tolerance to cobalt metal may develop after the initial acute reaction has been overcome.

The greatest damage caused by the cobalt metal is the obliterative bronchiolitis.

A single instance of bronchial adenomatosis resulted from prolonged focal retention of cobalt metal particles.

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The Biological Action of Particulate Tungsten Metal

Studies on Experimental Pulmonary Histopathology

G. W. H. SCHEPERS, M.D., D.Sc., Saranac Lake, N. Y.

Tungsten carbide has already received considerable attention as a causative agent of the respiratory symptoms in workers in the cemented tungsten carbide tool industry.* A measure of animal experimentation has also been conducted on the final product.† It does not appear, however, that either the tungsten metal itself or the tungsten mixed with carbon prior to the high-frequency vacuum furnace treatment in an atmosphere of hydrogen, which is needed to produce the carbide, has been studied for its biological action on animal lung tissue, though some information exists concerning the pulmonary lesions attributable to tungsten ores, such as wolframite and scheelite.‡ This account, amplifying the observation by Delahant,§ may, therefore, serve partially to fill in this scientific hiatus.

ACUTE REACTION TO PARTICULATE TUNGSTEN

The essential and immediate lesion provoked in the lung through the intratracheal introduction of 150 mg. of tungsten dust in three equal doses consists of an interstitial cellular proliferation in relation to entrapped particles. At most sites the alveolar walls are moderately thickened, but at isolated foci an almost solid cellular mass may result.

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Director, The Saranac Laboratory.

* References 1 and 2.

† References 3 and 4.

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The latter are more usually found near the lung surface (Fig. 1A). Where this type of cortical response is most marked, adjacent alveoli are often charged with fine metallic particles; hence it may be presumed that there is a quantitative relation between the regional concentration of particles and the severity of the pneumonitis.

Between these foci of more marked reaction, the lung parenchyma does not show too severe a response, but there is a considerable amount of macrophage catarrh into the alveoli. Numerous foci of perivascular cellular reaction may also be found (Fig. 1B).

The bronchi and bronchioles show some slight inflammatory change consisting chiefly of mucosal hyperemia. Some bronchioles may also be partly or wholly obliterated through encroachment of adjacent inflammatory processes.

Lymphoid tissue shows no response to the presence of the tungsten in the lungs, nor do the hilar nodes harbor any microscopically visible quantities of the particles.

CHRONIC RESPONSE TO PARTICULATE TUNGSTEN

After the passage of a whole year, one finds that this relatively innocuous seeming lesion has not vanished completely, as was the case with 10% tantalum oxide.¶ Some unfavorable residua, such as persistent focal interstitial cellular infiltration in relation to retained pigment, may persist. In addition, there is now a minor degree of atrophic vesicular emphysema. At many points residual bronchial catarrh may be seen, though most of the bronchi and bronchioles have recovered (Fig. 2A). Material degrees of

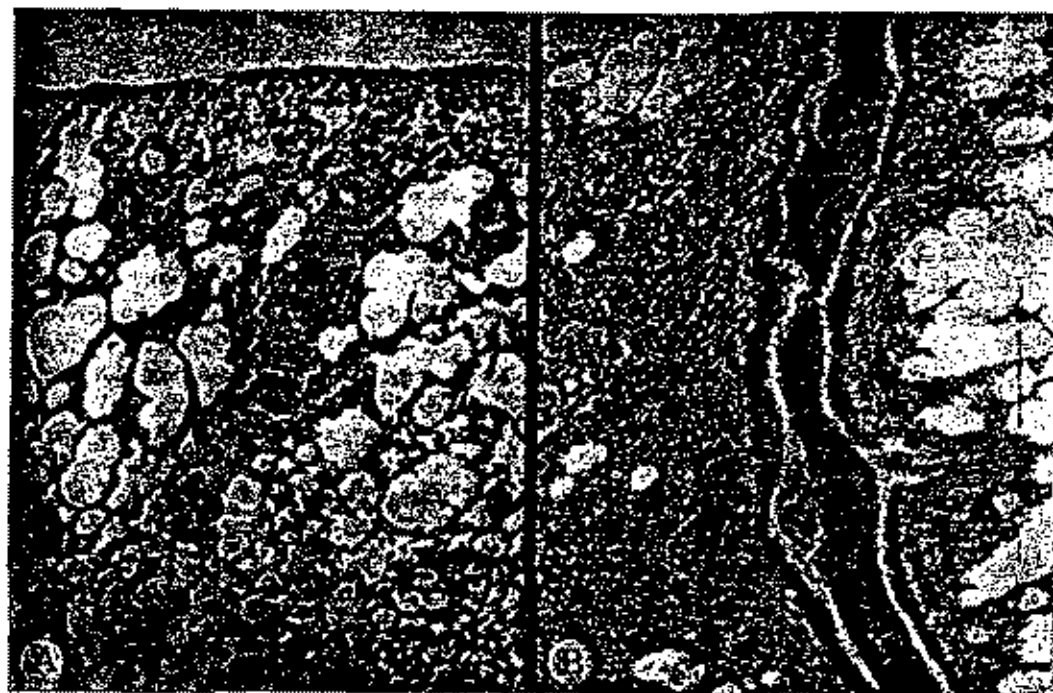
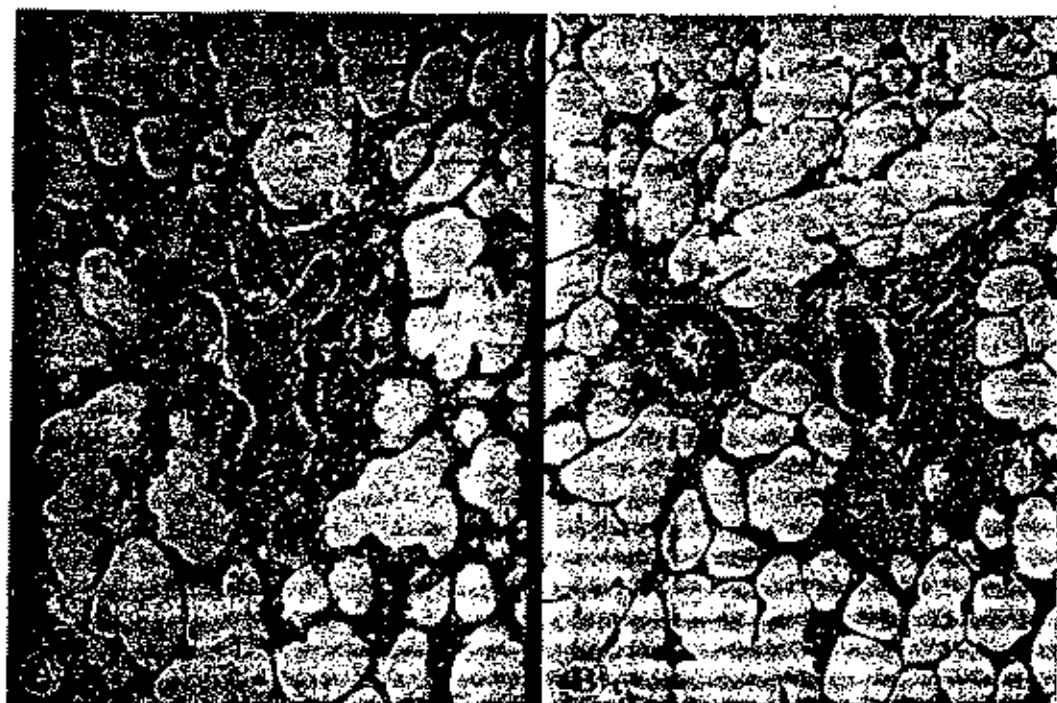


Fig. 1.—Acute pulmonary reaction to tungsten—guinea pig lung: one-month result. *A*, interstitial cellular reaction most marked around focally massed tungsten particles. *B*, perivascular cellular accumulation quite disproportionate to the amount of trapped tungsten.

Fig. 2.—Chronic pulmonary reaction to tungsten—guinea pig lung: one-year result. *A*, obliterative bronchiolitis, with catarrhal changes and disorganization of muscularis. *B*, perivascular and peribronchial fibrocellular reaction in relation to trapped tungsten particles.



peribronchial and periarterial fibrocellular reaction and endarteritis obliterans, with pigment located within the proliferated intimal layers (Fig. 2B), are certainly the least inviting features of this terminal response.

COMMENT

As none of the guinea pigs died as a result of the introduction of the tungsten dust, the substance may be classified as relatively benign. Its toxicity level compares with cobaltic oxide in this respect, but is in sharp contrast to that of cobalt metal.* The industrial significance of this finding might then be that exposures to the dust raised in pulverizing tungsten in the process of making tungsten carbide would be relatively safe, though not wholly free from risk. On the other hand, the exposures which might be incurred in handling cobalt metal fines, in the process of bonding tungsten carbide to steel, are likely to be noxious.

Once more it should be cautioned that one may not too freely extrapolate observations such as these on the guinea pig to human problems. At most it has perhaps been shown in this type of pilot or range-finding study that, while tungsten dust is not wholly inert, it is relatively so.

SUMMARY

1. The acute reaction to particulate tungsten when introduced into guinea pig lungs

involves the production of focal interstitial pneumonitis and bronchiolitis.

2. While recovery is almost complete after a year, peribronchial, peribronchiolar, and perivascular fibrocellular reactions, with bronchiolitis obliterans and atrophic emphysema, may persist focally.

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The Biological Action of Tungsten Carbide and Carbon

Studies on Experimental Pulmonary Histopathology

G. W. H. SCHEPERS, M.D., D.Sc., Saranac Lake, N. Y.

While tungsten metal has been shown to have a limited range of biological effects on guinea pigs,¹ the carbide has been incriminated as a minor respiratory hazard for man,² occasionally provoking metal dust pneumonitis. Experiments on the rat have, however, failed to produce either necrotizing or fibrotic pulmonary lesions.³ It is possible that the industrial cases may owe their origin to the cobalt which is usually present in industries involving the welding of tungsten carbide alloys to steel.

As Delahant⁴ showed, none of the guinea pigs receiving three successive doses of 50 mg. of tungsten carbide and carbon in a ratio of 94:6 died. The histological features of their lungs are in conformity with this finding.

The immediate response is a diffuse hyperemia with bronchial catarrh. By the end of the first month much of the tungsten carbide has been taken up by macrophages, many of which are multinucleated. Most of these cells still lie within the alveoli, but others have penetrated into the alveolar walls (Fig. 1A). There is not the same facility in reaching the perivascular lymphatics seen in the case of tantalum and cobaltic oxide,⁵ but some dust particles are aggregating about

smaller vascular components. Minor areas of interstitial pneumonitis may be found.

The lymphoid tissue appears to be considerably disturbed through the introduction of the tungsten carbide and carbon. There is marked lymphocytic hyperplasia, with infiltration of alveolar walls adjacent to the lymph foci. Some hyperemia also occurs in these areas (Fig. 1B). This lymphatic reaction continues for many months after the acute reaction has subsided.

After 12 months there may be isolated foci of confluent interstitial pneumonitis in relation to trapped dust masses. Most of the retained tungsten carbide occurs, however, as massed granules within relatively atrophic alveoli (Fig. 2A). Many such masses are partially or wholly phagocytosed by multinucleated giant cells.

Occasional subpleural granulomata may be found in which a minor degree of fibrocyte formation participates (Fig. 2B).

There is no persistent bronchiolitis or peribronchial and perivascular fibrosis, and the over-all impression is that the tungsten carbide and carbon mixture is less harmful to lung tissue than is the tungsten metal.

SUMMARY

The acute response to the intratracheal introduction of tungsten carbide and carbon is confined to hyperemia and bronchial catarrh, minor interstitial pneumonitis, and lymphoid hyperplasia.

The chronic residua include trapped dust masses and subpleural fibrocellular granulomata.

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Director, The Saranac Laboratory.

* References 5 and 6.

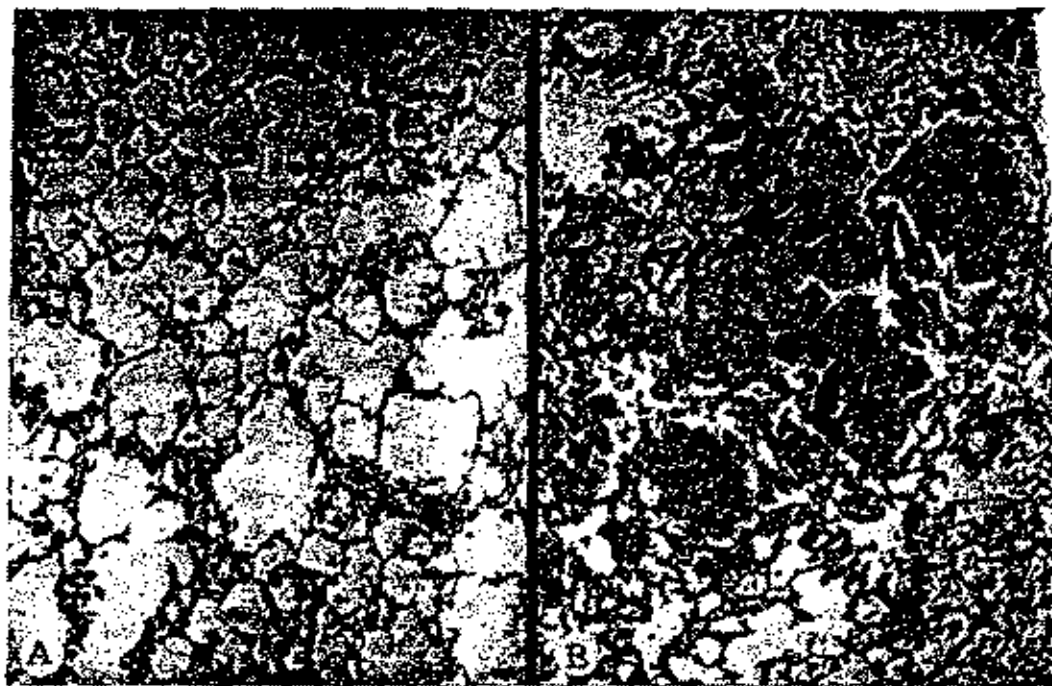
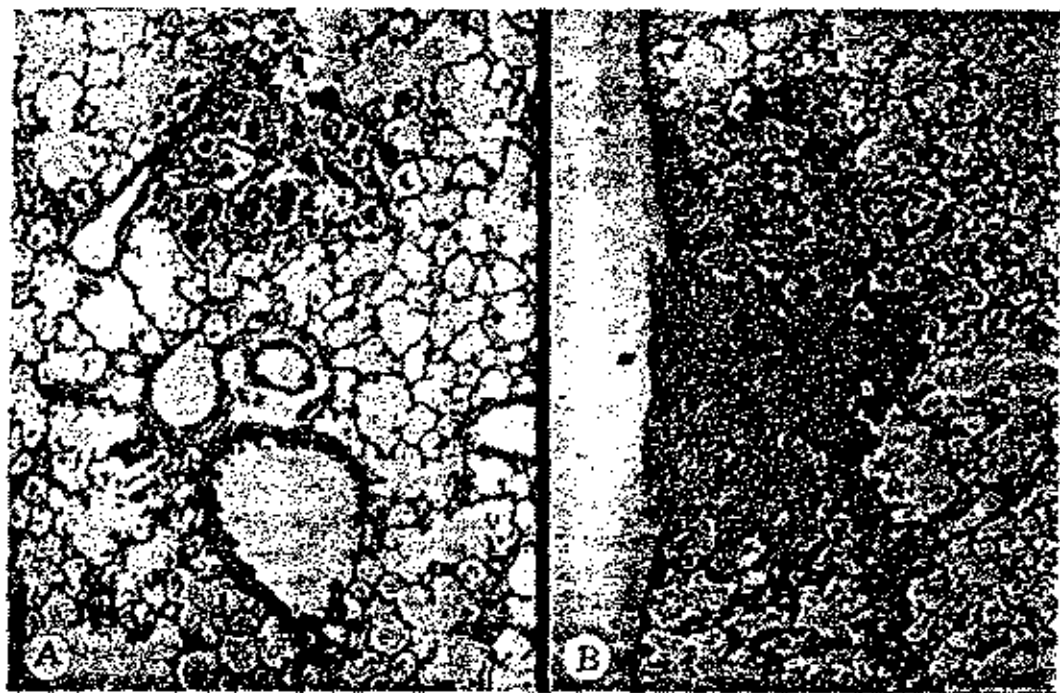


Fig. 1.—Acute reaction to tungsten carbide and carbon—guinea pig lung: one-month result. A, aggregates of particles lying within alveolar spaces or partly incorporated into alveolar walls. B, lymphoid hyperplasia, with invasion of alveolar walls adjacent to nodes.

Fig. 2.—Chronic pulmonary residua associated with the introduction of tungsten carbide and carbon—guinea pig lung: one-year result. A, focal accumulation of dust masses, most of which are contained in giant cells. B, subpleural fibrocellular granuloma.



BIOLOGICAL ACTION OF TUNGSTEN CARBIDE AND CARBON

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The Biological Action of Tungsten Carbide and Cobalt

Studies on Experimental Pulmonary Histopathology

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As has already been explained,¹ this experimental investigation of the effect of particulate tungsten carbide and cobalt metal on the guinea pig lung tissue comprises two phases, viz., an intratracheal study of tungsten carbide and cobalt in the ratio of 91:9 and an inhalation study of the effects of these substances in a ratio of 75:25. In the former study, a known quantity of 150 mg. of the foreign materials was introduced into each experimental animal. In the case of the 3:1 mixture, the tungsten carbide and cobalt dust was inhaled for a total of 35 days, with a rest period after 20 days, followed by reduction of the dust cloud to about a third of its earlier concentration for the balance of the period. Unfortunately, there was a high mortality among the animals so that a study of the histological results was partly interfered with. Sufficient data are available, however, to present a reasonably clear picture of the biological effects of these substances.

INTRATRACHEAL STUDY TUNGSTEN CARBIDE AND COBALT IN 10:1 RATIO

The predominating immediate effect on the lung of 150 mg. of a 10:1 mixture of tungsten carbide and cobalt is to provoke areas of dense fibrosis wherever massive deposits may be established. More generally there is cellular alveolar wall infiltration to the extent of producing almost confluent pneumonitic areas. Some macrophage catarrh,

with scanty particle ingestion, also occurs at this stage. Generally there are but one or two particles per konoiphore. The perivascular areas also become infiltrated with lymphocytes, which surround particulate aggregations (Fig. 1A). Yet there is no tendency toward involvement of the hilar lymphatics within a month from the time of intratracheal injection.

The bronchial epithelium and mucosa tend to escape any material damage except where massive accumulations of dust may be deposited. In such areas there is a tendency toward the development of bronchial crypts (Fig. 1B). The pigment tends to be incorporated in the bronchial mucosa, and a fairly firm fibrous reaction results around it. The epithelium overlying the deposit seems to be of the normal kind.

Where the dust has gained access to the pleura, a dense fibrocellular reaction may ensue.

Twelve months later focal accumulations of massed particles may still persist in the alveolar spaces and interstitial planes. Slight cellular and mild fibrous reaction around these deposits may be found, frequently with abundant eosinophilia. There may also be residual patches of pneumonitis (Fig. 1C).

Many of the bronchi show peribronchial fibrosis, and at isolated points there is some papillary hypertrophy of the bronchial mucosa. Arteries likewise reveal a tendency toward residual periarterial fibrosis (Fig. 1D).

At this stage a minimal amount of the particulate matter has been transferred to the hilar lymph nodes, where it is deposited in the subcapsular or perilymphatic zones rather than in the nodes themselves.

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BIOLOGICAL ACTION OF TUNGSTEN CARBIDE AND COBALT

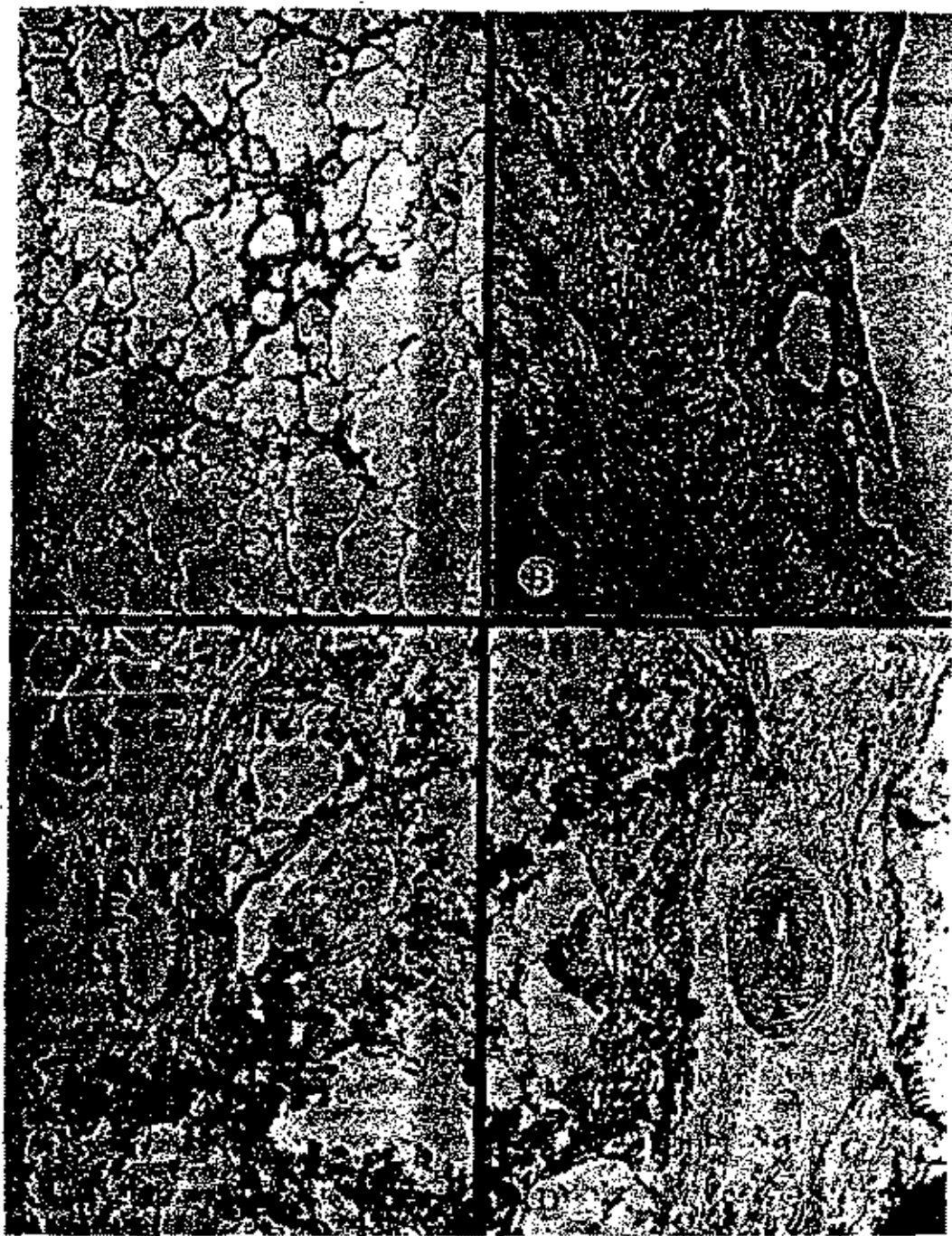


Fig. 1.—Pulmonary tissue reaction to injected tungsten carbide and cobalt—guinea pigs: intratracheal injection: 150 mg. dose in a ratio of 91:9. *A*, generalized alveolar wall thickening focally exaggerated with perivascular cellular infiltrate (reaction after one month). *B*, focal accumulation of metallic particles with surrounding fibrosis and bronchial mucosal crypt formation and hypertrophy (reaction after one month). *C*, localized deposit of metallic particles with associated cicatrization (reaction after one year). *D*, paravascular metallic deposit with perivascular fibrosis (reaction after one year).

While the above tissue reaction basically resembles that already established for tungsten carbide,² the tendency toward perivascular focalization of the reaction and also the stimulating impetus imparted to the bronchial epithelium may be attributes of the cobaltic component of the introduced dust.³ The explanation for the fibrotic response is not immediately apparent.

INHALATION STUDY

TUNGSTEN CARBIDE AND COBALT IN 75:25 RATIO

The inhalation of this 3:1 mixture of tungsten carbide and cobalt metal in high concentration rapidly provokes a diffuse inflammatory reaction but, except for small areas, no true pneumonia. At the end of three weeks the lung tissue presents a hemorrhagic appearance, both from dilatation of alveolar wall capillaries and through escape of erythrocytes into the alveolar spaces at many points. Plasma cells, lymphocytes, and polymorphonuclear leucocytes may be found in most alveoli, and a fair number of macrophages, the majority containing some ingested particles, are present. At numerous points the alveolar walls are lined by prominent septal cells. Neither the bronchi (bronchioles) nor the larger blood vessels show any significant deviation (Fig. 2A).

On withdrawal of the animals from this obviously intolerable dust environment at the end of three weeks and restoring them to fresh air for several weeks, a considerable degree of recovery from the acute alarming phase of the reaction occurs. At isolated areas some hyperemia may yet be observed at the end of six weeks, but at most sites the capillary hyperemia has receded almost entirely, and many of the alveolar walls are interrupted so that a mild degree of atrophic vesicular emphysema is present. The inflammatory reaction is now limited to a mild alveolar wall cellular infiltration, consisting primarily of polymorphonuclear leucocytes with occasional macrophages. The alveolar septal cells are also prominent, but there is very little liberation of alveolar phagocytes, though occasional pus cells are present. Around the smaller arterioles and venules,

these cellular infiltrations are more conspicuous. Dust particles are abundantly present in the alveolar walls but are always intracellular in their disposition, lying within the pulmonary macrophages (Fig. 2B).

Considerable quantities of the foreign material are obviously being transported from the lung to the hilar lymph nodes, for at six weeks a well-defined cortical zone of epithelioid reaction has become established in the latter. It would seem that the proliferation of these reticuloendothelial cells is a specific reaction to the presence of the dust substance, as neither the tungsten carbide nor the cobalt itself provokes this effect separately (Fig. 2C).

On reinstituting dust inhalation for 15 days, but now at a much reduced concentration, a diffuse hyperemia and alveolar edema once more result. On leaving the guinea pigs in normal air for six months hereafter, an entirely different type of result may be observed. Multiple foci of peribronchial and peribronchiolar parenchymal reaction and an unusual and exuberant type of metaplastic bronchial epithelial hyperplasia, with villous papilloma formation, constitute the main features of the condition at this stage and commence as early as six weeks after cessation of the exposure (Fig. 2D).

The peribronchiolar reaction consists partly of an interstitial cellular infiltration, many of the component cells being eosinophiles. The alveolar septal cells tend to be prominently developed, and several may be seen to be undergoing transformation into macrophages. Within the alveoli may be found aggregates of particle-laden macrophages, some polymorphonuclear leucocytes, plasma cells, and numerous eosinophile cells. Occasional multinucleated giant cells are to be seen. The alveolar capillaries are not conspicuous (Fig. 3A).

The bronchioles show quite a broad zone of plasma cell infiltration of their adventitia, with occasional pus cells and eosinophiles. The most spectacular change in the bronchioles, however, concerns the epithelium, which is heaped up at numerous points into papillomata consisting of many layers of

BIOLOGICAL ACTION OF TUNGSTEN CARBIDE AND COBALT

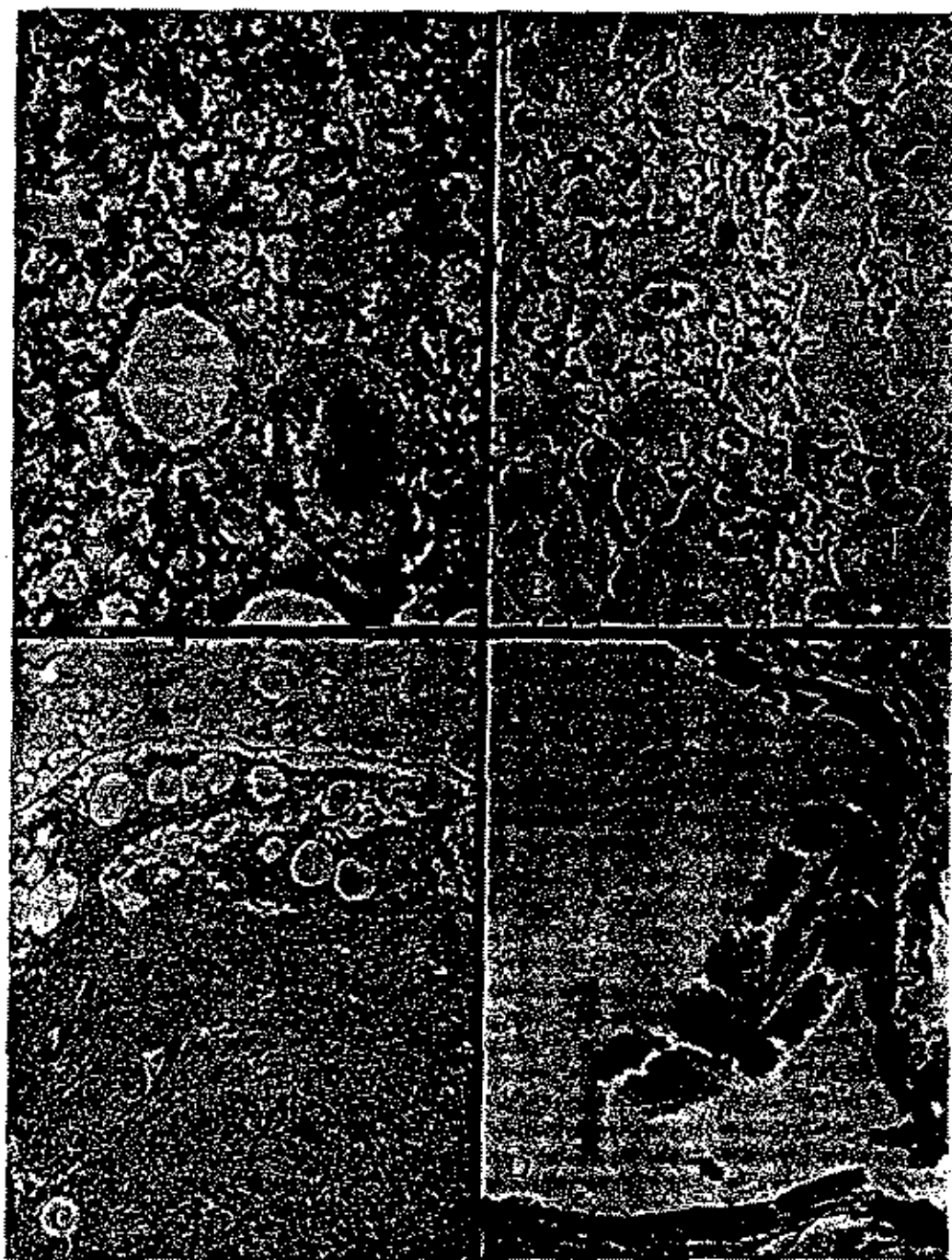


Fig. 2.—Acute reaction to inhaled tungsten carbide and cobalt—guinea pigs: inhalation experiment. *A*, hemorrhagic pulmonary reaction and alveolar wall hyperemia (reaction at three weeks). *B*, focal parenchymal reaction, dominantly intra-alveolar macrophage formation (reaction at six weeks). *C*, cortical endothelioid proliferation of the hilar lymph node (reaction at six weeks). *D*, villous mucosal proliferation of a bronchus, with incipient epithelial metaplasia (reaction at three months).

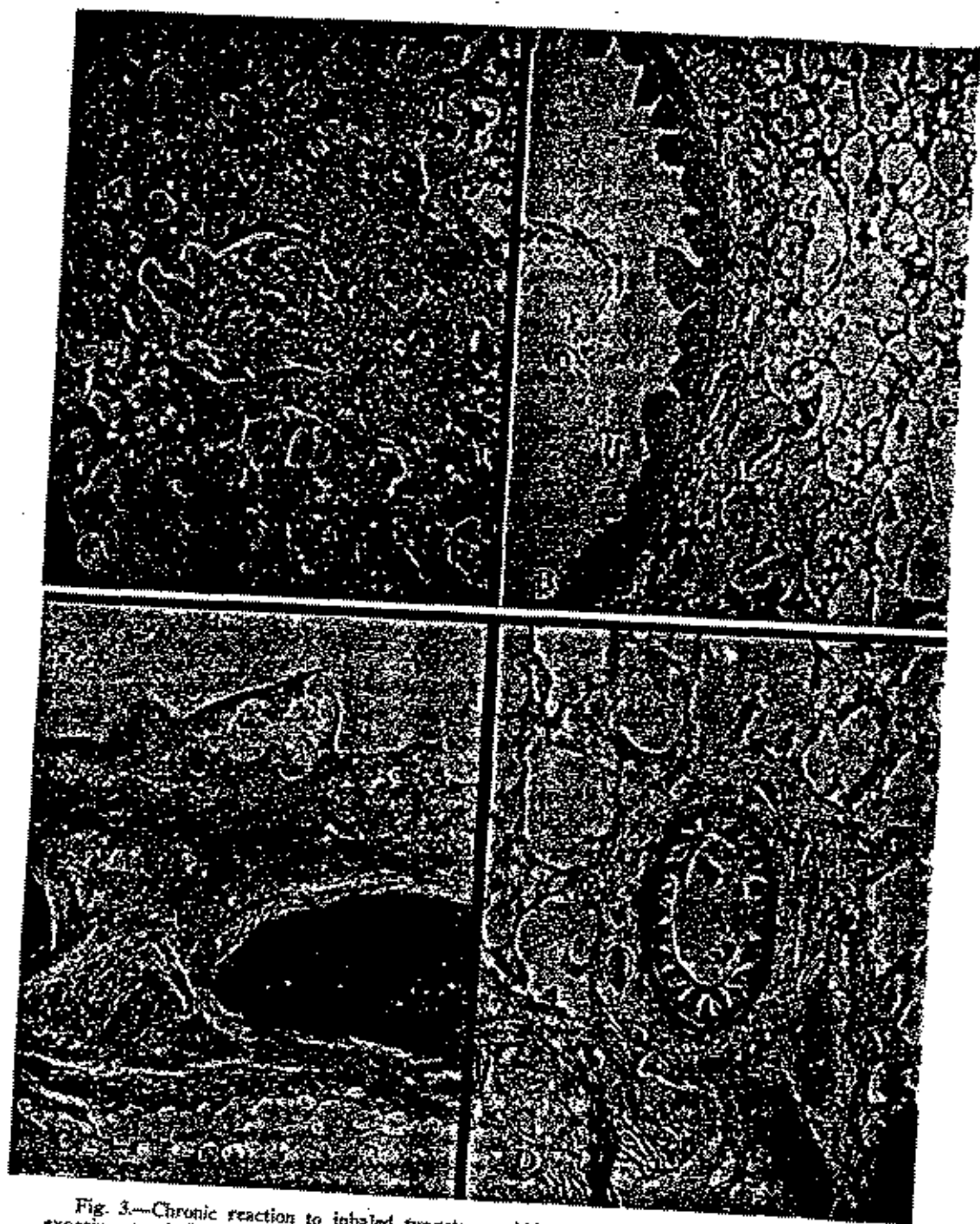


Fig. 3.—Chronic reaction to inhaled tungsten carbide and cobalt—guinea pigs: inhalation experiment. *A*, local degenerative bronchiolitis with peribronchiolar semigranulomatous inflammatory reaction (reaction at six months). *B*, incipient bronchial epithelial proliferation (reaction at six months). *C*, epithelial hyperplasia and superficial ulceration in the trachea (reaction after 21 months). *D*, limited residual peribronchial fibrocellular reaction (reaction after 21 months).

BIOLOGICAL ACTION OF TUNGSTEN CARBIDE AND COBALT

large nucleated epithelial cells containing a minimum of cytoplasm (Fig. 3B). Occasionally such papillomata contain a fibrous stroma which tends to be infiltrated by plasma cells and eosinophiles. The lumina of some of the bronchi and respiratory bronchioles are almost completely occluded by these proliferating epithelial cells and papillae, so that regional focal emphysema may ensue distally to these partial obstructions.

At several foci in the lung there are also small confluent endothelial granulomatous formations with central pus accumulations.

The lymph nodes within the lung are not materially affected by the tungsten carbide and cobalt except that there may be some measure of eosinophile infiltration. The hilar lymph nodes continue to show cortical endothelioid hyperplasia. The larger blood vessels are unaffected except for some adventitial cellular infiltrations.

After elapse of another 15 months, i. e., a total of 21 months from the onset of the experiment, the residual effects of the brief exposure to the tungsten carbide and cobalt metal may be assessed.

In the trachea and bronchi, the epithelial hyperplasia and metaplasia still persist and show extensive superficial ulceration, with cellular desquamation, so that the markedly thickened basement membrane may even be denuded (Fig. 3C). The major bronchi and bronchioles have largely recovered and are universally patent, with very little desquamated material in their lumina. Some peribronchial fibrosis is, however, apparent (Fig. 3D).

The parenchymal cellular deposits no longer are present. Isolated alveolar walls may still show residual infiltration or thickening. Rarely, fibrocellular foci may be found, with marked interstitial cellular proliferation. In yet other such foci, macrophages and giant multinucleated cells predominate. Along the lung periphery there are multiple areas of vesicular emphysema, and interalveolar septa are interrupted at numerous points.

The hilar nodes show persisting foci of endothelioid hyperplasia which may be cen-

trally located or disposed along the cortex and contain a little pigment at their periphery. The intrapulmonary lymph nodes have returned to normality.

COMMENT

The purpose in combining the tungsten carbide and cobalt in the ratios given in the foregoing accounts was to mimic for experimental purposes the circumstances in which industrial employees may on occasion be exposed to these substances while preparing mixtures for the purpose of making alloys.

If the sequence of events described for the guinea pig bear any relation to the manner in which human lung tissue may be expected to react, it would seem that great caution should be exercised so that the metal fines are not handled in such a way as to create an atmospheric contamination of any severity.

As was shown, the reaction to the dust mixture is appreciably less violent where the cobalt component is of the order of 9%. On the other hand, the more pronounced tissue response, and particularly the proliferative and metaplastic epithelial changes, may reflect a sensitizing propensity for which cobalt is already well known,⁴ though it had not previously been shown that cobalt acted in like manner on the lung tissues. It may be recalled,¹ however, that whereas a 5 mg. dose of cobalt metal appears to have no acute toxic effect on guinea pigs when introduced intratracheally, repetition of this procedure killed the majority of animals, and the probability that this is a sensitization phenomenon has already been suggested.⁵

The proliferation and metaplasia of the epithelium of the respiratory passages are reactions of potentially ominous portent. While a great range of occupational environmental dust exposures may lead to bronchitis, bronchiolitis, and asthma,² the underlying tissue reaction is usually of a chronic submucosal inflammatory nature without epithelial hyperplasia. Cobalt and tungsten carbide mixed with cobalt apparently constitute an exception to this rule, though chronic

experimental exposure of animals to Diesel exhaust soot and to Schneeberg rock drill dust⁸ has previously been shown to provoke epithelial hyperplasia. It is possible that in the case of the latter the cobalt in the mine ore is the factor in stimulating the growth of the epithelium. While the information now furnished is insufficient to warrant more than speculation about the possibilities of this effect of the cobalt on respiratory epithelium, the growing toll of lung cancer justifies further exhaustive study of this phenomenon.

SUMMARY

The intratracheal introduction of 150 mg. of tungsten carbide and cobalt in a 10:1 ratio produces a transient inflammatory reaction, with residual papillary hypertrophy of bronchial mucosa and peribronchial and periarterial fibrosis in the vicinity of retained particulate matter.

The response of lung tissue to the inhalation of tungsten carbide and cobalt in a ratio of 3:1 provokes an acute inflammatory reaction which is later replaced by focal pneumonitis and residual bronchial epithelial hyperplasia and metaplasia.

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The Pulmonary Disability Legislation of South Africa

A Rationale for its Enactment

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The enactment of the pulmonary disability legislation of the Union of South Africa followed the report of two recent Governor General's Commissions pertaining, respectively, to the occurrence of diseases attributable to the nature of employment in and about mines¹ and to the functioning of the Silicosis Medical Bureau.² At the same time it represents the culmination of a protracted struggle for greater health protection of the personnel not only of the gold mines but also of all other types of mines in which respiratory hazards have been known to exist but which did not appear to be taken care of by the existing silicosis legislation. The historical background for this Amendment of the Silicosis Act has been sketched in the preceding paper concerning the progress which has been made in the conquest of the occupational chest diseases at these mines.³ The legislation⁴ was introduced during 1952 as an Amendment of the existing Silicosis Act.⁵

DEFINITION OF PULMONARY DISABILITY

The main point about this legislative innovation is the legal definition which was introduced and which reads as follows (Act 63 of 1952, Paragraph 2, Subsection [3]):

"Pulmonary disability" means an impairment of the cardio-respiratory functions of a person which, in the opinion of the Bureau—

(A) has substantially and permanently diminished the capacity for manual work of the person in question; and

(B) resulted from the performance, by the person in question, of work in a dusty occupation;

but does not include silicosis or tuberculosis; and for the purposes of this Act a person shall be deemed to be, or to have been suffering—

(i) from pulmonary disability in the first stage, when the Bureau has found him to be, or to have been, suffering from pulmonary disability which, in the opinion of the Bureau, does not, or did not, incapacitate him from performing moderate manual work, but does or did incapacitate him permanently from performing manual work more strenuous than moderate manual work;

(ii) from pulmonary disability in the second stage, when the Bureau has found him to be, or to have been, suffering from pulmonary disability which, in the opinion of the Bureau, permanently incapacitates or incapacitated him from performing manual work more strenuous than light manual work.

As this new legal definition excludes both tuberculosis and silicosis, its full significance can be made clear only after the legal definitions for these concepts have also been quoted. They are as follows (Act 47 of 1946, Chapter 1, Section 1, Subsection [1]):

"Silicosis" means any form of pneumoconiosis due to the inhalation of mineral dust; and for the purposes of this Act a person shall be deemed to be or to have been suffering—

(A) from silicosis in the first stage (which corresponds with the ante-primary stage under the 1925 Act) when the Bureau has found that the earliest specific signs of silicosis, detected by any means whatsoever, are or were present in the lungs of the person in question, irrespective of whether his capacity for work has or has not been impaired by the said disease; or

(B) from silicosis in the second stage (which corresponds with the primary stage under

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the 1925 Act) when the Bureau has found that moderately marked specific signs of silicosis are or were present in the lungs of the person in question and that the said disease has not incapacitated him from performing moderate manual work; or

- (C) from silicosis in the third stage (which corresponds with the secondary stage under the 1925 Act) when the Bureau has found that marked specific signs of silicosis are or were present in the lungs of the person in question and that the said disease has incapacitated him from performing moderate manual work.

Apart from the initial absurdity of equating the specific disease "silicosis" with the generic term "pneumoconiosis" (which, though repugnant to the medical profession, the lawyers, however, found a satisfactory type of legalistic figment to employ), this definition appears straightforward enough until its full implications are more critically analyzed. Probably it will be immediately evident that by equating "silicosis" with "pneumoconiosis" no true legal definition has yet been created, as "pneumoconiosis" is not itself defined.

The tuberculosis definition similarly appears superficially satisfactory, reading as follows (Act 47 of 1946, Chapter 1, Section 1, Subsection [1]):

"Tuberculosis" means tuberculosis of the respiratory organs and a person shall, for the purposes of this Act, be deemed to be suffering from tuberculosis—

- (A) if the Bureau has found the said person's sputum to contain tubercle bacilli; or
(B) if the Bureau has found the said person to be suffering from 'closed' tuberculosis which seriously impaired his working capacity.

To the discerning mind this definition is equally full of loopholes. Taking both definitions on good faith, however, one may assume that the South African laws intended silicosis or tuberculosis to be certified present when detectable and had now added a new entity, namely, pulmonary disability, to be likewise recognized if it existed.

It will be apparent that second-stage pulmonary disability is equated to third-stage silicosis in respect to the degree of severity

of the functional incapacitation used as its differentiating criterion. The financial benefits and legal restrictions which accrue in respect to each of these conditions have therefore been equated through the Act. Tuberculosis is treated on a different basis.

Second-stage silicosis is likewise broadly equated to first-stage pulmonary disability. However, there is an important difference here in that, while first-stage pulmonary disability necessarily presupposes partial incapacitation, second-stage silicosis does not and may be certified on radiological criteria only. The South African law emphasized this difference further by providing that when second-stage silicosis and first-stage pulmonary disability are present simultaneously the person shall be deemed to be in a stage equivalent to third-stage silicosis. Again, when pulmonary disability in the first stage is found in association with silicosis in the first stage, the law provides additional cash financial benefits for the affected person, in principle again presuming that he suffers from two separate diseases. Pulmonary disability in the first stage found in association with tuberculosis is equated to third-stage silicosis for purposes of financial benefits.

Though the definition specified that pulmonary disability could be legally certifiable by the Bureau only, the law got around this by providing for the appointment of special committees whose decisions would be deemed to be findings of the Bureau itself (Section 15, Subsection [1], Paragraph [A]). The Minister of Mines accordingly by special proclamation created such a Pulmonary Disability Committee and defined its powers and mechanism of functioning.*

The exclusion of silicosis and tuberculosis from the definition of pulmonary disability is the first issue to which attention should be addressed, as this makes for an intentional fundamental legal distinction. The first interpretation which needs to be considered may be that the law intended to distinguish between "silicosis in the third stage," "closed tuberculosis," and "pulmonary disability in

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the second stage," in all three of which a serious degree of incapacitation for work is a prerequisite to diagnosis. This may have been a device of the legal draftsmen to obviate certification of more than one compensable disease on the basis of the same set of diagnostic criteria. However, the phrase excluding silicosis and tuberculosis from the pulmonary disability definition is introduced before its two stages are defined, so that one must presume that first-stage pulmonary disability must also exclude both tuberculosis and silicosis. The legal experts made a fine point by explaining that what was intended was that silicosis, tuberculosis, and pulmonary disability are to be regarded as three distinct medicolegal diseases, each capable of causing incapacitation in its own peculiar way.

The clue to further understanding of this subtle distinction resides in the introduction into the pulmonary disability definition of the words "an impairment of the cardio-respiratory functions." Silicosis and tuberculosis are thus regarded as morphological diseases, and it is to be presumed that any disablement which they are capable of provoking would be due to direct effects, sequelae, or complications of the anatomical lesions caused by the inhaled dust or tubercle bacilli. Pulmonary disability, on the contrary, is to be viewed, in terms of this distinction, as a physiological deviation not necessarily associated with the specific type of structural tissue reaction generally associated with the concept, pneumoconiosis or silicosis. The extremes of contrast envisioned may be illustrated by comparing the incapacitation which may result from massive pulmonary fibrosis (such as may, for example, occur in advanced silicosis, tuberculosilicosis, asbestosis, or anthracosis) with the disability which may be more subtly yet irreversibly engendered by factors such as bronchitis with bronchospasm, alveolar membrane thickening or impairment, degenerative changes affecting the lung reticulum and elastic system, emphysema, capillary or arteriolar occlusion, vascular short circuits with reduced perfusion of aerated pulmonary

segments, or any of the many physiological combinations which may be found in indisposed miners and which ultimately lead to anoxemia and cor pulmonale. The whole group of functional effects thus produced would now be classifiable as pulmonary disability. It is doubtful whether such a heterogeneous selection of effects could be included in a definition of silicosis, having regard to the fact that there is fair agreement that this is a nodular disease of the lungs. Nor would the concept pneumoconiosis readily embrace all these conditions, as it is generally assumed to have at least an element of pulmonary fibrosis to it. It is also well known that there is no predictable or necessary correlation between the degrees of morphological changes associated with the pneumoconioses and the degree of disability which may be found in the affected person. This may be because a multiplicity of factors differentially collaborate in producing these separate effects. Thus it is possible for a miner's x-ray film to reveal advanced macronodular silicotic infiltration or extensive tuberculosilicotic consolidation without any associated subjective disability or material incapacitation for physical exertion. On the other hand, a working colleague from the same mine, with a much shorter industrial history and the merest scintilla of micronodular dust reaction, may rapidly become a respiratory cripple and may die at an early age from cor pulmonale. It had not previously been possible under South African laws to admit more than first-stage silicosis in the latter type of case, and the Pulmonary Disability Amendment was intended to bridge this gap.

Attention must be drawn to the fact that the definition of pulmonary disability differs from that of silicosis (pneumoconiosis) in a further significant way, namely, with regard to the etiological issue. Silicosis, or, for that matter, any pneumoconiosis, can be conceived of only as a disease arising from the effective occupation of the lungs by mineral dust, and in the absence of a specific type of tissue reaction to such dust, there can be no question of silicosis or pneumoconiosis. Pulmonary disability, on the contrary, is defined as a

cardiorespiratory functional impairment resulting from the performance of work in a dusty occupation. It may, therefore, be due to the inhalation of mineral dust, as is silicosis (pneumoconiosis), or it need not be due to such mineral dust. A chest condition arising from nonmineral dust encountered during mining operations (e. g., bacteria, fungal spores, rotting timber, chemical fumes, smokes, and gases) can in no circumstance be called silicosis or pneumoconiosis. But such conditions became certifiable as pulmonary disability in terms of the new South African legislation.

Pulmonary disability, furthermore, need not, in terms of this definition, arise as a result of the inhalation of dust, even though reference is made to dusty occupations. The stress is on the words "performance of work." Injurious environmental conditions which are inseparable from mining, such as excessive humidity, temperature fluctuations, recurrent infections, exposure to fumes, gases, or smokes, overwork, and radioactivity, may all in theory collaborate in provoking the syndrome of pulmonary disability in a person performing physical labor in such adverse circumstances. In this case then pulmonary disability rates as the generic concept, and the disability resulting from silicosis (pneumoconiosis) or tuberculosis may also be interpreted as a specific manifestation limited to reaction to dust deposition in the lungs, had these two conditions not been specifically excluded by the wording of the pulmonary disability definition. Indeed, had there been no silicosis definition in the third stage or a definition of closed tuberculosis, the pulmonary disability definition would have adequately taken care of all the cases which are now classified under such headings.

STATISTICAL RELATIONSHIPS BETWEEN PULMONARY DISABILITY AND INCAPACITY RESULTING FROM SILICOSIS AND TUBERCULOSIS

Since the promulgation of the Pulmonary Disability Amendment, approximately 1000 white miners alone have been certified to be suffering from this condition. In about one-third of these cases, the pulmonary disability was found as an isolated phenomenon, i. e., without silicosis or tuberculosis. Of these cases, more than two-thirds were instances of disability in the first stage and the balance were in the second stage. In the remainder, pulmonary disability was found in association with silicosis or tuberculosis. In Table 1 the relative prevalence of these conditions for the period 1953-1954 is presented. It will be im-

TABLE 1.—Prevalence of Pulmonary Disability in Relation to Silicosis and Tuberculosis
South African Gold Mines
White Miners—Period 1953-1954

Pulmonary Disability									
Stage 1					Stage 2				
Alone	Plus Silicosis Stage 1	Plus Silicosis Stage 2	Plus Silicosis Stage 3	Plus Tuber- culosis	Alone	Plus Silicosis Stage 1	Plus Silicosis Stage 2	Plus Silicosis Stage 3	Plus Tuber- culosis
265	146	91	1	4	108	61	87	1	15
406					173				

TABLE 2.—Prevalence of Occupational Chest Diseases
South African Gold Mines
Period 1953-1954

Source	Pulmonary Disability			Silicosis			Tuberculosis		Total
	Alone	Silicosis	Tuber- culosis	Stage 1	Stage 2	Stage 3	Alone	Plus Silicosis	
	1953	1954	1955	1953	1954	1955	1953	1954	
White miners, approxi- mately 85,000	365	320	9	1,053	763	400	43	62	3,024
Negro laborers, approxi- mately 300,000	50	12	18	1,876	407	2	1,086	479	3,763

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mediately apparent that the prevalence of pulmonary disability proper is inversely proportional to the severity of the associated silicosis or the presence of tuberculosis.

To gain a clearer understanding of the relative incidence of pulmonary disability in relation to the other occupational chest diseases, recourse must be had to the data assembled in Table 2. For the white men the figures under each category are self-explanatory. The infrequency with which pulmonary disability, as a legal syndrome, is found in association with tuberculosis may be particularly emphasized, and it is also to be noted that it is much more prevalent than tuberculosis itself. The very high total figures for this period are also artificial and explained elsewhere.⁸ Silicosis and tuberculosis may have to be scaled down to about one-third or one-quarter of the cases mentioned here in order to obtain the probable yearly rate of production of new cases, the present excessive series representing an accumulation of delayed certification which are being dealt with. However, this period is deliberately selected for purposes of comparison, because the pulmonary disability cases are also derived from a retroactive backlog of five years which the law took cognizance of. As the cases reflected in the Table represent the totals discovered among a little more than one-third of the applicants, it may be possible that the annual rates of development of the condition will stabilize at about half of the present figures. Perhaps it will be even lower, as many of the disabled men had suffered from their complaints for 5 to 15 years. If later, when the backlog has been eliminated, the condition is likely to be certified promptly, as it develops, it may be that the annual production rate will decrease to perhaps an even smaller fraction.

The numbers of cases found among Negro laborers is surprisingly low, having regard to the large numbers of new cases of silicosis and tuberculosis which were found among them during the same period. There may be relatively simple explanations for this. The fact that so many cases of silicosis and tuberculosis were found in the Negro labor-

ers itself militated against the certification of a separate condition of pulmonary disability, as, in the case of Negroes, full financial benefits accrue to men on first certification of silicosis or tuberculosilicosis or when tuberculosis is found after completion of an aggregate of eight years of service. No legal purpose could therefore be served in examining such men for pulmonary disability, and they were therefore not sent for assessment of their incapacitation. The Negroes who have left the mines rarely return for subsequent reassessment of their condition, as there is no proper legal provision for routine examinations of this type and they are mostly too ignorant to know how to set about lodging an application. A Negro who already has some symptoms of disease is not likely to be persuaded by a recruiting agent to return to the mines. The statute of limitation in the case of current miners, moreover, is one year, and in many instances where some form of application is lodged either by the Negro or on his behalf this is done too late. It is probable that the condition of pulmonary disability is quite prevalent among the Negroes already acknowledged to be suffering from silicosis or tuberculosis, but it is to be doubted that it is likely to occur in as great proportions as among the white miners. It must be realized, however, that the majority of Negro laborers are relatively young men who spend a comparatively short time in the mines only. In comparable circumstances there need be no reason for any difference in pulmonary disability rates in the two races, unless the more highly developed pulmonary lymphatic system of the Negro is likely to influence the underlying pathological process unduly.

The probable statistical relationship between pulmonary disability and silicotic incapacitation is graphically represented in Figure 1. In this diagram the serial annual certifications of second- and third-stage silicotics among living white miners has been plotted for the period 1916 to 1954. In constructing these slightly idealized trend curves, the recent high rate of certification has been ignored for the reason that many

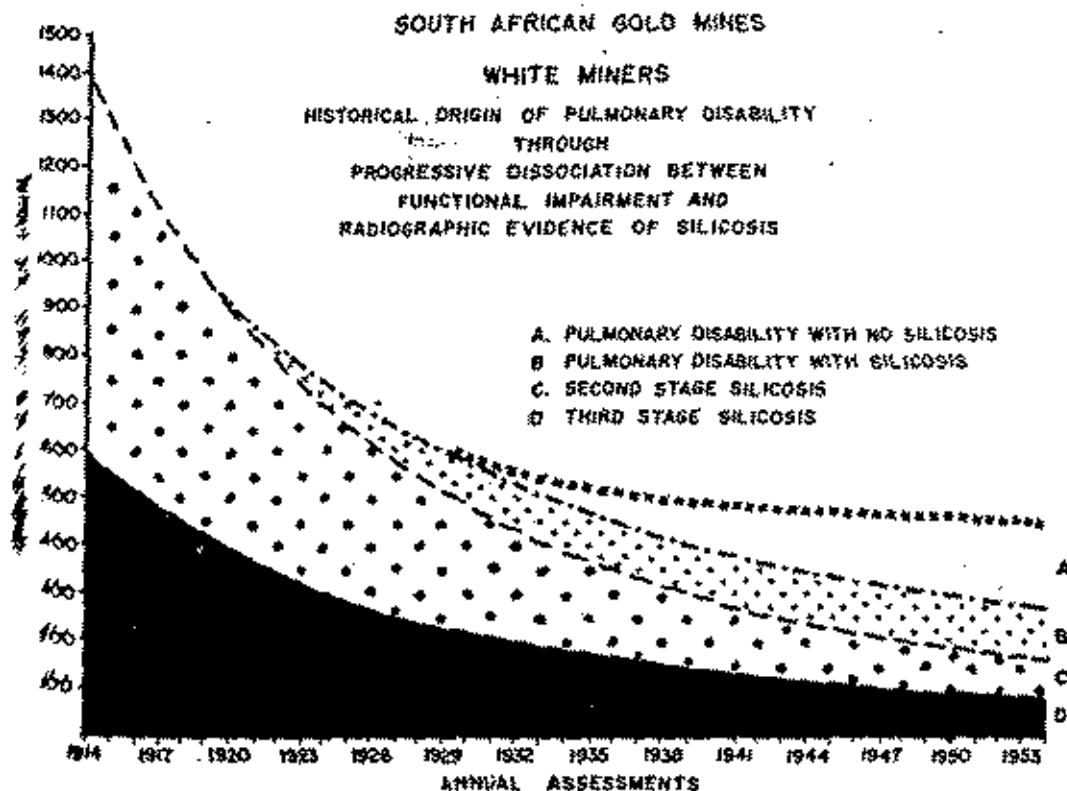


FIGURE 1

The cases belatedly certified as third- or fourth-stage silicotics were sufficiently disabled to merit certification but did not qualify radiologically in respect of the standards employed by the Bureau in previous years. They have been included in the group designated as pulmonary disability with silicosis. The curves for pulmonary disability and silicosis plus pulmonary disability, respectively, are imaginary but are reconstructed from the excess of cases of third- and second-stage silicosis combined with the 1000 cases of pulmonary disability already found among about 2000 applicants, representing the cumulative disability for a five-year retroactive period. In this use is made of personal intensive experience with these men dating back to the time when pulmonary disability dissociated from silicosis was prevalent and may therefore be presumed to have arisen at even earlier periods though it went unrecognized.

The main point brought out by this analysis is that, while the annual production rates of the third and second stages of radiological silicosis decreased at a decelerated rate during the past 40 years, the rate of production of pulmonary disability increased progressively and in two phases of progressive dissociation between the presence of radiological silicosis and the degree of demonstrable disability.

During this protracted period, four fundamental changes occurred among miners on the Witwatersrand, namely, they survived longer, worked longer, developed less tuberculosis and radiological silicosis, and breathed a diluted, moistened, and perhaps altered dust under steadily changing subterranean environmental conditions of heat, humidity, ventilation, barometric pressures, etc. In addition, the men were now a highly selected group, mainly of indigenous South African stock. Which of these many factors

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stands out as a probable correlate and cause of the disability?

Altered service periods may be considered first. To probe this possibility, 155 cases of first-stage pulmonary disability not associated with tuberculosis or silicosis were analyzed and compared with the patterns characteristic of the latter two diseases. An additional 90 cases of first-stage radiological silicosis combined with legal first-stage pulmonary disability are likewise included (Fig. 2). It will be immediately apparent that the four conditions manifest themselves at different service periods. Tuberculosis predominates in the earliest phase of dust exposure, and the majority of cases occur before the 14th year of service in dusty occupations. Silicosis, on the contrary, except for a minor group of exceptionally susceptible persons, manifests itself much later, and for the 1939-1948 group the modal peak appears after the 21st year of service only. Silicosis is therefore shown to be dominantly

a function of duration of dust exposure. There are equally large numbers of miners who show undue susceptibility or manifest abnormal resistance to the disease.

Pulmonary disability is shown to behave in two distinct patterns according as it is associated with radiological signs of silicosis or occurs independently of such x-ray signs. The latter group appears early, and those with associated silicosis have a delayed onset, although in one extreme example silicosis and pulmonary disability were already present in a young miner after only one year eight months of underground employment.

Rather suggestively, the group with associated silicosis represents cases in which the silicosis manifested itself first and the disability later, although, as we are dealing here with an accumulation of cases from many years previously, it is possible that these men did also develop their disability first and the nodules were superimposed at a later stage. The fact, moreover, that in the first group

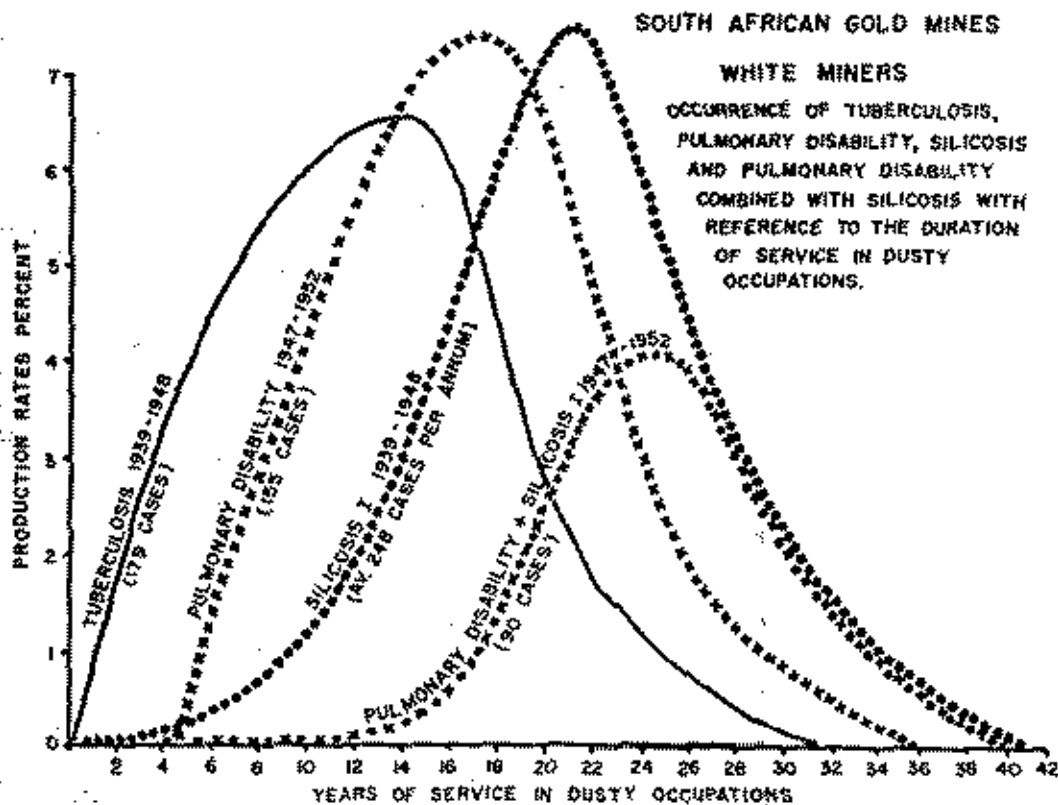


FIGURE 2

SOUTH AFRICAN GOLD MINES

WHITE MINERS

PRODUCTION RATES PERCENT OF PULMONARY DISABILITY AT DIFFERENT AGES COMPARED WITH THE AVERAGE ANNUAL AGES OF TUBERCULOTICS, SILICOTICS AND TUBERCULOSILICOTICS FOR THE PERIOD 1916 TO 1952

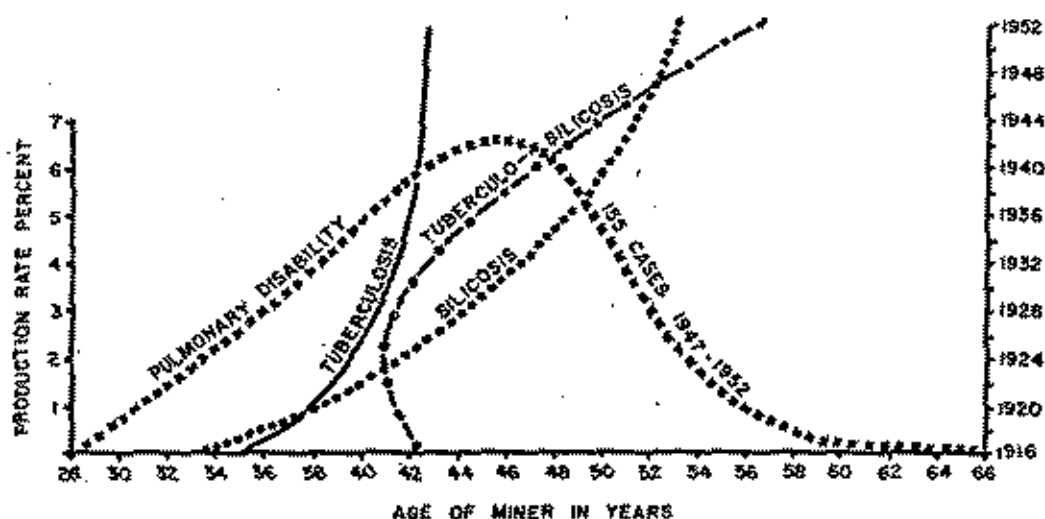


FIGURE 3

of pulmonary disability sufferers there is not yet any evidence of nodular silicosis does not preclude the subsequent development of such nodules. It will be noted that the large majority of these men had become functionally incapacitated before the 18th year of their service in dusty occupations, i. e., before the modal peak for silicosis manifests itself.

An analysis of the ages of the men certified as suffering from pulmonary disability immediately disposes of any theory that the cause of the disablement may reside in the longer survival of the men, so that in large measure disability is merely a manifestation of an aging process in the lung tissues and pulmonary blood vessels of the dust-exposed worker (Fig. 3). The dispersion of the various ages of a group of 155 disability sufferers who had no associated radiographic silicosis was plotted against the average ages of silicotics, tuberculous, and tuberculosilicotics certified successfully in the years 1916

to 1952. It is immediately apparent that the majority of silicotics are almost a decade older than the sufferers from pulmonary disability. Tuberculosilicotics are likewise much older. Only the tuberculous are, on an average, younger than those who have been classified as suffering from pulmonary disability. It is seen also that the curves for silicosis and tuberculosilicosis intersect the current modal peak for pulmonary disability at years 1931 and 1938, respectively. This may explain the relative scarcity prior to those times of pulmonary disability before either silicosis or tuberculosilicosis manifested themselves in the affected individuals.

THE NATURE OF PULMONARY DISABILITY

The dominant symptoms associated with pulmonary disability in the gold miners of the Witwatersrand comprise chronic, increasingly productive cough, progressive exertional dyspnea, transthoracic pain and constrictive sensations, minor hemoptyses,

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predisposition to chest colds, chronic fatigue, malaise and weakness, joint pains, and dependent edema. In the severer grades, there may be nocturnal asthmatic episodes, and orthopnea.

Physical signs tend to emphasize poor respiratory excursions, the thorax tending to assume a rigid semi-inflated shape, however, with some atrophy of the upper portion. Breath sounds assume a harsh truncated character or may be distant and frequently accompanied by marginal crepitations and rhonchi. Areas of poor air entry and decreased vocal resonance may be found. Slight cyanosis and finger clubbing or curved nails are rather common. While the vital capacity is not necessarily reduced, the maximal breathing capacity frequently is. Total lung volume is not always increased, but the residual air may be considerably increased. Exercise tolerance is generally poor, with both exaggerated signs of objective dyspnea and tachycardia.

Electrocardiography tends to show all grades of right auricular and right ventricular enlargement and eventually stress, with right partial bundle branch block in a high proportion of cases.

Radiographically the main features (where there is no associated silicosis) include areas of increased radiotranslucency, alternating with regionally increased linear markings. Bronchography may display regional attenuation or widespread bronchial and bronchiolar cylindrical distention. Glandular crypts are often present. The smaller blood vessels tend to be narrowed and distorted, and in many areas their ramifications become markedly diminished. The central pulmonary arterial trunks are often prominently distended, being often double the normal diameter. This distention may reach aneurysmal proportions and affect the primary and secondary tiers of branches. The azygos veins are often prominently distended. The heart shadow is not often significantly enlarged, except in the later stages of the disease, but the right outflow track and right ventricle may be shown to be distended, and electrokymography reveals markedly increased pulsational amplitude in those fields.

Laboratory findings are in the main negative except for progressive polycythemia, the packed cell volume often serving as a good index of the gravity of the case, those cases with readings in excess of 65% often proving rapidly fatal. Allergies were remarkable for their absence.

The commonest clinical syndromes inferred from this array of findings have been chronic bronchitis, with or without associated bronchiolitis, bronchiectasis or bronchiolectasia, and bronchospasm. Next in order of significance appeared to be emphysema, with some associated diffuse fibrosis, although the latter feature was not too strongly emphasized as a clinical diagnosis. The most important finding was, of course, cor pulmonale, with or without failure. The most remarkable feature about this cor pulmonale was the degree to which it could advance before terminal failure and the virtual irreversibility of the latter once it has reached a certain critical degree.

UNDERLYING PATHOLOGICAL CHANGES IN PULMONARY DISABILITY

Much of the underlying pathological changes in pulmonary disability remain a mystery. It had been assumed many years ago in South Africa that the detailed pathology of silicosis, tuberculosilicosis, and pulmonary tuberculosis of gold miners had been adequately elucidated through the researches of McCrae,⁹ Watkins-Pitchford and Moir,¹⁰ Mavrogordato,¹¹ Simson and Strachan,¹² and Simson, Strachan, and Irvine¹³ and that no more need be added to the subject. It was generally accepted that quartz particles less than 3μ in size are the causative agent with tuberculosis acting as a powerful adjuvant; that silicosis is a nodular or massive fibrotic process; that the disease can readily be diagnosed in life by means of good radiograms and after death by macroscopic examination of the lungs; that it causes disability by virtue of fibrosis, emphysema, and bronchitis, and that up to 75% of silicotics die of tuberculosis and the balance either of cor pulmonale, intercurrent infec-

⁹ References 9 and 10.

tions, or some unrelated cause. The Bureau had codified all these points and had not anticipated the growing quota of "atypical" cases or the introduction of legislation to provide for functional impairments rather than morphological deviations. Histological and experimental research was resumed only after the Allen Commission,¹ had indicated its intention to recommend appropriate legislation. Indeed, the whole report favoring the existence of such a condition as a pulmonary disability (other than that secondary to silicosis) was concluded in spite of the very negative evidence submitted by Bureau officials.

That the lungs of affected sufferers show extensive chronic bronchitis (with or without bronchiolar stenosis, distortion, or distention), emphysema (mainly vesicular but also some perifocal alveolar duct and respiratory bronchiole distention), alveolar wall damage and thickening, and small blood vessel occlusion or narrowing has since been adequately demonstrated. In many of these cases there are also microscopic silicotic nodules which would not be demonstrable by naked eye inspection of the cut surface of the lung or palpation of the tissues.

These lesions are by no means new phenomena among the gold miners of the Witwatersrand. They had previously been reported by Mavrogordato, Simson, and Strachan in connection with silicosis and tuberculosilicosis. Irvine had summed up the clinical syndrome of silicosis as being ushered in by a preceding "dust bronchitis," and Strachan had expressed the view that emphysema, and not the pulmonary fibrosis, is the cause of cor pulmonale in silicotics.

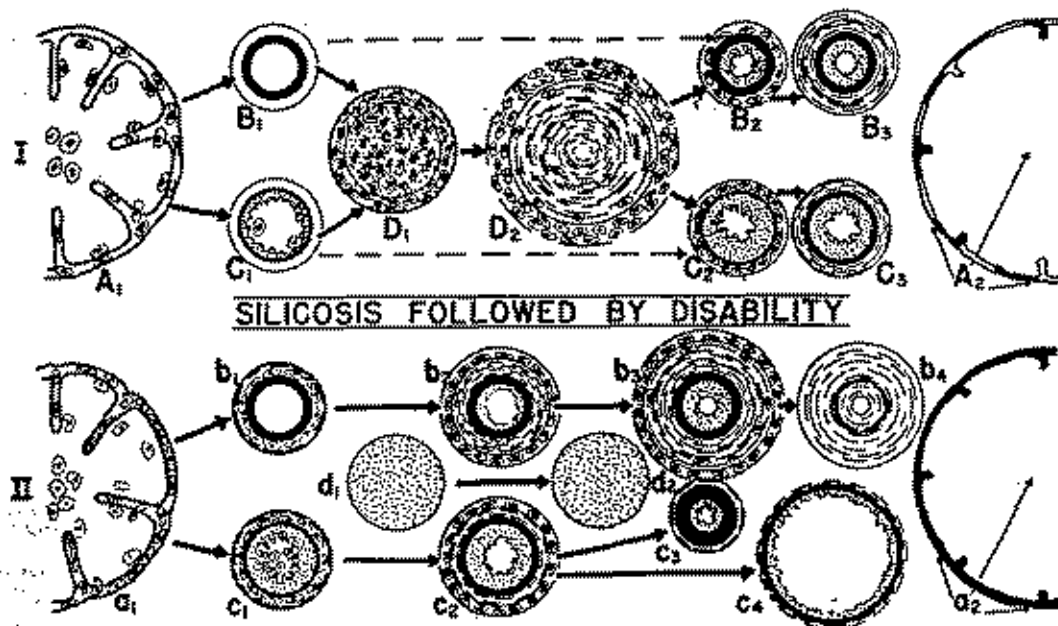
Mavrogordato, Simson, and Strachan had all viewed the dust involvement of peribronchiolar and perivascular lymphatics as a transient phenomenon preceding the overflow of dust into the lymphoid tissue aggregated throughout the lung tissue, in the pleura, and at the pulmonary hilum. It had been tacitly assumed that this overflow phenomenon was the important event in the miner, as it led to the ultimate development of the silicotic nodule. What had not been

envisioned was that, through some as yet inexplicable modifications in the histopathological process, the focus of emphasis of the reaction would shift from the lymph node to the peribronchiolar and perivascular loci. Whereas destruction of the lymph deposits merely implied dealing with them as nature intended that they should be done by, interference with the patency or expansibility and the peristaltic or pulsatile activities of the respiratory and vascular systems of the lungs at their strategically most vulnerable sectors is something not conducive to continued good health of the affected miner. The essential change is summarized in Figure 4.

At least one possible mechanism seems to suggest itself as an explanation for this altered histopathological process. Withdrawal of tuberculous infection as a component process in the chest disease was one of the most worth-while objectives of the antisilicosis measures. It, however, left the miner's lung without the added factor to lend mobility to the koniophores conducting quartz particles from the alveoli to the lymph nodes via the peribronchial and perivascular lymphatics. In the presence of tuberculosis, these cells are known to travel great distances rapidly, and accumulations of dust may in such cases be found in the porta hepatis, the cervical lymphatic nodular chain, and even as far afield as the groins. Such lesions are never seen in simple noninfected silicosis.

This factor, namely, the absence of a tuberculosis element, perhaps together with a reduced dust load, may thus have slowed up the movements of the koniophores, which thus tended to accumulate and die in the perivascular and peribronchiolar lymphatics, thereby exposing these structures to the full deleterious influence of the quartz. It is possible also that, through the increasing mechanization and ever-improving drilling and blasting techniques, mine dusts carry higher proportions of the extremely noxious ultra-microscopic quartz particles. It is possible also that the water-spraying techniques of dust suppression have mainly reduced the proportion of larger particles in the mine

PATHOGENESIS OF PULMONARY DISABILITY



DISABILITY PRECEDING SILICOSIS

FIGURE 4

I

- A_1 —Normal pulmonary alveoli, with quartz-laden koniophores entering mural lymphatics.
- A_2 —Emphysematous alveoli, with partial degenerative mural sequelae of retention of quartz dust.
- B_1 —Normal arteriole, with koniophores passing through perivascular lymphatic plexus.
- B_2 —Arteriole, with delayed koniophore accumulation around it and intimal thickening.
- B_3 —Perivascular fibrosis and endarteriolar proliferation.
- C_1 —Normal bronchiole, with koniophores passing through its adventitial lymphatic plexus and others being expelled via its lumen from the alveolar spaces.
- C_2 —Delayed peribronchiolar koniophore trapping and bronchiolitis.
- C_3 —Peribronchiolar fibrosis, with hypertrophy of muscularis mucosae and mucosal hypertrophy resulting in bronchiostenosis and bronchiolar spasm.
- D_1 —Lymph node undergoing early and cumulative koniophore infiltration.
- D_2 —Silicotic nodule evolved at the site of the lymph node.

II

- a_1 —As for A_1 but with more koniophores being retained in the alveolar walls.
- a_2 —Emphysema and extensive alveolar wall damage as an end-result of the initial accumulation of quartz-laden koniophores here.
- b_1 —Early accumulation of koniophores and fibrocytes around pulmonary arteriole and commencing collagen deposition.
- b_2 —Perivascular fibrosis, with continued koniophore and fibrocyte accumulation around the collagen.
- b_3 —Abundant perivascular fibrosis and intimal hypertrophy.
- b_4 —Perivascular nodules, with disorganization of muscularis and occlusion of vascular lumen.
- c_1 —Early peribronchiolar koniophore and fibrocytic accumulation and endobronchiolitis.
- c_2 —Peribronchiolar fibrosis and hypertrophy of bronchiolar muscular layers.
- c_3 —Bronchiostenosis and bronchiolar spasm.
- c_4 —Bronchiolectasia.
- d_1 —Lymph node not affected at early phase of disease.
- d_2 —Lymph node remains unaffected at a late stage in the disease.

atmospheres, leaving the ultramicroscopic particles still in aerial suspension. Such fine quartz particles when inhaled would have a more rapid damaging effect on the pulmonary tissues and would kill the keniophores before these scavengers could manage to transport them to the regional lymph nodes. One might finally interpose a query also concerning the possible role of elements such as uranium which are known to accumulate in the lung tissues.

Answers to all these questions will come only through further research.

SUMMARY

The South African legal definitions of pulmonary disability, silicosis, and tuberculosis are compared and shown to emphasize, respectively, functional, morphological, and infective disturbances.

While there is no apparent statistical relationship between legal pulmonary disability and tuberculosis, silicotic and nonsilicotic pulmonary disabilities occur at different service periods and ages and in inverse rates of prevalence.

Thus nonsilicotic pulmonary disability now is most prevalent in men of an age group and at a service period which precedes the optimum for the onset of silicosis or tuberculosilicosis. Tuberculosis, however, tends to occur at an earlier stage in the mining careers and at an earlier age than do all three of the former.

The disease is seemingly less prevalent among Negroes who tend, however, to develop silicosis, tuberculosis, and tuberculosilicosis faster than do the white miners.

Pulmonary disability without associated radiographic silicosis or with incipient silicosis is progressively assuming the role formerly played by macronodular and massive silicosis in the causation of physical incapacitation among white miners.

The dominant clinical syndromes of which pulmonary disability is comprised devolve on the triad of chronic bronchitis, emphysema, and cor pulmonale.

In those cases where dust is the causative factor, a possible explanation for the enter-

gence of pulmonary disability without associated or preceding silicosis may be found in the retarded transportation of quartz particles and their deposition around terminal bronchioles and pulmonary blood vessels and in alveolar walls instead of their transportation to lymph nodes.

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Evaluating Disability in Compensation for Pneumoconiosis

Legal Aspects

THEODORE C. WATERS, Baltimore

In our approach to the discussion of the subject which has been assigned to me, I should like to call to your attention that provisions for the compensation of pneumoconioses have presented some of the most controversial subjects in state legislation. In 22 states,* benefits payable for silicosis or asbestosis are subject to limitations which are not applicable to injuries resulting from trauma; in 15 states,† compensation is not payable for partial disability, and with respect to those statutes providing compensation for pneumoconioses, there is extensive variation in the benefits paid and in the concept of disability resulting from these diseases. In my opinion, the reasons for this legislative hiatus are as follows:

1. The fact that, upon enactment of the occupational disease compensation statutes, an employer became liable for the so-called "accrued" liability resulting from the inhalation of dust prior to the time that the law became effective.
2. Problems incident to the proper diagnosis of the disease.
3. Differentials in the concept of compensable disease.
4. Evaluation of disability.

Recorded for publication April 7, 1955.

* Alabama, Arizona, Arkansas, Colorado, Florida, Georgia, Idaho, Iowa, Maryland, Massachusetts, Michigan, Minnesota, New Hampshire, New Mexico, Oklahoma, Oregon, Pennsylvania, South Dakota, Texas, Utah, Vermont, and West Virginia.

† Arizona, Colorado, Florida, Idaho, Massachusetts, Michigan, Minnesota, New Hampshire, New York, Ohio, Oklahoma, Pennsylvania, South Dakota, Utah, and Vermont.

With respect to the first of these items, "accrued" liability is perhaps a misnomer, because what industry was faced with upon the enactment of the compensation statutes was potential liability for pulmonary changes resulting from extended exposure of employees to the inhalation of dust prior to the effective date of the statute. We must bear in mind that upon the enactment of the compensation statutes the employer became an insurer of the health of the employee as to these diseases. He was stripped of his common law defenses, and the continuation in employment by employees automatically imposed upon the employer responsibility for compensation.

With respect to the diagnosis of pneumoconioses, I do not need to tell this audience of the limited general medical knowledge that existed some years ago, at the time of the enactment of our compensation statutes making the diseases compensable. Industrial medicine has made great progress in this field, although there is still room for continuing improvement. In the trial of any given compensation case, commissions and courts follow the general administrative policy of giving to the claimant the benefit of every doubt; and if there is medical evidence in the record to support a diagnosis and finding of the existence of the disease, our administrative agencies are inclined to hold that the disease is compensable, irrespective of the fact that reputable, competent medical testimony will refute an affirmative diagnosis. This reason alone caused great concern to those industries having dust hazards and to insurance carriers responsible upon such risks.

With respect to concepts of disability, we again find material differences in the legislative provisions of our compensation laws.

In summary, they fall into four classifications, as follows:

1. Inability of the injured employee to earn full wages in the employment in which he was last employed.[†]

2. Total disability rendering the employee unable to perform any further work in his then occupation or in any other trade, business, or occupation.[‡]

3. The event of becoming incapacitated, either partially or totally, from performing his work in the last occupation in which he was exposed to the hazard of such disease.^{||}

4. The event of becoming incapacitated from performing his work or from earning equal wages in other suitable employment.[§]

There can be no doubt that the basic concept of "disability" upon the enactment of the workmen's compensation laws was to provide monetary compensation for injuries resulting in a loss of wage-earning capacity resulting from the traumatic injuries or occupational diseases arising out of and in the course of employment. Unfortunately, that original concept has changed. In an effort to liberalize the administration of the laws, compensation has been, and is being, awarded not for wage loss but for what might be termed to be damages sustained by an employee during the course of his employment irrespective of wage loss. While I admit my own prejudice on behalf of the employer and the insurer, the fact is that our legislatures, commissions, and courts, interpreting and administering workmen's compensation laws, are tending to award compensation for loss of earnings irrespective of cause. Perhaps that result is socially desirable; I am not here to argue that point pro or con, but in

[†] Illinois, Indiana, Michigan, New York, and Rhode Island.

[‡] Arizona, Colorado, Nevada, New Mexico, Utah, and Vermont.

^{||} Florida, Georgia, Idaho, Kansas, Maryland, North Carolina, South Carolina, and South Dakota.

[§] Iowa. (Disability not defined in the States of Alabama, Arkansas, California, Connecticut, Delaware, Kentucky, Louisiana, Maine, Massachusetts, Minnesota, Missouri, Montana, Nebraska, New Hampshire, New Jersey, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Texas, Virginia, Washington, West Virginia, and Wisconsin.)

fairness to the employer and to the employee and to the public, I feel that the carrying out of such a policy will make the employer an insurer of the health of the employee, whether or not the employee's illness is attributable to conditions that are characteristic of and peculiar to his employment.

Bearing in mind this change in concept of the basic purpose of workmen's compensation legislation, we now come to the fourth reason above set forth, namely, the evaluation of disability in compensation for pneumoconioses.

It has been my privilege to participate in the trial of a number of compensation cases involving claims for pneumoconioses, and I know of no problem of greater importance and more difficult of solution than the attempted evaluation of disability. While the medical profession has improved its technique for the diagnosis of this condition, little progress has been made in the establishment of some formula for the evaluation of disability. Admittedly, the inhalation of dust over an extended period of time will cause pulmonary changes demonstrable on roentgen examination. All of us are exposed to dust, and I assume that it is correct to say that with advancing age such changes are inevitably demonstrable.

Let us assume that a given employee is exposed to the inhalation of dust, and let us assume further that such inhalation causes pulmonary changes. When does that condition become disabling within the concepts of that term as above referred to? When should the employee subject to exposure be removed from his employment? When should such employee be deprived of his privilege of continuing at work in the occupation in which he may be engaged? What methods are available to medical science to evaluate partial disability? What methods are available to medical science to pronounce that the employee is totally disabled? What sequelae result from a diagnosis of partial disability? Should the employee at that time terminate his employment? Should he be paid "X" dollars and have that payment

EVALUATION OF DISABILITY

effect a release of continuing liability to his employer? Should his ability to procure other employment free from dust exposure deprive him of any continuing benefit under the compensation law? What methods are available to our commissions and courts to properly evaluate disability free and clear of prejudiced medical testimony that may be offered by the claimant? By the employer? Or by the insurer? These are the imponderables with which we are faced in our consideration of this subject.

We still do not know all the answers to these questions, but I would like to review with you briefly some of the standard legislative provisions which have attempted to deal with these matters and to establish directives to administrative agencies in handling claims. The principal legislative provisions to which I would refer are as follows.

1. DENIAL OF COMPENSATION FOR PARTIAL DISABILITY

From the medical standpoint, the evaluation of partial disability resulting from pneumoconioses differs materially from scheduled injuries presently compensable for loss, or loss of use, of other parts of the body, such as an arm, leg, hand, etc. The Saranac Laboratory has been a leader in medical research attempting to find some method for the evaluation of partial disability, but its present distinguished Director, his predecessors and their associates, and other scientists engaged in these studies have not as yet found the answer to the problem. Of necessity, the attempted evaluation of a fixed percentage of disability is exceedingly complicated and unsatisfactory. Therefore, the employer and the insurer contend that compensation should not be paid unless the claimant has suffered wage loss or that compensation, if any, payable for partial disability should effect the discharge of the employer's liability within a reasonable time after termination of employment. Contra, the employee has, in fact, received some injury from the inhalation of dust and development of demonstrable disease. Perhaps legislative provisions denying compensation for partial

disability are not thoroughly satisfactory or fair to the parties concerned with the administration of the laws, but unless and until the medical profession gives its approval to some method of evaluation of partial disability, strong arguments may be presented for this type of legislative provision.

2. COMPENSATION FOR TOTAL DISABILITY

No one can challenge the propriety of paying compensation for total disability for pneumoconioses. However, what do we mean by total disability? Under the definitions above referred to, it may mean one of several things:

- a. The inability to earn any wages in the employment where last employed.
- b. The inability to perform any further work in the occupation in which the employee was engaged.
- c. The inability to earn equal wages in other suitable employment.

Under the first concept of disability, complete loss of wage is a condition precedent to an award of compensation.

Under the second concept, the employee must be unable to perform any further work in his occupation. In this class, we are faced with the administrative and court rulings that have the effect of awarding compensation in those cases where the administrative agency is of the opinion that continuing exposure is hazardous and detrimental to the claimant and, therefore, compensation for total disability should be awarded even though the claimant is able to make as much, and in some cases more, in other employment.

In the third classification, the right to recover compensation is dependent upon proof that the claimant has been incapacitated from earning equal wages in other suitable employment.

Simply to state these phases that enter into the determination of what is and what is not a compensable claim illustrates the problems facing our compensation commissions in disposing of issues presented by this disease.

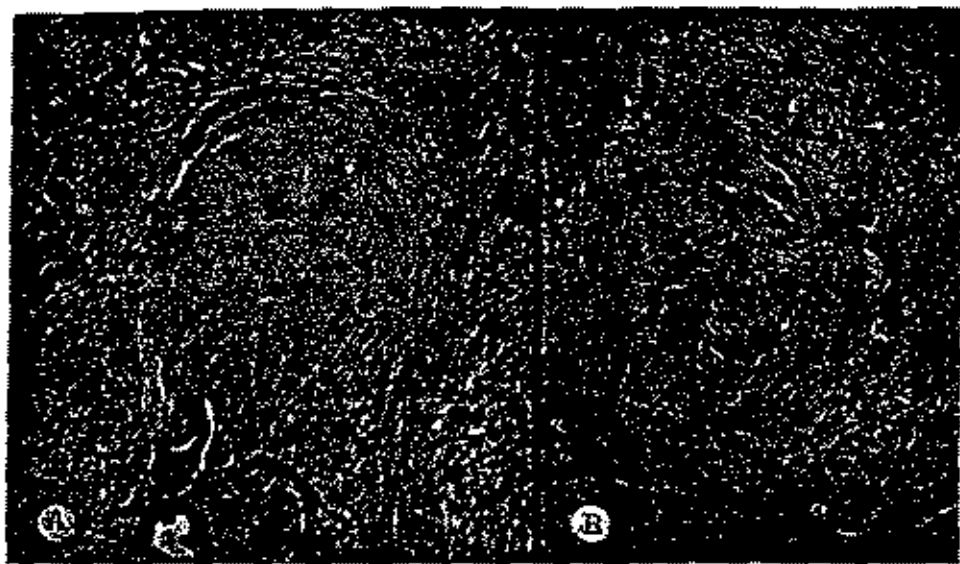
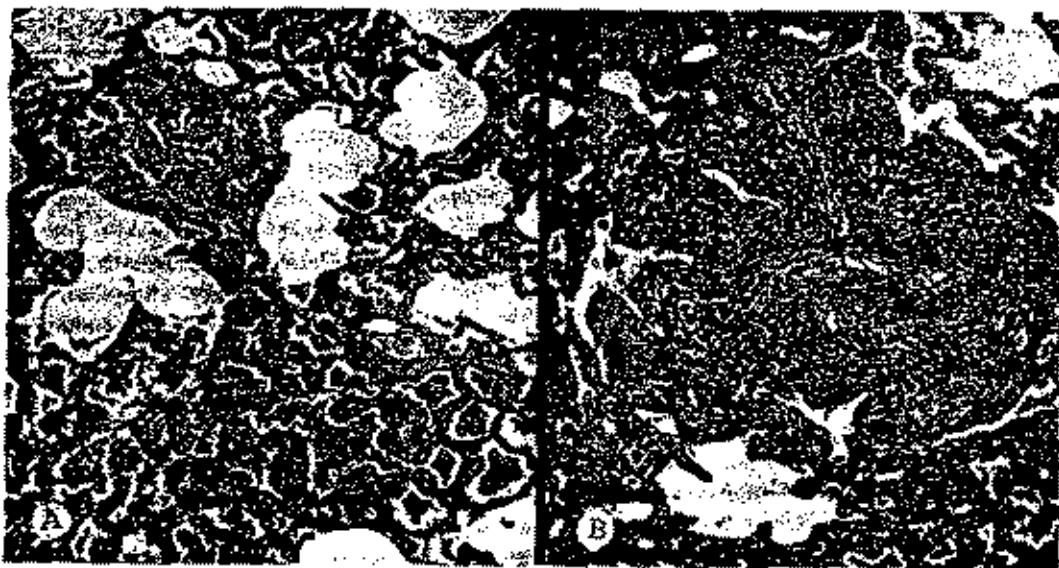


Fig. 7.—Capacity of aluminum hydroxide to arrest the progression of silicosis. Experiment 805—rabbits received 500 mg. of quartz particles for one month in 10 equal intravenous injections; six months later half of the animals received 10 injections of 0.2% $\text{Al}(\text{OH})_3$ for five weeks. Microscopic sections. *A*, liver of aluminum-treated animal, showing limited hyalinization and partial regression of silicotic nodules at end of one year. *B*, liver of untreated animal, showing complete hepatic fibrosis at end of one year.

Fig. 8.—Capacity of intracardially introduced aluminum hydroxide to prevent completely the development of silicosis after six months of exposure to quartz dust, provided that no further exposure to quartz dust follows. Experiment 804—guinea pigs. Microscopic sections. *A*, lung of animal exposed for six months to inhalation of quartz dust, followed by intracardial $\text{Al}(\text{OH})_3$ therapy and residence for six months in fresh air; reaction limited to macrophage accumulation within the alveoli. *B*, lung of animal exposed for six months to quartz dust, followed by intracardial $\text{Al}(\text{OH})_3$ therapy and a further six months' exposure to inhalation of quartz dust; partial protection only; cellular nodules with partial central fibrosis and necrosis.



3. VALUE OF MEDICAL BOARDS IN THE STATE ADMINISTRATIVE AGENCY

One result of the problems presented by compensation for pneumoconioses is legislative recognition of the value of Medical Boards to assist the administrative agency in its determination of issues presented in claims. The basic questions involved are medical, namely: (a) whether or not the claimant has a disease; (b) the nature and extent of disability. Owing to the highly technical nature of the medical testimony presented on behalf of the claimant or the employer, the need for Medical Boards to evaluate that testimony is imperative. The net result is that now 17 states[#] have Medical Boards whose decisions are either conclusive with respect to the medical issues involved in the claim or advisory to the administrative agency.

In the past, too little attention has been given to the role of the medical examiner in the administration of workmen's compensation laws. Time does not permit an extended discussion of this matter, but I express the hope and opinion that in the future our legislatures and commissions will not only recognize the need for such Boards but accept and enforce their opinions in preference to the prejudiced opinions of witnesses testifying on behalf of litigants.

4. EXISTING LEGISLATIVE METHODS PROVIDING COMPENSATION FOR TYPES OF DISABILITY

Time does not permit the detailed discussion of this phase of the subject that is merited, and I can only generalize with respect to it. However, I should like to call your attention to the following features of legislative provisions:

a. Denial of compensation for partial disability (discussed above).

[#] Arizona, Colorado, Georgia, Idaho, Iowa, Maryland, Minnesota, Nevada, North Carolina, Ohio, Oregon, Pennsylvania, South Carolina, South Dakota, Texas, Utah, and West Virginia.

b. Monetary limitations of compensation, awarding limited compensation for partial disability and escalator provisions for total disability.

c. Limitation provisions barring right to recovery dating from the termination of employment.

With respect to these matters, I commend to you for consideration the statutes of Arkansas, Maryland, North Carolina, West Virginia, and Wisconsin. None of them are perfect, but they have attempted to define some method for the proper compensation for partial disability with termination of continuing liability of the employer.

Perhaps the most grievous defect in all statutes is found in those sections dealing with limitation provisions relating to the time when claims must be filed in order for them to be compensable. This is a major problem and one which presents the opportunity for extended discussion. From the standpoint of the employer and the insurer, they desire the termination of liability within a reasonable period of time after employment has ceased. From the standpoint of the employee, he feels that he is entitled to compensation beginning at any future time when the disease becomes demonstrable or disabling irrespective of the date of termination of his employment. Certainly from the standpoint of legislation, we do not know the answer to this problem.

CONCLUSION

The foregoing discussion has been presented for the purpose of directing our thoughts to those questions, medical and legal, involved in the evaluation of disability. I have attempted to address my remarks to the legal issues presented. Our state legislatures and our commissions and courts have not found the answers to the problems so presented. In cooperation with our brothers of the medical profession, it is to be hoped that greater uniformity of legislation and administration may develop in this field and that justice may be done to those affected by the administration of our compensation laws.

The Radon Problem in Deep-Level Mining

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PAST EXPERIENCES

The occupational exposure of workers to radioactive dust and gas has only recently become of general interest. Interest increased as uranium became an important and widely sought after mineral. This development has resulted in the employment of large numbers of miners, so that a problem that was once of apparently minor importance in this country has become one that demands a solution. It is the purpose of this paper to present data on levels of radon found in uranium and in nonuranium mines, to refer briefly to possible biologic effects, and to make a plea for the careful examination of existing data which should help in the determination of a safe working level of radon and its degradation products.

All uranium ores contain radium, and therefore the radioactive gas radon is continuously produced and is released into mine atmospheres. This gas and its immediate daughters, RaA through RaC', are regarded as the most important radioactive elements present in uranium mines from the standpoint of their possible biologic effects. The question then is: What are the effects produced by the inhalation of alpha-emitting radioactive elements? The result of human exposures should provide the data in establishing proper working levels, but, unfortunately, such records are limited with regard to the elements with which we are now concerned.

Recorded for publication April 7, 1955.

Sanitary Engineering Director, Occupational Health Field Station, Division of Special Health Services, Public Health Service, U. S. Department of Health, Education, and Welfare (Mr. Holaday). Presented by W. Clark Cooper, M.D., Medical Director and Chief of the Division of Special Health Services, Public Health Service, Cincinnati.

Available data are confined almost entirely to the experiences in the Schneeberg and Joachimsthal mining areas, of Germany and Czechoslovakia, respectively, where an abnormally high incidence of lung cancer was found among miners who had worked for years in mines which were shown to contain high concentration of radon. Peller,¹ in 1939, analyzed the cancer mortality experienced by the Joachimsthal miners. He states in his summary that the miners in Joachimsthal had a high percentage of cancers (53%) among causes of deaths. This greatly increased cancer mortality rate was due to an enormous frequency of pulmonary cancers in the age group from 35 to 54; there was an exceptionally high proportion of primary lung cancers, a reduced incidence of cancer in nonrespiratory organs, and an increased mortality from causes other than cancer in the younger age groups.

After the existence of the cancer problem had been demonstrated, measurements were made of the atmospheric concentrations of radon in these mines. Evans and Goodman,² in summarizing these data in 1940, concluded that the average concentration of radon in the mines was approximately 1000 μ cc (micromicrocuries) per liter.

LACK OF ADEQUATE DATA

Bale^{*} has summarized some of the uncertainties in retrospective interpretation of the foregoing data as an aid to defining present standards. In the first place, we do not have adequate data on lung cancer rates in this region of Europe compared with other mining areas where radon was absent or present in low concentrations, and, secondly, the radon concentrations as measured might

* Bale, W. F.: Personal communication to the author.

not be the same as those that were common in the mines some years earlier. The long latent period for lung cancer might mean that the exposure 10 to 30 years before the development of symptoms was the important one.

From our own work in mines, we know that minor amounts of ventilation will reduce radon concentrations markedly as contrasted with those existing under conditions of no ventilation. Thus even limited efforts to reduce the radon levels in the European mines may have lowered the atmospheric concentrations by large factors.⁸ Perhaps the greatest uncertainty is due to the complete lack of information on the atmospheric concentrations of the immediate daughters of radon whose importance as inhaled sources of radiation has been recognized only recently.

Shapiro⁴ has demonstrated that only a minor part of the radiation dose is delivered to the lungs by radon, with about 95% of the total alpha dose resulting from the inhalation of RaA, RaB, and RaC. Thus a measurement of the radon concentration only is a poor index of radiation exposure. Even small amounts of ventilation change the ratios between radon and its daughters in mine atmosphere, and so it is impossible to infer the amount of the latter elements present in the European mines even where the radon concentrations are known. Altogether, it does not seem that such data as we have on human exposures in uranium mines of Europe are reliable enough to be of much assistance in establishing maximum allowable or acceptable concentrations.

COLORADO PLATEAU URANIUM MINES

While we have pointed out that the records of European experience are not complete enough to enable us to establish maximum

safe working levels, it still is of interest to compare the reported atmospheric concentrations of radon in those areas with the levels that have been found in American uranium mines. During studies of the Colorado Plateau mines carried out by the Public Health Service in collaboration with the Atomic Energy Commission and the health departments of the interested states, several hundred atmospheric samples were taken and analyzed for radon and its alpha-emitting daughters. The unpublished results of some of this work are summarized in Tables 1 and 2.

Table 1 shows the atmospheric concentrations of radon found in a number of uranium-

TABLE 1.—Concentrations of Radon in Uranium Mine Atmospheres by Mining Areas

Area, No.	No. of Mines	Median Ra, $\mu\text{R}/\text{Liter}$	Max. Ra, $\mu\text{R}/\text{Liter}$	Min. Ra, $\mu\text{R}/\text{Liter}$
1.....	37	8,300	48,700	1,300
2.....	4	4,200	6,000	8,100
3.....	31	4,100	59,000	1,000
4.....	37	3,900	22,000	130
5.....	4	1,100	3,200	160
6.....	6	670	23,000	70

mining districts. The results are summarized by mine areas. Thus, in Area 1, samples which were taken in 17 mines showed a minimum radon concentration of 1300 $\mu\text{R}/\text{liter}$ and a maximum concentration of 48,700 $\mu\text{R}/\text{liter}$, with a median value of 8300 $\mu\text{R}/\text{liter}$ for all samples. It will be remembered that the average concentration in the European mines was estimated at 1000 μR of radon per liter of air.

Table 2 shows the distribution and the cumulative distribution of miners by levels of radon daughter concentrations. Thus 140 of the 733 miners were exposed to concentrations between 1000 $\mu\text{R}/\text{liter}$ and 2000 $\mu\text{R}/\text{liter}$, but 469 (approximately 64%) were

TABLE 2.—Distribution of Uranium Miners by Radon Daughter Concentrations

Item	$\mu\text{R}/\text{Liter RaA + RaC}$						
	0-100	100-400	500-900	1,000-1,900	2,000-4,900	5,000-10,000	10,000
No. of miners (733).....	136	111	71	140	135	80	126
Per cent.....	18.6	15.0	9.7	19.1	18.4	10.9	17.2
Cumulative no. of miners.....	136	247	318	458	593	673	733
Per cent.....	18.6	33.7	43.1	62.2	80.8	91.7	100.0

Average (all mines)—4,200 $\mu\text{R}/\text{liter RaA + RaC}$
Median (all mines)—1,300 $\mu\text{R}/\text{liter RaA + RaC}$

RADON PROBLEM IN DEEP-LEVEL MINING

exposed to atmospheric concentrations of RaA plus RaC' greater than 1000 $\mu\text{mc}/\text{liter}$ (1000 $\mu\text{mc}/\text{liter}$ of RaA plus RaC' is equivalent in alpha activity to 500 $\mu\text{mc}/\text{liter}$ of radon at equilibrium with its immediate daughters).

CALCULATION OF DOSE TO LUNGS

We have referred to alpha radiation dose to the lungs, and it is interesting to review some unpublished calculations by Bale, (Table 3), showing what the magnitude of this dose may be.[†] These calculations were based on continuous exposure to an atmosphere containing 10 μmc of radon per liter, with an equivalent amount of RaA and 5 $\mu\text{mc}/\text{liter}$ of RaB, RaC, and RaC'. Using

TABLE 3.—Assumptions Used in the Calculation of Tissue Dose

1. Retention in the respiratory tract is 25%.
2. These elements remain in the respiratory system until they have decayed through RaC'.
3. Fifty per cent of the degradation products are taken out in the bronchial tree.
4. The weight of the lungs is taken to be 1000 gm.
5. The effective depth of alpha radiation in tissue is 40 μ .
6. The total air breathed in a 168-hour week is 160 cubic meters.
7. The relative biologic effectiveness of alpha particles is 10.

assumptions for retention of dust and weight of tissue affected similar to those used by the National Committee on Radiation Protection, the weekly dose to the lungs from radon degradation products is 0.043 rem and to the bronchi, 0.72 rem. For estimating exposure levels for workers, we should remember that the concentrations of radon daughters used in these calculations are much lower than would be found in operating uranium mines; hence it appears that the respiratory system of a person working in such atmospheres will receive a large radiation dose. For example, a level of 1000 $\mu\text{mc}/\text{liter}$ of RaA, with 500 $\mu\text{mc}/\text{liter}$ of RaB, RaC, and RaC', will give a calculated dose to the lung amounting to 4.3 rem per week and 72 rem per week to the bronchi. Calculations made using these assumptions give doses in animals comparable to those determined ex-

perimentally by Shapiro.⁴ This suggests that the calculated values are an approximation of those which would be received by humans under the above conditions.

It must be pointed out in this connection that it is not possible to consider radiation doses to an organ like the lung by the standards for whole-body external radiation. The latter standards were established with reference to the effect of radiation on the blood-forming organs. Such criteria cannot be applied to tissues where the creation of malignant neoplasms is the important factor.

NONURANIUM MINES

As uranium is widely distributed throughout the earth's crust, it appeared likely that mines other than those that produce uranium would also have some radon in them, and this opinion has been confirmed by several studies. Jacoe⁵ has reported the results of studies in mines in Colorado, and Harris⁶ has reported similar work in New York. In 35 metal and clay mines surveyed in Colorado, the lowest radon concentration found was 10 $\mu\text{mc}/\text{liter}$ and the highest was 2100 $\mu\text{mc}/\text{liter}$. This latter figure is not strikingly different from the average figure of 1000 $\mu\text{mc}/\text{liter}$ found in the European mines. In the New York mines, the lowest radon concentration found was 2 $\mu\text{mc}/\text{liter}$, while the highest was 110 $\mu\text{mc}/\text{liter}$. These and additional surveys in other parts of the United States suggest that radon is a normal constituent of mine atmospheres.

BIOLOGIC EFFECTS

Saltzer and Hursh⁷ have proposed that urinary polonium measurements may serve as a rough measure of cumulative lung exposure to radon and its daughters, since the daughters decay to Pb^{210} , a lead isotope with a long effective half-life in the body and a decay scheme producing Po^{210} . In a comparison of the urine findings of 19 uranium miners of the Colorado Plateau with those of unexposed laboratory personnel, it was found that the miners chronically exposed to high radon concentrations had amounts of

[†] Bale, W. F.: Unpublished data.

Po²¹⁰ varying from 2 μ c/liter to 38 μ c/liter, while no polonium was found in the urine of the laboratory group. Thus it would appear that the miners had inhaled and retained radon and its degradation products.

A PLEA FOR THE EXAMINATION OF EXISTING DATA

These studies, together with unreported work by other groups, indicate that occupational exposure to appreciable amounts of ionizing radiation has been common among miners and has existed for a long time. The existence of such a large group of persons who have been exposed for long periods to relatively low levels of radiation (compared with those that occur in uranium mines) suggests that it might be possible to evaluate the effect of inhaled alpha-emitting elements on the basis of past experience. However, such a study could only be done in an area where a large enough group of workers with a defined working and medical history can be followed. This means that the mining population must be as stable as possible, that medical records must be sufficient to determine the cause of illness or death, and that the environmental history of the mines can be obtained or estimated from present atmospheric concentrations and records showing when ventilation was introduced.

Such conditions are difficult to meet in the United States where miners are a very mobile group indeed. However, it is possible that such a study could be successfully carried out in mining areas in other countries with more stable populations and more complete medical records. Any conclusive results that would be obtained from an investigation of this type would be of invaluable assistance in estimating the extent of the hazard created by the inhalation of radioactive elements, regardless of whether or not the study showed that there had been discernible effects on the health of the workers. The number of uranium miners is increasing rapidly, and every effort should be expended to obtain information that will permit the establishment of safe working conditions. In addition, there are many metal mines

which have atmospheric concentrations of radioactive dust and gas which exceed any working levels which have been suggested for uranium mines. Undeveloped data which will indicate the biologic effects of exposure to radon and its degradation products probably exist, but it will require a concerted effort on the part of a number of organizations to assemble and analyze the information.

CONCLUSIONS

High concentrations of radioactive dust and gas can be demonstrated in a high proportion of uranium mines. However, appreciable concentrations have likewise been demonstrated in many nonuranium mines. Adequate data are not available for interpreting these concentrations in terms of effects on human health, but it is very important that standards be agreed upon. It is urged, therefore, that a concerted effort be made to study records of miners who have worked for years in nonuranium mines, in hopes that data bearing upon the establishment of reasonable maximal allowable concentrations can be obtained.

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Current Problems in Dust Control in Metal Mines

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The control of dust in metal mines presents problems that vary in many respects. This is so not only from mine to mine but also between parts of the same mine. Some of the problems are new, in the sense that they have assumed importance through changed conditions. Some are old, still presenting a challenge. All, however, are continuing affairs, inasmuch as constant efforts are required to maintain exposures at a practicable minimum.

This paper deals with the principal problems in Ontario mines—problems which, it is suggested, probably obtain in many mines elsewhere. The text is based on 20 years' association with endeavors of this kind in an industry that has achieved a fair measure of success in the prevention of silicosis.¹

THE MINING INDUSTRY OF ONTARIO

The mining industry as a whole employs some 35,000 persons, about two-thirds of whom have dust-exposure occupations. Most mines are multilevel underground operations in steeply dipping veins. The veins vary in width from less than a foot to several hundred feet and may or may not be branching systems. The depth of operations ranges from a few hundred feet to approximately 8200 ft. below surface. The primary products of the underground group are gold, silver, cobalt, copper, nickel, iron, talc, fluor spar, and gypsum. Uranium will soon be added to the list.

Recorded for publication April 7, 1955.

Safety Director and Chief Engineer and Secretary, Committee on Silicosis, Mines Accident Prevention Association of Ontario.

There are a few open-pit mines. However, these are temporary in type because, as the outcrops are removed, the mining is done below surface. Primary products of the open pits are asbestos, copper, nickel, iron, magnesium, and nepheline syenite.

Daily production of ore ranges from less than 100 tons to about 15,000 tons, though it is considerably more at some open pits. The ore is crushed, screened, and treated by appropriate metallurgical processes.

The risk of silicosis obtains mainly in underground operations, also in crushing and screening.

This general picture may be concluded by referring briefly to the Mining Act of Ontario. In essence the Act requires wet-mining methods underground and suitable ventilation to avoid exposure to harmful dusts and gases. These legal precautions, supplemented by x-ray examinations of the chest and compensation for silicosis, were requested by the mining industry many years ago and have contributed much to achievements in the prevention of this disease.

PERMISSIBLE LIMITS OF ATMOSPHERIC DUSTINESS

The vexatious question of permissible limits of atmospheric dust deserves comment at the outset because it is a current problem in the minds of many. It will remain a problem for years to come, because there are so many variables which defy assessment.

Most of the silicosis in Ontario had its origin in gold mines, where it would appear the amount of quartz in aerial dusts ranges from 14% to 28%, as determined by x-ray diffraction-pattern assays.

Although some research has been effected with the thermal precipitator, all routine dust-sampling and test work at Ontario

mines has been done with the circular konimeter for the past three decades.

Konimeter samples are heated to about 1000 F before and after treatment with warm 50% hydrochloric acid for two minutes. They are counted at a magnification of $\times 150$ against a dark field. The illumination is a 100 watt frosted electric bulb, placed 9 in. from the mirror of the microscope. Considerable research has been done seeking relief from the tedium and eyestrain when counting samples; microprojection and comparison methods have been tested. To date, however, the problem remains.

Through the years, we have come to appreciate that, in our case, konimeter counts of the order of 100 to 300 particles per cubic centimeter (ppcc) are "good"; those of the order of 500 to 700 or 800 ppcc are "fair" only, while those in excess of 1000 ppcc are "poor."

The sins of the past have been erased for the most part, and the dust counts at many installations and operations perfected in recent years approximate 100 ppcc.

However, we still have problems, and always will have them, because methods of mining, ground conditions, and personnel change. The same applies to other industries.

DRILLING

Drilling is a major operation in any metal mine. Most of it is done by percussive drills operated by compressed air. Dust sampling has proved, however, that wet drills of this kind still liberate undesirable amounts of dust. The diamond drill, a rotary machine, presents no problems in this respect.

Much of the dust from percussive drills is caused by air which leaks past the piston into the fronthead of the machine, whence it passes down the hole in the drill steel as bubbles in the water. As these emerge from the hole, they release dust.

This condition was improved, however, in the so-called "dustless" drifter, which has vents in the fronthead to allow this air to escape. This type of machine had its origin in South Africa. It was introduced into

Ontario mines about 1930 in headings and stopes. Some companies used it in all such operations. A number of these drills are still in service. Utility of the vented fronthead was demonstrated by the fact that if horizontal holes were properly started the average dust count during drilling could be reduced to about 300 ppcc or even, in some instances, to about 150 ppcc.

Dispersal of dust was reduced also by increasing the amount of water. This was done (a) by paying more attention to pressures—an important aspect, (b) by enabling more water to get through the machine itself, and (c), in the case of some bits, by providing more holes for water to be delivered to the cutting edges.

Collaring, or starting a hole, is the most vital factor in the dispersal of dust at any drill. If this operation is done wet, the dust liberated is not a serious problem. If it is done dry, the amount dispersed may completely obliterate the utility of all other means to control dust incorporated in the drill. The industry therefore welcomed the automatic air-and-water throttle when it became available in 1938 and promptly put it to good use—first on Leyners, or mounted, machines and recently on some stopers and airlegs.

The automatic air-and-water throttle is a good device when properly used, because a lower dust count will obtain at a drill so fitted than can be expected at a machine where collaring is done by the old-fashioned method. However, its utility is defeated in many instances by the provision of a hand-valve in the hose for water at the drill so that the machine man can control the supply of water when starting a hole and minimize splashing.

The advent of the steel holder or hole spotter for Leyners helped this situation much. It also improved safety and decreased wear in the chuck of the machine by preventing the drill steel from wobbling. Much good has been done also by a persistent educational campaign in collaring. But the problem is still with us.

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The light-weight airleg machines and various kinds of bits introduced in recent years revolutionized drilling practices and re-created problems in dust control. The vented frontheads and automatic air-and-water throttles disappeared rapidly, though they have lately reappeared on light drills.

As for the use of bits tipped with tungsten carbide, the dust counts were not nearly so good as expected, especially when some types of chisel bits were being used. The reason would appear to be that sufficient water does not reach the cutting edge. The chisel bit with only one sidehole for water is an example.

It is difficult to control dust while drilling holes upward. The principal reasons are inability to maintain a seal of water in the hole and the use of compressed air to keep cuttings out of the working parts of the machine. Obviously the condition with respect to dust dispersal deteriorates in confined spaces, being most difficult in dead ends such as raises.

The remedies are not easy. Manufacturers have improved machines used to drill up-holes by increasing the flow of water and decreasing the amount of air by blowing and, in a few cases, by providing the automatic air-and-water throttle; there are also a few vented frontheads in service. As for ventilation, it can be maintained in a timbered raise, but we have yet to discover how to provide adequate facilities of this kind in an untimbered or raw raise. Research to this end is being done.

Drill dust is important also because of its fineness, a characteristic that it possesses to a greater degree than dust from ore handling or crushing, for example. The finer the degree of subdivision, the greater the possibility that dust so produced may enter the air sacs of the lung. In theory also, a dust which is finely divided should have an enhanced chemical activity on human lung tissue.

A further major reason for dust control at drills is not only that the dust is fine and in some circumstances apt to be present in unhealthy amounts but more especially that it is

liberated and breathed for a considerable period during the working shift. The dust cloud from blasts may be much denser and the component particles just as fine, but the bulk of it is created and removed in circumstances that ordinarily do not give rise to excessive exposure. In drilling, the direct opposite occurs. Moreover, persons working beyond the immediate source of pollution may be subject to its effects, though to a slighter extent than the machine men.

Some years ago, investigators in England suggested that freshly fractured dust may be more active chemically than dust which has been made for some hours. The reason concerns an unsatisfied oxygen valence on the surface of the particles. If this is so, there would be further justification to control dust well at drills.

Another reason is yet more important. Dust control at these sites is necessary to supplement ventilation. It is perfectly true that good ventilation will provide good air conditions at any drill. It is equally true, however, that the application of adequate air circulation is not feasible for this purpose at all drills at all times in our mines. The same may be true in others.

Our industry has done much to reduce dust from this source, with beneficial results. During recent years, however, drilling equipment and practices have changed notably. Field observations have indicated that the time has come to reassess exposures in these operations in order that the operator and the manufacturer of drilling equipment may be guided properly in continuing to prevent silicosis of this origin. In November, 1954, therefore, we commenced a comprehensive series of tests on drilling equipment under controlled conditions at an underground location. Three engineers—two of our own and one lent by a group of mines—are engaged in this research on a full-time basis, assisted by various operating personnel. The tests will continue at least through April, 1955. When the research has been completed to our satisfaction, a report will be published.

It is our belief that the maker of a piece of equipment, the developer of a process, which produces or entails a hazard to health, should be interested in the elimination of that hazard and that the manufacturer is in a better position than the user to design and publicize remedial measures for the equipment which he markets. It might be good business for him to do so, too. It would help also if purchasing agents were kept informed of dust aspects.

The manufacturers of drilling equipment presently being tested by us are cooperating extensively in this research, and, as for the mines, especially the one where this work is in progress, they are indeed generous in their assistance.

MINING METHODS

Methods of mining and of handling broken ore and waste have been changing too in recent years. Rising costs of labor and supplies hasten many of the changes. There was also the desire or the necessity to extract large low-grade ore bodies by means that were safe and efficient. There are today extensive operations in which the ore is undercut and caved, or broken in huge stopes by drilling and blasting long holes from sub-levels on a retreating basis, or removed by some kind of room-and-pillar method.

The changes thus effected have all added up to a substantially increased rate of production. This, in turn, has meant the creation of more dust. The problem therefore has been to get rid of it. The risk of silicosis in these large-scale operations has, however, decreased because fewer men are involved. Moreover, the size of the undertakings is such as to justify the provision of excellent ventilation in most cases. The problems involved have been numerous. Invariably, though, they have been associated with the provision of major increments to the ventilation of the mine concerned.

MECHANICAL SHOVELS

Years ago, when a hand shovel was used to load cars in a heading, the dust count could be held to 150 ppcc if the muck was kept wet.

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Use of a small mechanical shovel in comparable circumstances automatically raised air dustiness two to four times. Larger loading devices of this kind are in service now in many mines. Continuous loaders are also employed in some parts of the United States and Canada. This has necessitated a constant battle to maintain good air conditions.

Control of dust at mucking machines depends on the extent to which water and ventilation are applied. There is a limit to which water can be used in some mines. Heat is the handicap in a few instances. However, in the majority of such mines the difficulties are due to the nature of the material being handled, for example, talcose rocks and some iron ores. On the other hand, it would appear that in most metal mines the use of water to allay dust has not yet been fully exploited.

The ventilation of places where mucking machines are operated falls into two categories. Some loaders are operated at draw-points and in back-stopes. The only problem in the ventilation of these working sites is that of insuring that the system for the mine as a whole serves them adequately. Ventilation of room-and-pillar operations (a system of mining seldom seen in Ontario because of the nature of our deposits but one that is to be used extensively in the uranium mines in one district) has been developed highly in some operations in the United States.

The majority of our mechanical shovels are operated in headings, where auxiliary ventilation is necessary. There is slow but growing appreciation of the importance not only of removing dust from such places by means that do not pollute other workings but also of maintaining satisfactory drafts at the face itself. In this connection, experience proves that the best results are obtained by the dual, or push-pull, system.

There are few problems in the practices of auxiliary ventilation. There is, however, a very real one in regard to costs, because metal ducts for this purpose are expensive. Flexible tubing is not popular in Ontario.

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SCRAPERS AND SCRAMS

Development of mechanical shovels to load muck into cars was paralleled by extensive application of scrapers or boes to drag ore or waste to transfer passes or loading points. The scrapers vary in width up to 6 ft. The hoists that pull them by means of cables range in size up to 150 h. p. The small ones are operated by compressed air; the large ones, by electricity.

As in the case of mechanical shovels and loaders, control of dust raised by scrapers is important. Water and ventilation are the remedial measures.

The majority of the smaller scrapers are used to move ore and spread fill-in stopes where intermittent cut-and-fill operations are practiced. They are used also in many other kinds of stoping to drag ore to drawpoints of one kind and another, for example, down the footwall of an irregular deposit inclined at 40 degrees being mined by open-stope methods. The task is, as always, to keep the muck wet by sprays and to dilute and carry away dust that is raised. The fact that in many multilevel mines it is not practicable to split the general ventilation to the extent feasible in flat deposits extracted by the room-and-pillar method is another handicap. These and other aspects in the use of small scrapers suggest the advisability of giving maximum attention to the use of water in conjunction with good general ventilation.

In those operations in which large tonnages are moved by scrapers, the ore may be broken in huge stopes of the sublevel type or by undercutting and caving the ground above. It is removed through drawpoints, which feed into a scraper drift, or "scram," beneath the deposit, by a scraper dragged back and forth.

The introduction of this kind of mining posed many problems. It was early recognized that the facilities for ventilation had to be much larger than those serving most other types of extraction. It was necessary, for instance, to rid the scrams of dust and smoke rapidly and thereby to be able to

see throughout their lengths. Cost of provision was, however, pared to the bone as it depended on ability to move much muck in short time. It was recognized also that a from scrams should be taken to surface by untraveled routes in most cases, its dust content rendering it unfit for breathing.

Initial designs were based on air speeds of 85 to 100 ft. per minute in scrams. This has been found not to be enough. Good practice is to use 50% more.

VENTILATION OF LARGE-SCALE OPERATIONS

It is at once obvious that the provision of adequate ventilation for this kind of mining is a major undertaking as well as an expensive proposition, especially in a deep mine.

The changes necessary are difficult to effect satisfactorily in any existing mine—for numerous reasons beyond the scope of this paper. On the other hand, it is gratifying indeed to see new producers taking full advantage of the experience of pioneers in this field.

It is always good practice to consider general ventilation when mine layouts are made. Where large-scale operations, such as those discussed above, are contemplated, it is essential that this be done.

The general ventilation of many Ontario mines is accomplished by the push-pull system; that is, air is blown underground and is exhausted by fans at or near the surface, preferably in the latter location. The push-pull system is particularly desirable where mining is done by sublevel stoping, caving, and the use of scrams, because the control of air movement is facilitated.

Control is vital in such mining, as the workings are huge and the rate of mining is high. For dust to be effectively controlled, the amounts of air circulated have to be large, with the result that much money has to be invested in ventilation.

A major problem has been the development of stoppings strong enough to withstand severe concussion. The strong blasts

necessary in this kind of mining require that heavy steel, concrete, and timber be used for this purpose.

Experience has shown also that in some mines it is necessary to install booster fans in return air circuits solely to insure that a given group of, say, five scrams will get its fair share of the total available ventilation. That is the only purpose of these units. Such fans range in capacity from 30,000 to 60,000 c. f. m. at pressures under 1 in. water gauge. Some operators would like to use a small exhaust fan at the tail end of each scram but cannot find one able to take the concussion.

The new fan capacity installed for general ventilation in Ontario mines since 1938 totals about 6,500,000 c. f. m. The increment for the year ending in April, 1955, will be some 700,000 c. f. m. Almost all this new ventilation has gone into metal mines, in most instances to serve the kind of mining discussed above.

HEAT AND COLD

It is pertinent to refer to heat and cold, at least briefly, because they affect dust control in metal mines.

In some respects we in Ontario are fortunate in having a cold climate. But the blessing is mixed, for it brings with it real handicaps in ventilation.

The ground-level temperature approximates 40 F. The geothermal gradients are favorable. Misener² reports the following:

Area	Gradient
Timmins.....	1 degree F per 200 ft.
Kirkland Lake.....	1 degree F per 160 ft.
Sudbury.....	1 degree F per 112 ft.

This means that heat is not a major problem at Ontario mines. There are, however, a few where it is becoming troublesome. Up to the present, the operators of these mines have been able to maintain satisfactory air conditions by good ventilating practices. Deeper operations will alter these circumstances. Preparations are accordingly being made to cool air in summer—and warm it in winter—by facilities in which Mother Nature plays a major role.²

It is not heat but the lack of it which troubles most mines in Canada. The new producer has no old workings through which subzero air may be circulated to temper it before delivery to active parts. Trouble of like kind is particularly experienced in older mines that are shallow.

In such circumstances, the operator has only two courses to follow: to heat the incoming air or to struggle through a winter of four to five months, battling ice in the downcast due to seepage of ground water. Cementation is widely practiced to combat this condition. Sometimes it is successful; oftentimes it is not because of extensive fractures in the ground.

The plants to heat air vary in capacity; a few handle more than 100,000 c. f. m. Coal is the principal fuel used. "Coke-fly" from a steel plant is employed in one case; fuel oil, in another. Low-pressure steam is circulated through coils of the fin type in most installations. Recently, however, there has been a preference for a kind of heating in which air is forced through tubes around the "fire-pot." Installations of this type can be made fully automatic and are reported to be trouble-free, which is not the case at most of those where steam is employed.

As a mine ages, its staff gains experience with this problem. The workings deepen, and open ground is accumulated on upper levels. Ground waters tend to disappear from the downcast through fissures connecting with sections outside of the arteries for air or are conducted to the latter. There then is more space to temper air. In such circumstances there comes a time when the plant to heat air may be dismantled and a major annual change eliminated as was done at one Ontario mine two years ago. It must be pointed out, however, that this is the exception, not the rule. Fortune sometimes smiles but not on many.

CONCLUSION

The most important problem in dust control in any mine is the provision and maintenance of a stimulating interest in this subject.

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Management holds the key to this. If its attitude is good, much will be accomplished. If it is not, results will be mediocre. It is recognized, however, that it is as yet impossible to control all harmful exposures to dust all the time and in all places where men work and travel.

It is my conviction that, despite the good history of health in some industrial occupations, prolonged exposures to high concentrations of any dust do no good and in time may do harm. They are also bad for morale and affect efficiency adversely.

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The Disability Found in Persons Exposed to Certain Beryllium Compounds

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In presenting this paper, I have chosen, first, to summarize the evidence for the conviction that there is a man-made disease produced by exposure to certain beryllium compounds and, secondly, to point out the unfolding clinical character of this disease.

The need for discussing the existence of beryllium poisoning became apparent with the appearance of the article by Shilen and his group² in a recent issue of *Industrial Medicine and Surgery*, implying that no illness has appeared in certain beryllium exposures in the extraction and alloy-manufacture industry. This article and several in trade journals based on it have resulted in confusion in the minds of those responsible for industrial hygiene measures in beryllium-using industries. The fact that no M. A. C. has been adopted by the American Standards Association or the American Conference of Governmental Industrial Hygienists is an index of the uncertainty of industrial hygiene thinking about beryllium toxicity. The M. A. C. levels at present enforced in some beryllium-using operations are figures recommended by the Beryllium Advisory Committee of the Atomic Energy Commission, Division of Biology and Medicine, for use in A. E. C. projects.

The evidence from Europe is that plants in Russia,* Italy,⁴ and Germany† engaged in extraction of beryllium and manufacture of beryllium alloys have experienced and re-

ported worker illness. The illness involved both the upper and the lower respiratory tract and was in some cases fatal. Reports from abroad appeared in 1933 and stopped with the beginning of World War II. Mention was made in the 1936 report from Russia of illness occurring in workers some distance from operations using beryllium, foreshadowing the American experience with neighborhood beryllium poisoning.

Van Ordstrand⁵ in 1943 described chemical pneumonia in a beryllium extraction and alloy-manufacturing plant in Ohio. Shilen and associates² reported respiratory ailments and dermatitis from similar operations in Pennsylvania in 1944. Restudying these reports and the 1945 report of Van Ordstrand and his group,⁶ in which they described their clinical findings under the general term of beryllium poisoning, one is greatly impressed that the clinical features and work exposures are identical in the European, Pennsylvania, and Ohio reports. Shilen's observation that the illness he found was due to acid fumes rather than beryllium compounds is a minority opinion. Illness experience associated with the wide variety of exposure to acid fumes in many industries does not support his conclusion that such exposures were responsible for the illness he reported. Important evidence of the crucial role of beryllium in producing a distinctive, acute pneumonitis is supplied in the report of Aub and Grier.¹⁰ These authors describe a clinical picture and x-ray findings similar to those reported from extraction plants. The workers whose illness they describe were exposed to dust and fumes of beryllium metal and beryllium oxide. In the reports discussed thus far, we are dealing with acute illness. Such illness has been cor-

Recorded for publication April 7, 1955.

*References 2 and 3.

†References 5 and 6

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related with intensity of beryllium exposure by Eisenbud and associates.¹¹

The worker suffering from acute beryllium poisoning, unless overwhelmingly exposed, will recover when removed from the contaminated working atmosphere and given rest and oxygen as needed. To clinch the correlation of beryllium exposure with such acute reaction in the respiratory tract, Stokinger and his associates¹² have shown by careful and convincing animal studies that beryllium is the causative agent. A final corroboration of cause and effect lies in the fact that beryllium extraction and alloy-manufacturing plants that have adopted industrial hygiene measures no longer report cases of acute respiratory tract disease except in the event of breakdown of protection equipment.

Much more complex is the evaluation of the disease called by our group beryllium poisoning, by others berylliosis or pulmonary granulomatosis of beryllium workers. Earlier, Gardner liked the term generalized pulmonary granulomatosis or beryllium sarcoid. As our knowledge grows, this latter term seems useful. In Europe, this chronic industrial disease has been termed chronic large-celled pneumonia and pulmonary sclerosis.

To review fully the published references to chronic disease following beryllium exposure would be tedious. There are well-documented reports of worker illness, with common clinical features, x-ray findings, lung function disturbance, and pathological pictures held together by beryllium as the common etiology. To reach a common ground in judging evidence for the existence of such a disease, let's agree for this meeting on criteria for a diagnosis of chronic beryllium poisoning. The establishment of real beryllium exposure either by exact epidemiological evidence or measurement of beryllium level in working atmosphere and/or by the finding of beryllium in body fluids or tissue, together with a characteristic granulomatous, pathological reaction, will serve as diagnostic criteria. The industries reporting such evidence of worker illness are those engaged in beryllium extraction, alloy manufacture, fluorescent and

neon-powder mixing, lamp manufacture and salvage, beryllium metallurgy, manufacture of x-ray-tube windows, brass-tube manufacture, various ceramic operations, radio-tube manufacture, and atomic energy development. No disease is known to us in processing beryllium ore or in the use of finished beryllium alloys containing less than 2% of the element. Tebrock and Machle¹³ have reported no illness among fluorescent-lamp workers after the beryllium content of the phosphor was reduced below 3% by weight. This reduction took place in January, 1943, and beryllium was dropped from the phosphor altogether in 1949. Because of the curious delay in onset of chronic beryllium poisoning, a delay which can occasionally be as long as 10 years between last exposure and appearance of symptoms, Tebrock and Machle's observation must wait the test of time. These same authors report that x-ray, electron diffraction, and crystallographic studies show that the upper limit of solubility of beryllium oxide in the phosphor lattice is about 3%, with the result that above 3% free beryllium oxide is present. Tebrock and Machle hold this compound responsible for the illness in the fluorescent-lamp industry. While the evidence that beryllium oxide is present in most or all beryllium operations that have caused illness is striking, one nevertheless wonders if it can be true that beryllium oxide alone is harmful.

Continuing the documentation of chronic beryllium disease, let us discuss the experience in the beryllium extraction and alloy-manufacturing industry. De Nardi and associates¹⁴ have reported chronic worker cases, and Chesner¹⁵ chronic neighborhood cases from this industry in Ohio. Lieben¹⁶ has reported cases, previously discussed by Jackson,¹⁷ of chronic beryllium disease in men working in a brass foundry using a beryllium alloy containing about 4% of the element. The sick workers were exposed to beryllium-containing scrap dust and to the fumes from the melting of the alloy. Goldwater[‡] has seen worker illness from the Pennsylvania

[‡]Goldwater, L.: Personal communication to the author.

industry manufacturing beryllium alloys which he believes can be properly documented as beryllium disease. Through the kindness of Dr. John Bishing, of Reading, Pa., we have recently studied the illness of a worker who was engaged in the manufacture of beryllium alloys from 1940 to 1942. This patient worker fulfills the criteria of chronic beryllium poisoning. Dr. George Chamberlin, also of Reading, Pa., presented an exhibit at the Pennsylvania State Medical Society Meeting in November, 1954, of seven cases he diagnosed as berylliosis. With these clinical reports, it seems fair to conclude that the Pennsylvania extraction and alloy-manufacturing industries have had illness experience associated with exposure to certain beryllium compounds similar to that reported from European and Ohio industries engaged in these same operations. In reviewing the three reports of Shilen and his colleagues—one published in 1944,⁴ one in 1949,⁵ and the most recent in 1954,³ a reasonable interpretation may be that this group concluded, erroneously in our opinion, that the worker illnesses designated as beryllium poisoning by European and Ohio observers were due to inhalation of acid fumes. In the 1954 analysis of their findings, Shilen's group not only failed to include medical follow-up of workers no longer at the plant but also did not mention that experience of physicians in the community who might be caring for possible cases of chronic beryllium poisoning was sought. We know that because of delay in onset patients with chronic beryllium poisoning are seen first by the family physician, rarely by the plant physician. Frequently, community tuberculosis sanitaria staffs discover cases of berylliosis through routine chest x-ray surveys and because the disease can be readily confused with military tuberculosis. From this case-finding experience, we infer that Shilen's report of 1954 is incomplete, and therefore the implied conclusion that there are no cases of chronic beryllium poisoning in workers from the plant studied is not justified.

In addition, evidence has accumulated that beryllium compounds are capable of an ex-

traordinary number of reactions, chronic as well as acute, in the experimental animal. Schepers,⁶ of the Saranac Laboratory, in recent correspondence, has furnished the information that pulmonary carcinomata of a triple variety appear with consistent frequency after about 14 months in rats exposed to beryllium sulfate for a minimum period of six months. Assuming by analogy with what happens in the experimental dust diseases that one month of a rat's life may be equated to a year of a human life, Schepers points out that we may shortly expect to know if respiratory tract neoplasm will appear in the worker population exposed to certain beryllium compounds. We have at present no clinical evidence of malignant neoplasm in the respiratory organs in persons with chronic beryllium poisoning. To my knowledge, there are as yet no studies of the incidence of lung neoplasm in a beryllium-exposed population free from evidence of beryllium disease.

In summary, epidemiological, industrial hygiene, clinical, and animal experimental evidences document the conclusion that distinctive disease occurs in beryllium-using industries, exclusive of those using finished low beryllium alloys (less than 2%) and those engaged in mining beryl ore. There is adequate evidence that no beryllium extraction and alloy-manufacturing industry in the United States, of which we have knowledge, is completely free of the worker illness, fulfilling the criteria laid down in this paper for the diagnosis of chronic beryllium poisoning.

Knowledge of the man-made disease, beryllium poisoning, berylliosis, or whatever name you like, is less than 20 years old, counting all reports, and only 10 years old in the United States. The particular point to be made in the second half of this report is that, as a consequence of its newness, the clinical characteristics, life history, x-ray and pathological variants of this disease are still unfolding. Since this is true, it is not accurate to speak of a classic case of beryllium poisoning or to insist that a particular case cannot

⁶ Schepers, G. W. H.: Personal communication to the author.

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be berylliosis because the clinical course appears unusual. To illustrate the presently known clinical syndromes for the 1955 Saranac Symposium, the following temporary classification of beryllium disease, based on our clinical experience at the Massachusetts General Hospital, is prepared. This descriptive classification embodies a clinical conception based primarily on the patient's ability to do his usual work. To illustrate the picture of chronic beryllium disease, an example of a case in each category will be given.

I. BERYLLIUM EFFECT—NO DISABILITY

Beryllium effect without disability is illustrated by the case of B. D., a young Italian woman of 33 years. She was exposed to un-

Classification of Beryllium Disease

- I. Beryllium effect—no disability
- II. Beryllium effect—probable disability
- III. Mildly symptomatic beryllium disease
- IV. Moderately disabling beryllium disease
- V. Severely disabling beryllium disease
- VI. Completely disabling beryllium disease
- VII. Recovery from beryllium disease
 - (A) With residual evidence of irreversible pathology
 - (B) With no evidence of disease

known amounts of beryllium-containing phosphor, off and on, for eight years, beginning in 1940. During a routine chest x-ray survey conducted by the plant where she worked, abnormalities, such as are seen on the film, were noted four years ago. These changes were reported as fine mottled bilateral increase in densities from the hilum to the periphery. Careful study in two hospitals and lung function studies revealed no other abnormalities. The worker has no complaints. She leads her usual life, hindered only by anxiety, because she knows of the illness and subsequent death of several young women with whom she worked at jobs similar to her own. This represents a beryllium effect not productive of symptoms, because the process does not involve enough tissue to embarrass function. The pressing question is whether or not the process by exacerbation will produce

symptomatic disease or by irreversible fibrotic pulmonary change gradually diminished lung function. We have followed a similar case for 10 years without the patient as yet developing symptoms.

II. BERYLLIUM EFFECT—PROBABLE DISABILITY

An allied category has been arbitrarily called beryllium effect with probable disability. This group, in our experience, is growing in size. The case used for illustration is that of a 37-year-old engineer, previously in good health, who, after a respiratory infection in 1950, was found to have dramatic chest x-ray changes. Pulmonary tuberculosis was carefully ruled out. The patient was referred to us for study because of a history of 16 months' intimate exposure to fluorescent-lamp-manufacture operations. Beryllium in the urine established exposure. The man was under great strain because of watching his wife die a slow and painful death due to cancer. His chief complaint was fatigue and some weakness, and, if pressed, he thought he was a little dyspneic on real effort. Lung function study showed slight increase in residual air. In 1955 this man feels well. His present problem is that he finds difficulty in getting a job because of his chest x-ray changes. The amount of change shown on x-ray and the mode of onset make it likely that functional disability will appear and progress. In addition, the employment handicap of the abnormal chest x-ray may be rated as a kind of disability.

III. MILDLY SYMPTOMATIC BERYLLIUM DISEASE

The next group of workers, suffering from what has been designated as chronic beryllium poisoning with mild disability, is also growing. A typical example is a 32-year-old man who worked in beryllium-alloy manufacturing between 1940 and 1942, during which period he had a vesicular rash with itching. The skin reaction was mild and did not prevent him from continuing his work. In 1953 a diffuse mottling of both lung fields

was seen by x-ray. This coincided with a severe respiratory infection, a slight weight loss, and the onset of cough and dyspnea on exertion, accompanied by intermittent low-grade fever. Lung function study in 1954 revealed increased arterial oxygen difference at rest as well as on exercise. Biopsy of the lung revealed pathology consistent with a diagnosis of beryllium disease, and the element was found in the lung on spectrographic analysis.

This man works every day, repairing airplanes. He is, however, aware of dyspnea on effort, increased when he has a respiratory infection. As in the previous category, men in this group have trouble finding jobs and understandably become anxious about their future. Since considerable pathology is present, it seems likely that pulmonary reserve is constantly being decreased by irreversible fibrotic change.

IV. MODERATELY DISABLING BERYLLIUM DISEASE

In the group of cases suffering moderately disabling beryllium disease, we are concerned with medical management now that cortisone has been shown to improve lung function. To illustrate this group, the case of S. A., a 34-year-old accountant, is presented. During 1943-1944 he spent 30 weeks in a fluorescent-lamp-manufacturing plant as a cost clerk. During this time he was in all parts of the plant. Beryllium, found in the urine, corroborated this exposure history. In 1948, S. A. lost 20 lb. and developed a cough and gradually increasing dyspnea. The chest x-ray, when we first saw him in 1952, was reported as showing reduction in size of both upper lobes and extensive emphysema with bleb formation in both lower lobes, while throughout both lung fields there was finely mottled increased density. Lung function studies showed abnormalities in all values. The EKG, at first normal, now shows evidence of right ventricular hypertrophy.

After several hospital trials with corticotropin and cortisone, this patient is able to lead an ambulatory but restricted life. With

the aid of 75 mg. of cortisone a day, he works 40 hours a week but must limit his social activities in order to rest and has stopped his exercise completely. Infections increase the dyspnea which is not entirely under control. We believe that S. A. illustrates that the prognosis for life as well as activity is unfavorably altered in this group in spite of cortisone therapy.

V. SEVERELY DISABLING BERYLLIUM DISEASE

In the severely disabled group of cases of chronic beryllium poisoning, we include women who can do some housework and men who work intermittently at sedentary jobs. The severity is judged on the basis of frequent trips to the hospital, complications, and obviously bad prognosis.

M. J. illustrates this group, which is, we think, getting smaller in size, in part because of the character of beryllium disease and in part because of the success of long-term use of steroids. M. J. worked as a draftsman for one year in a fluorescent-lamp-manufacturing plant during 1940-1941. Increasing dyspnea, cough, and chest x-ray findings of miliary densities brought him to the hospital for diagnostic study in 1952. Beryllium in the tissue and characteristic pathology were found on lung biopsy. This patient shows marked clubbing of fingers and toes, cyanosis, and secondary polycythemia in spite of cortisone therapy. M. J. has shown hypercalciuria (independent of cortisone effect) and relative hyperglobulinemia, evidence in support of the concept that beryllium poisoning is a constitutional and not exclusively a pulmonary disease. Bouts of headache and fever, two episodes of abnormal deposition of calcium in soft tissue, a fractured rib, and two serious respiratory infections have complicated this man's course in the past two years. Some of the difficulties are due to cortisone effect, but without the drug the patient is completely disabled. With encouragement the patient works about half time as a draftsman. Should he work at all? For his morale we believe that he should, but there is certainly strain on his right heart. In this group cortisone

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prolongs life and makes the patient more comfortable but probably does not change the outcome.

VI. COMPLETELY DISABLING BERYLLIUM DISEASE

It is possible that there are too many groups in this presentation, but this grouping has been done deliberately to emphasize the broad spread of the clinical picture of beryllium disease and the relationship of these syndromes to disability. The extraordinary tenacity to life of the completely disabled cases of chronic beryllium poisoning is illustrated by F. A. This young woman worked in fluorescent-lamp manufacturing from 1940 to 1943. Cough began in 1943; weight loss, dyspnea, and marked x-ray changes followed, until by late 1945 the patient was unable to do anything except the lightest housework. From 1947 on she has been a total invalid, completely dependent on oxygen therapy. To compress a long story, she has had episodes of spontaneous pneumothorax, pleurisy, erythema nodosum, and epistaxis; she shows cachexia (weight, 75 lb.), clubbing, cyanosis, enlarged liver, and evidence of congestive heart failure. Her biochemical studies show hyperglobulinemia now and from time to time have shown abnormalities in liver function. This is the type of case I wrote about in 1946, when the fluorescent-lamp-manufacturing industry first reported an unusual number of cases of what we then named delayed chemical pneumonitis. Cortisone and corticotropin act in this group also to prolong life and increase comfort. However, the failure of the right heart manifests itself as the terminating complication, in spite of complete rest, oxygen therapy, and the use of steroids.

VII. RECOVERY FROM BERYLLIUM DISEASE

After almost 10 years of study of chronic beryllium disease, it is now possible to speak of remission and possible recovery, in contrast to the desperately ill group just described.

F. L., a case reported by Cass¹¹ and also studied by us, represents a spontaneous,

symptomatic recovery with residual pathology. He worked in close exposure to the early high beryllium phosphors and was extremely disabled for 18 months with cough, dyspnea, and severe gastrointestinal symptoms. He gradually recovered with only supportive therapy and now works steadily at a desk job. His chest x-ray shows fine densities throughout both lung fields. F. L. has passed three small renal calculi at intervals, a reflection of disturbed calcium metabolism noted in a number of cases of chronic beryllium poisoning. Time alone can tell whether or not he will have an exacerbation of his symptoms and whether his obvious pathology will materially alter his life expectancy. There are a small but definite number of studied cases with a similar history of remission.

Finally, the case of L. B. suggests that it may be possible to cure beryllium disease with cortisone. Of course, time alone, perhaps, would have resulted in a similar outcome. L. B. is a 27-year-old woman who was exposed to beryllium oxide when shaking the material for sizing purpose during 1944-1945. After pelvic surgery in 1950 and a subsequent respiratory infection, she was troubled by a nonproductive cough and gradually increasing dyspnea. Her chest x-ray showed nodular densities from apex to base, bilaterally. She gradually became disabled because of dyspnea. In 1952 she had evidence of abnormal lung and liver function and was in bed a great deal because of shortness of breath and weakness. Gradually, with the steady use of cortisone after trials of intermittent corticotropin, she improved until in July, 1954, she found that she was able to work 40 hours a week, and her chest x-ray is considered to be normal. The dose of cortisone has been slowly reduced.

Clinical material similar to that here described is accumulating steadily. Because of the continuing acquisition of knowledge, it is impossible at present to make accurate statements as to prognosis and incidence of complications. There is no doubt that the steroids not only have increased comfort but also have lengthened the lives of patients with chronic

beryllium disease. Our one case suggests that long-term cortisone therapy may result in a true cure. This statement may have to be amended, as we learn of spontaneous complete remission in beryllium disease.

This discussion may serve to sustain your interest in the unfolding facts of this extraordinary man-made disease. It may well prove that Gardner's informal title of beryllium sarcoid was apt, indeed. From knowledge of this disease of known chemical etiology, it may be possible to study the pathogenesis of the sarcoid-like diseases of unknown etiology, which are so fascinating and so baffling.

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DISCUSSION

DR. KOVEN: What criteria have been set up for accepting a case of berylliosis for admission to the registry?

DR. HARDY: The registry is currently just being established, and as yet none of the cases have been accepted with finality. I have two physicians helping me who have not been intimately associated with the study of beryllium poisoning, and thus lend objectivity. In addition, there is an Advisory Committee, which meets annually to help us, and, finally, we have advice on handling the statistical data and proper recording from the Department of Preventive Medicine at the Harvard Medical School.

DR. KOVEN: By what means are other chronic pulmonary granulomata distinguished from that caused by beryllium?

DR. HARDY: I think this question should be answered now in terms of my opinion rather than what will ultimately reach the registry because of the above-described newness of that project. Since the pathologists do not agree on the specificity and uniqueness of the microscopic picture of beryllium disease, the finding of beryllium in tissue must be the crucial factor. This seems not unlike bacterial etiology, such as the finding of tubercle bacilli.

DR. KOVEN: Is the finding of beryllium in tissue considered diagnostic in berylliosis?

DR. HARDY: If beryllium is found in tissue without pathological reaction, the presence of the beryllium is interpreted as meaning exposure. Study of autopsy tissue from persons who have worked in beryllium-using industry shows the presence of beryllium as might be expected. Because of our knowledge that beryl occurs in many places in the earth's crust in this country, it is possible that

beryllium will be found if looked for. However, it seems critically reasonable that the combination of a granulomatous reaction and beryllium is adequate support for a diagnosis of beryllium intoxication. It is well to point out that there is no correlation between the quantity of beryllium found in tissue and the pathological reaction.

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The Effects of Inhaled Talc-Mining Dust on the Human Lung

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Talc belongs in the group of silicates that have been under suspicion for many years as a cause of pneumoconiosis. The literature contains a number of reports of studies which indicate that industrial workers exposed to talc dust sometimes develop changes in the lungs, and several investigators have used the term "talcosis" to describe the pulmonary condition produced in those exposed workers.

Pure talc, a hydrous magnesium silicate, is a specific mineral, but, as Schulz and Williams¹ pointed out, the word "talc" as used in industry usually refers to a product which meets certain physical requirements rather than to a substance of definite chemical composition. In commercial talc, the mineral talc itself may be only a minor component. Schulz and Williams found that in 51 samples of commercial talc the amount of the talc component, based on the count of particles smaller than 10 μ , never exceeded 52% of the sample. Other prominent minerals in their samples were serpentine, dolomite, and tremolite. A review of the data on 35 "talc" samples received at The Saranac Laboratory for routine analysis revealed that the composition varied widely. In 8 of the 35 samples there was no more than a trace of the mineral talc present, and all the 35 contained a substantial amount of one or more other components, such as tremolite, mica, carbonates, and clay minerals.

The extent to which the mineral talc is responsible for the changes in the lungs is still in doubt. Certainly the experimental and clinical evidence incriminating pure talc as the principal etiologic agent in so-called talcosis has so far been much less convincing than similar evidence supporting the views that silicosis is caused by inhaled quartz dust or that asbestosis is provoked by inhaled asbestos fibers. Nor is there complete certainty yet concerning the pathognomonic features of the specific talc disease.

In spite of these uncertainties, reports on 21 clinical and roentgenological and 13 autopsy studies exist in the literature, commencing with the first paper by Thorel² in 1896. Jaques and B  nirschke³ have recently reviewed these cases. The main emphasis appears to be on a radiological pneumoconiosis, ranging from diffuse bilateral reticulation without predisposition to tuberculosis to conglomerate massive shadows frequently tuberculous in nature. Clinically the disease varies from a benign to a rapidly developing fatal process, with emphasis on cor pulmonale as the cause of death. There may be a prolonged symptom-free induction period. Tuberculosis, emphysema, and bronchitis vary in their prevalence. Pathologically the condition has been described mainly as a dense type of fibrosis, with peribronchial and perivascular prevalence and sometimes with nodularity. Talc has been demonstrated in the tissues of some cases, and the suggestion has been advanced that the talc shows certain erosion changes in the human tissue not present in the original state. A point which has by no means previously been settled concerns the role of substances inhaled in association with the talc as the cause of the disease process. Speculation has mainly concerned the effect of the quartz, which has frequently been demonstrable. On the other hand, cases

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exist in which neither quartz nor talc have been demonstrable.

Passing reference should also be made to the extensive literature on the granulomata associated with the surgical use of talc and the fact that talc lesions have been observed not only in the lungs but also in the pericardium, the epicardium, and the gastric mucosa, besides surgical wounds. It is evident that a great deal may yet be added to the sum total of our current knowledge concerning this dust disease. With this object in mind, observations are presented in this paper on dust surveys conducted by The Saranac Laboratory of certain mines and mills of the talc industry of Northern New York State, together with the chemical findings and histopathology of eight deceased employees from that same industry.*

SURVEY OF DUST CONDITION IN CERTAIN MINES AND MILLS OF THE TREMOLITE TALC INDUSTRY OF NORTHERN NEW YORK

The rock mined and milled in the area in Northern New York studied by The Saranac Laboratory, although sold as talc, is a mixture of talc and tremolite accompanied by a smaller amount of anthophyllite. All three minerals are silicates. The talc usually develops in thin, flexible, white laminae that are characteristically greasy to the touch, but in some samples from this area it occurs in fine fibers instead of the usual plates. The tremolite and anthophyllite normally occur as coarse crystal grains, but in the area studied

and elsewhere those minerals sometimes break up into long narrow fibers and then exhibit the structure and properties of asbestos. It should be pointed out that the term "asbestos" does not refer to one specific mineral but rather to any mineral capable of splitting into long, thin, flexible fibers and resistant to heat and chemical agents. Two distinct types of mineral are used commercially as asbestos; the bulk of the product is chrysotile, which is a fibrous variety of the silicate mineral serpentine; the important remainder belongs to the group of silicates known as amphiboles and includes the varieties amosite and crocidolite. Tremolite and anthophyllite are also members of the amphibole group. Since the experience in South Africa shows that at least one of the asbestiform amphiboles—crocidolite—is capable of causing typical asbestosis, there is reason to suspect that the fibrous amphiboles from the area studied by The Saranac Laboratory also might cause reaction of the asbestosis type. It is likewise possible that any portion of the talc which may be present in fibrous form might have a similar effect on tissue.

Representative samples of the mine product from three mines and of ground talc from two mills in the area were analyzed by chemical, petrographic, and x-ray diffraction techniques. The results appear in Table 1. At the same time samples of air-borne dust were collected with an electrostatic precipitator in two of these three mines, near a miner operating a jackhammer drill, and in the working area of both mills. Later precipitator samples were collected in the third mine also. Analysis revealed that the distribution of minerals was somewhat different in the atmospheric samples (Table 2) than

* These cases are part of a series collected by the late Dr. L. U. Gardner. A manuscript under preparation by Dr. Gardner had not been completed by the time of his death. The present account is an independent study of the material without reference to this manuscript.

TABLE 1.—Composition of Mine Product and of Milled Talc from Tremolite Talc Industry of Northern New York

Mineral	Mine Product			Milled Talc	
	Mine A, Per Cent	Mine B, Per Cent	Mine C, Per Cent	Mill D, Per Cent	Mill E, Per Cent
Talc.....	20	40	50	12	30
Tremolite.....	40	30	25	55	55
Anthophyllite.....	35	2	7	30	7
Serpentine.....	1	2	5	8	6
Calcite.....	<1	4	6	2	2
Quartz.....	4	30	<0.5	3	0.5

Mill D used the mine product of Mines B and C, and Mill E was supplied by Mine C.

TABLE 2.—Composition of Atmospheric Dust Collected with Electrostatic Precipitator in Mines and Mills of Tremolite Talc Industry of Northern New York

Mineral	Atmospheric Dust					
	Mine A*		Mine B, Per Cent	Mine C, Per Cent	Mill D, Per Cent	Mill E, Per Cent
	Per Cent (a)	Per Cent (b)				
Talc.....	15	25	25	10	25	25
Tremolite.....	60	35	15	40	55	50
Anthophyllite.....	2	2	2	40	18	18
Serpentine.....	1 (?)	1 (?)	1	2	2	10
Calcite.....	20	10	50	2	2	2
Quartz.....	2	1	5	0.3	2	0.3

* The two samples of atmospheric dust from Mine A were collected in different levels of the mine. They were taken several months later than those from Mines B and C and Mills D and E.

in the mine product and in milled talc. This finding is in agreement with previous observations* that the composition of air-borne dust may differ considerably from that of the source material from which the dust originated. Even in the same mine there may be substantial difference in the composition of the air-borne dust: one atmospheric sample collected in Mine A had a quartz content of 7%, while for another sample, taken at about the same time but in a different level, the quartz value was only 2% (Table 2). This variability in the quartz content is illustrated again by comparing the analyses of various samples of rock, mine-product, and air-borne dust taken in Mine A and in Mine B (Table 3). It will be noted that the per cent of quartz in the Mine A samples ranged from 21% to 0.3%, and in the Mine B samples from 41% to 9%.

This matter of quartz content is mentioned in some detail: first, because previous investigators* have reported that they found only a negligible amount of quartz in samples of rock and of ground material from this area; second, because it has been demonstrated (Table 4) that at least some quartz was present in the lungs of one miner and one miller from this local industry who had no other industrial exposure to dust, and, third, because quartz is a known pulmonary pathogen. The quartz may not be uniformly

distributed throughout the entire tremolite talc bed, but the analyses in Table 3 show that it can be present in substantial amount. Owing to erratic distribution, the quartz deposits may be missed by random sampling.

In attempting to take cognizance of the potential pathogenic role which may be played by the quartz in the talc, sight must not be lost of the fact that the quartz found in the lungs of deceased miners who had also worked in other industries may have been derived from exposures in those industries.

CHEMICAL AND PETROGRAPHIC STUDY OF THE LUNGS OF EIGHT DECEASED TALC-INDUSTRY EMPLOYEES

The series of autopsy specimens studied consisted of the lungs of seven miners and one miller from the tremolite talc industry. All the miners had been engaged in drilling rock for periods ranging from 10 months to 27 years. The mill worker (Case 3) had been employed for six years, but, as his body had been exhumed for study 18 months after his death, the findings are only of limited value. A portion of the autopsy material was taken for gross specimens and for histologic examination, and the balance was reserved for chemical, petrographic, and x-ray diffraction examination. For the component chemical analysis and a few of the mineralogical analyses, samples of tissue

TABLE 3.—Quartz Content of Rock, of Mine Product, and of Atmospheric Dust from Mines A and B

	Quartz Content									
	Mine A, Per Cent					Mine B, Per Cent				
Rock chips.....	0.3	11	11	10	..	15	..	..	41	..
Mine product.....	..	..	..	4	21	..	..	..	20	11
Atmospheric dust.....	2	10	9	..	..	10	17	9	..	..

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TABLE 4.—Analysis of Lungs of Industrial Workers Exposed to Dust in the Tremolite Talc Industry of Northern New York

Autopsy Case No.	1	2	3	4	5	6	7	8
	%	%	%	%	%	%	%	%
Ash, per cent of dried tissue	17.43	11.22	17.00	8.20	12.41	12.22	6.47	7.43
Mineral Constituents, Per Cent of Ash								
Minerals								
Quartz	88.1	8.5	2.5	7.5	14.0		8.0	
Talc	Tr	90	25	18	10		5	
Tremolite	NI	8	14	18	14		1	
Anthophyllite	NI	3	12	6	4		8	
Feldspar	46				Tr		Tr	
Mineral Constituents, Per Cent of Dried Tissue								
Minerals								
Quartz	5.5	1.0	0.4	0.8	1.8		0.5	
Talc	Tr	2.4	4.4	1.5	1.2		0.3	
Tremolite	NI	0.5	1.5	1.8	1.7		0.1	
Anthophyllite	NI	0.1	2.1	0.7	0.5		0.2	
Feldspar	5				Tr		Tr	
Component Analysis, Per Cent of Ash								
Components								
SiO ₂	68.1	40.0	51.8	20.0	52.1	52.6	20.4	23.5
FeO	4.4	4.8	1.5	2.5	11.0	8.2	14.1	15.9
Al ₂ O ₃	11.9	8.4	10.5	2.1	8.1	7.9	8.4	5.0
CaO	0.7	11.1	0.1	16.1	8.8	8.3	21.4	17.2
MgO	0.8	4.8	4.7	2.4	2.4	2.1	3.0	2.0
MnO	2.2	15.5	15.8	10.3	12.0	12.0	2.4	4.7
Na ₂ O	4.5	3.2	6.5	2.3	2.7	2.5	8.8	8.8
K ₂ O	4.0	4.2	4.1	10.0	2.2	2.2	0.4	11.6

NI—None Found.

were removed from representative portions of the lungs and mixed. The samples were then dried overnight at 105 C and ashed in a muffle furnace.³ Most of the mineralogical determinations were based upon other mixed portions of tissue digested with 30% hydrogen peroxide by the method of Sundius and Bygden⁴ to avoid the alteration in mineral structure sometimes caused by dry ashing. The results of the chemical and mineralogical determinations are shown in Table 4. It should be pointed out that the values given for some of the minerals are only approximate estimates. The quartz content was determined by a special chemical and petrographic method, and is fairly accurate, but the values in the table for talc, tremolite, and anthophyllite may be somewhat above or below the true value.

PULMONARY HISTOPATHOLOGY ASSOCIATED WITH TALC-DUST EXPOSURE

Though our series of eight cases appears limited, we were particularly fortunate in having available for study such a diversified range of dust exposures and lung lesions (Table 5). At the one end of our scale we have Case 1, with but 10 months' exposure to talc dust as a miner and 17 years' general mining. At the other extreme is Case 8, with

27 years' talc mining exposure and 10 years' general mining.

The associated exposures included service as miners of zinc, lead, coal, and iron pyrites. This helps to elucidate the essential talc reaction, as the normal result of exposure to dust hazards in mines of the latter types is fairly well understood.

Our best fortune, however, for the present purpose is Case 7, a person who had worked 23 years only as a talc miner before dying from an unrelated cause without any intercurrent superimposed pulmonary disease. This case may therefore serve as a classical example of a talc miner pneumoconiosis.

Case 3 would have been equally valuable, as this worker had been exposed during his six years of employment as a surface crusher man and mill sweeper. Unfortunately, the studies were not made until his body was exhumed 18 months after burial, and so not much detail was preserved. However, it confirms certain essential points.

FUNDAMENTAL PULMONARY TALC REACTION

The primary reaction present in Case 7 consists of multiple irregularly shaped foci (1 to 3 mm. in diameter) comprised of virtually pure fibrocytic proliferation and macro-

TABLE 5.—Industrial Exposures, Causes of Death, and Pulmonary Pathology in Eight Deceased Tremolite Talc-Industry Employees

Case No.	Dust Exposure		Age at Death	Cause of Death	Dominant Pulmonary Lesions		
	Talc	Other			Talc Pneumoconiosis	Silicosis	Infection
1	Mine ? 10 mo.	Zinc mine 10 yr. Unknown 1 yr.	1	Cop. pneumoniae	Fibrocellular, with perivascular granulomatous	Advanced diffuse, with hyaline nodules	NP
2	Mine Drilling 4 yr.	Lead mine 1 yr. Iron mine 1 yr.	25	Cop. pneumoniae	Massive diffuse fibrocellular	Diffuse with focal necrosis	1 Histoplasmosis
3	Surface Crusher 2 yr. Sweeper 4 yr.		48	?	Diffuse dominant-ly cellular perivascular	NP	Basal lobes tuberculosis
4	Mine Drilling 14 yr.	Zinc mine 8 yr.	49	Tuberculosis	Massive fibrocellular	Massive confluent and multifocal	Chronic basal tuberculosis with bronchogenic spread
5	Mine Drilling 10 yr.	Coal mine 3 yr. Iron mine 3 yr.	51	Cop. pneumoniae	Multifocal massive fibrocellular	Confluent nodular and massive fibrocellular	Tuberculosis with necrosis
6	Mine ? 17 yr.	Zinc mine 1 yr. Pyrites 6 yr.	52	Tuberculosis	Diffuse massive fibrocellular	Tuberculo-silicosis	Tuberculo-silicosis with cavitation
7	Mine ? 23 yr.		57	Nephritis with cardiac failure	Perivascular discrete focal	NP	NP
8	Mine ? 27 yr.	Mining 10 yr.	60+	Congestive cardiac failure	Diffuse fibrocellular	Massive multifocal	NP

phage accumulation. The cellular deposit tends to be arranged in a stellate manner around medium-sized and smaller blood vessels (Fig. 1A). There is fairly abundant visible pigment, which either is found within isolated konoiphores or seems to lie in the interstices between the fibrocytes. Some of these particles are brilliantly birefringent and may be present as spicules, some of which measure 0.5μ by 5μ (Fig. 1B).

These characteristic macules are easily distinguished from isolated mature silicotic nodules which are also present. Some of the latter possess a halo of cellular elements and are probably composite talc and silicotic lesions (Fig. 4B).

Elongated terminally clubbed bodies, measuring 20μ to 50μ long and in no obvious respect distinguishable from asbestos bodies, are present in fair abundance (Fig. 7) mainly within alveoli, where they tend to occur in clusters held together by konoiphores (Fig. 8A). A moderate number also occur among the fibrocytes, and in these sites where there are fewer dumbbell types, there are also more instances of degenerative changes. The intra-alveolar "talc bodies" are generally stained intensely by means of

Prussian blue, while those which lie among the fibrocytes may be losing their iron-containing sheaths as the Prussian blue reaction is fainter and more widely dispersed. Many of the konoiphores in the alveoli show this blue staining too.

The larger blood vessels trapped within these foci do not show much deviation from the normal. It should be clearly appreciated that the focal lesions appear as isolated macules in section only and really represent cellular sheaths accompanying the blood vessels for variable distances. The smaller arterioles may show some endarteritis obliterans, and rarely a talc body may be found embedded in the vascular walls. The fibrocytic infiltrate abuts directly on the vascular adventitia. However, there is no appreciable modification of the lamina elastica of the blood vessels. Capillary circulation through the fibrocytic masses is poorly developed.

But little collagen is laid down among these fibrocytes. The supporting stroma instead consists of a delicate web of reticular fibers embracing groups of fibrocytes rather than subtending individual cells (Fig. 2A). Elastic tissue is absent from the centers of the cellular areas (Fig. 4A).

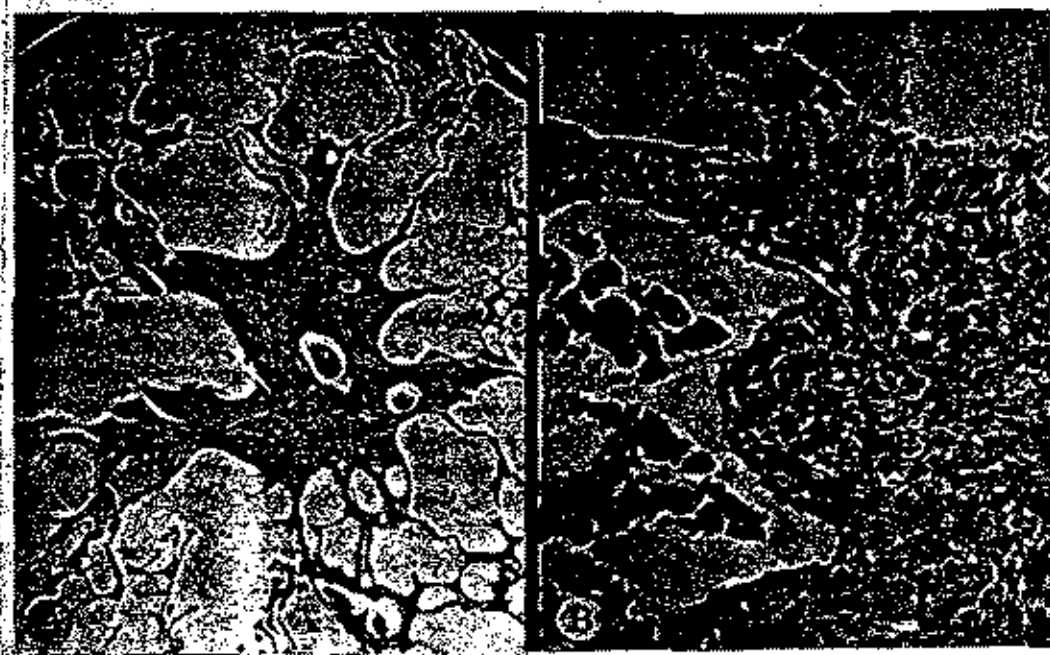
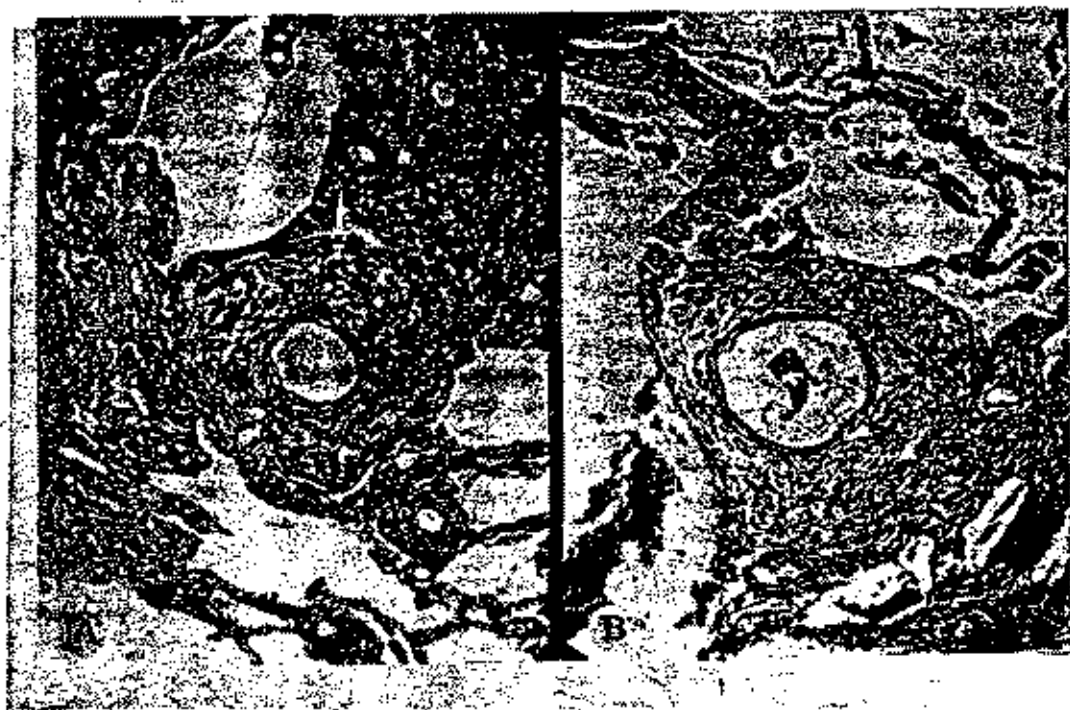


Fig. 1.—Primary lesion; talc mine dust exposure only. *A*, perivascular cellular aggregation. *B*, high-power view, showing massed macrophages and fibrocytes and talc spicules.

Fig. 2.—Stroma of perivascular deposits of talcosis. *A*, reticulum supporting the macrophages and fibrocytes in the primary lesion, with talc components only (low quartz content in lung ash). *B*, collagen abundantly deposited with fewer cells (high quartz content in lung ash).



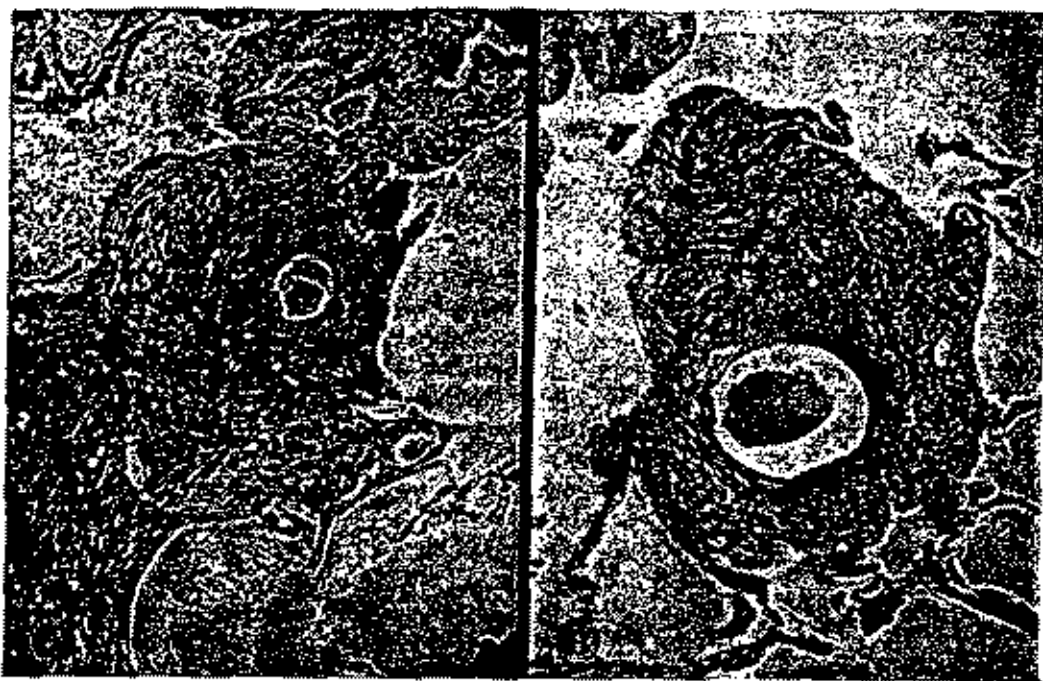
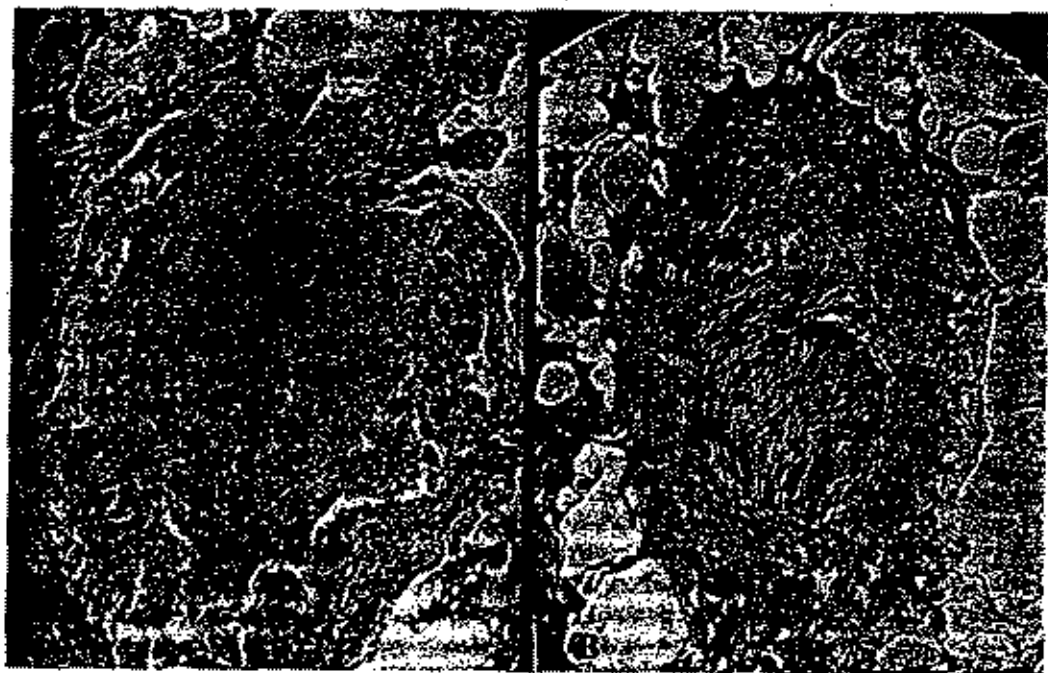


Fig. 3.—Perivascular fibrosis in talcosis. *A*, abundant fibrocellular reaction around vessel (moderate quartz content in lung ash). *B*, marked collagen deposition with paravascular nodule (high quartz content in lung ash).

Fig. 4.—Parenchymal nodules found in talcotic lung. *A*, dominantly cellular nodule, with central amorphous change and talc bodies (low quartz content in lung ash). *B*, hyalinized whorled nodule, with peripheral cellular reaction (high quartz content in lung ash).



EFFECTS OF INHALED TALC-MINING DUST

At isolated sites focal necrosis has supervened within the cellular areas. There is no apparent zonulation around these necrotic areas or any tendency to collagen deposition or caseation. No suggestion of tuberculosis exists, and the cause may be ischemic in view of topographically evident arteriolar occlusion or luminal narrowing. On the other hand, the histological features are highly suggestive of histoplasmosis.

The perivascular fibrocytic deposits tend not to invade adjacent alveolar walls in massive columns, though large numbers of alveolar walls are moderately thickened owing to cellular infiltrates, and this change is the more evident at the points of junction of individual septa. At isolated points the alveolar walls are inclined to be thin, but there is only a slight tendency toward rupturing, as alveolar spaces are inclined to be moderately reduced in diameter. The resultant tendency to atrophic emphysema is most distinct toward the lung periphery.

Septal cells are not conspicuously developed, and there is no evidence of macrophage or septal cell catarrh into the alveolar spaces. Virtually no excessive collagen is present within these alveolar walls, but a delicate reticular skeleton supports its center. Elastic bundles are poorly represented and occur in a fragmented fashion among the fibrocytes. Alveolar wall capillaries are occluded along some stretches where fibrocyte deposition is particularly abundant, but more generally the capillary circulation is undisturbed.

Columns of cellular reaction accompany the interlobular septa to the pulmonary periphery, thus producing a coarsely webbed sectional effect. There is more collagen in these septa than elsewhere (Fig. 11B). The pleura shows slight cellular infiltration and mild collagen deposition internally to the lamina elastica. Numerous talc bodies may be found here, and some can be seen to partially penetrate the elastica. Superficial to the latter, a vascular zone of fibrocellular reaction of variable thickness is to be seen. Isolated silicotic nodules occur in this zone. It is covered by mesothelium (Fig. 12).

Lymphoid tissue is scantily present in the lungs, and the granulomatous reaction appears to avoid these foci almost completely, though these granulomata may abut on such lymphoid tissue. The hilar lymph nodes show hardly any hyperplasia and exhibit minimal pigmentation only. No talc bodies are to be found. However, minute circumscribed silicotic nodules are present.

Many of the bronchioles and some of the smaller bronchi are markedly distended and distorted and are the seat of chronic inflammatory change without, however, any material impairment of the epithelium (Fig. 9B). The latter indeed tends to be hypertrophic, with goblet cells predominating. The bronchial glands are also somewhat hyperplastic. A little plasma cell infiltration into the mucosa is evident, but there is no collagen deposition. The muscularis mucosae does not seem to be hypertrophic, because its component columns are so widely separated. However, this is illusory, and there is in reality fairly well-marked muscular hypertrophy. Sometimes this is focal in distribution (Fig. 9A). How effectively this muscular system may operate is left in some doubt, in view of the patent invasion of the bronchiolar adventitia by fibrocytes at many sites, as the peribronchial veins and arteries are similarly invested by the proliferating reaction.

MODIFIED TALC LESIONS

The basic lesion just described may be recognized throughout this series of cases, though modified by the associated pathological processes induced by other dusts. It is the more remarkable to note that the cellular proliferative phenomenon is present even in Case 1, where the history of talc-dust exposure is as short as 10 months, and persists in virtually similar form not only in Case 7, with a history of 23 years of talc exposure, but also in the instance of Case 8, where there was a 27-year talc-exposure history, together with 10 years' exposure to dusts encountered in zinc and lead mining.

There may be a greater tendency toward the formation of massive lesions and subpleural reaction where there is an associated

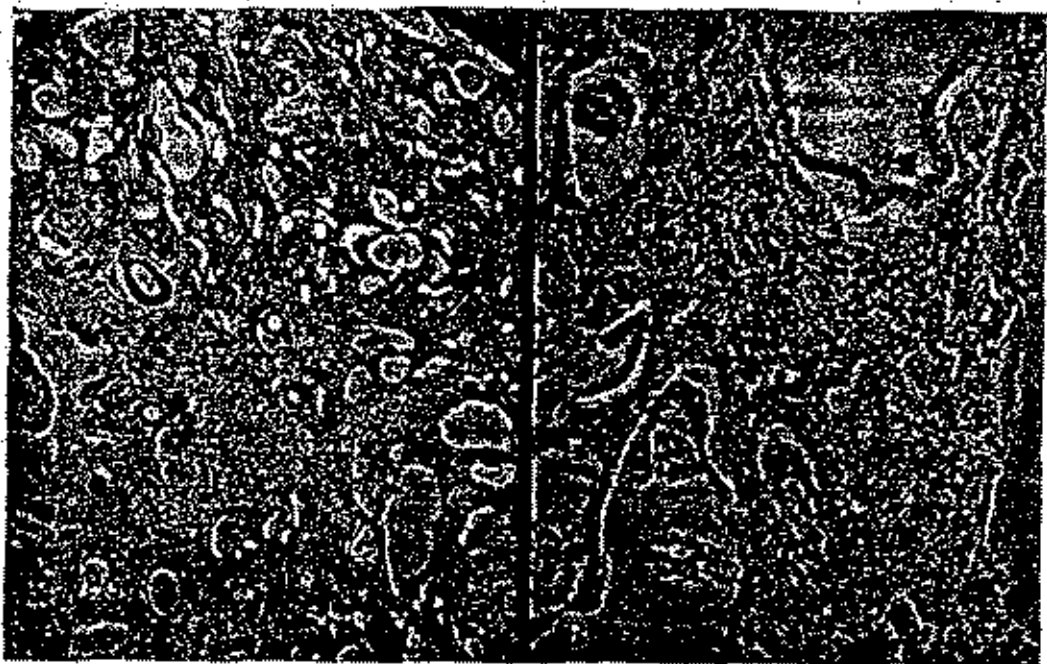


Fig. 5.—Parenchymal cellular deposits in talc miners. *A*, loose cellular web, with atrophic alveoli (moderate quartz content in lung ash). *B*, pigmented iron-staining stellate cellular deposit (moderate quartz content in lung ash).

Fig. 6.—Stromal reactions in talcosis. *A*, pigmented fibrocellular granulation tissue, with atrophic alveoli (moderate quartz content in lung ash). *B*, dense diffuse fibrosis, with surviving elastic skeleton of occluded blood vessel (high quartz content in lung ash).



EFFECTS OF INHALED TALC-MINING DUST

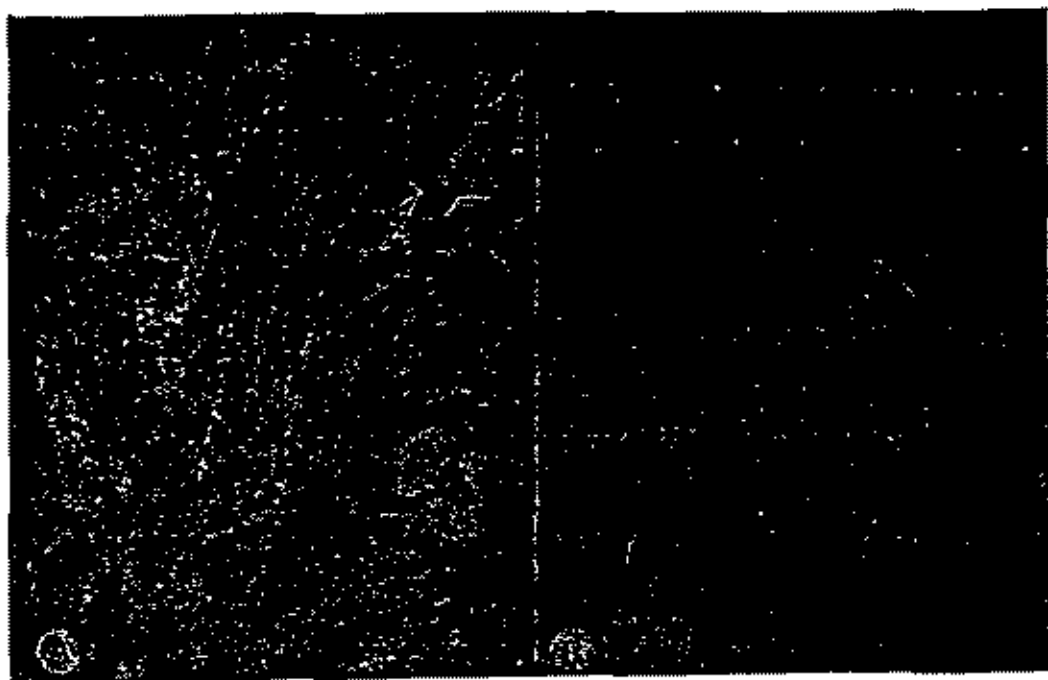
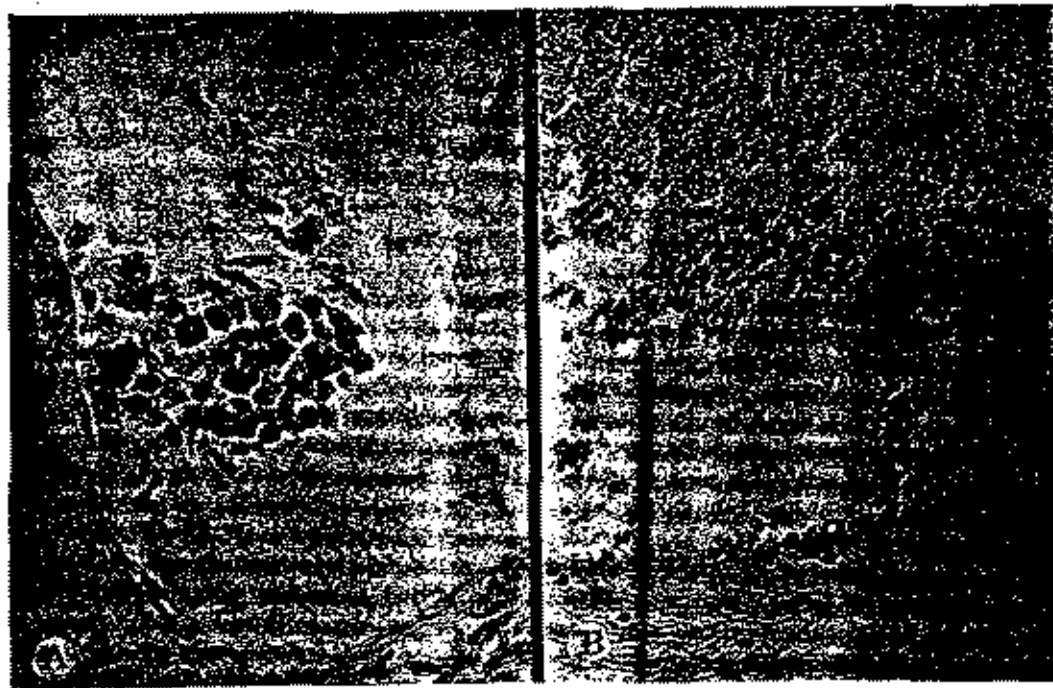


Fig. 7.—"Talc" bodies in human lung tissue. *A*, slender elongated "talc" bodies embedded in fibrous tissue. *B*, short dumbbell body partly engulfed by a macrophage and showing intense iron staining.

Fig. 8.—Talc bodies in human lung tissue. *A*, accumulation of konoiphores, showing a high degree of iron staining and containing short lengths of talc fibers. *B*, talc body among erythrocytes within the lumen of a blood vessel.



quartz reaction. In Cases 2 and 6, collagen formation is restricted to a minimum and the supporting stroma tends to be of a reticular nature of variable density. In Cases 1, 5, and 8, there is a greater tendency toward collagen formation. It is to be noted that of these cases Cases 1 and 5 yielded a relatively high value for quartz in the lung tissue but Case 8 showed a very low quartz level. Birefringent quartz particles are a prominent feature of the tissues in Cases 1 and 5 and are but poorly demonstrable in other instances.

The interstitial alveolar wall reaction is also more marked in the cases with heavy quartz-dust exposure, and there is considerable collagen deposition even with some hyalinization in Cases 1, 2, 5, and 8. Indeed, in these cases the alveolar wall involvement is so pronounced as to overshadow somewhat the essentially perivascular distribution of the underlying talc reaction.

The damage sustained by the alveolar walls is further modified by the presence of quartz particles which involve marked macrophage and plasma cell infiltration, marked enlargement and proliferation of the superficial septal cells, often associated with cellular catarrh into the alveolar spaces, and finally moderate to marked impairment of the capillary circulation through these alveolar walls. The latter is not, however, a constant phenomenon, and there may be advanced alveolar wall disease without appreciable loss of capillaries (e. g., Case 6).

When collagen is present, it fails to be arranged in the form of silicotic nodules in all but rare locations (e. g., Cases 1 and 5). Incipient fibrous whorls are present also in Cases 2 and 8. Some lie against blood vessels (Fig. 3B). It seems possible that the abundantly cellular talc reaction is incompatible with the complete evolution of the nodular silicotic lesions.

Subpleural deposits follow the same pattern, being most marked where exposures to both talc and quartz have been considerable. The resultant lesion is, however, an exaggeration of the primary talc reaction except for the greater prominence of the collagen where quartz is abundantly present. Essen-

tially, then, there are three cortical zones, viz., a fibrocellular internal component which may be variably pigmented and which may contain distended bronchioles, an intermediate exaggerated lamina elastica, and an external highly vascular fibrocellular layer usually covered by mesothelium (Fig. 12B).

The parenchymal stroma is considerably exaggerated in the presence of a quartz reaction superimposed on the talc phenomenon (Fig. 5). This is largely a perivascular change, and within these linear columns of fibrosis partially or wholly occluded blood vessels may be seen, sometimes so effectively incorporated within the scars as to be betrayed only by their residual elastic tissue skeletons (Fig. 6).

Vascular damage is indeed very much more in evidence in those cases with the longest history of hard-rock mining or where the highest free-silica content was discovered. Two essential processes are present, namely, an endothelial proliferation in the least vessels ending as endarteritis or endophlebitis obliterans and a periarteriolar fibrocytic proliferation, with fibrotic stricturing or partial invasion of the muscular coats (Figs. 2B, 3B, 10, 11). This process is present in its most exaggerated form in Cases 1 and 6, in which multiple periarteriolar granulomata may be found. Such lesions cause marked pulmonary ischemia, the more so as the lesions are not limited to the pulmonary circulation but may also involve the bronchial vascular system at numerous points, thus effectively precluding establishment of any collateral circulation.

While the essential reaction to talc appears to include exaggerated distention of bronchioles and smaller bronchi, this change, though present in a variable degree in all cases of the present series, is not universally observed throughout the lungs where reaction to quartz dust is concurrently present. Instead, there is a tendency toward narrowing of the bronchial lumen, epithelial desquamation, mucosal hypertrophy, sometimes with papilloma formation, and inflammatory infiltration, with adventitial fibrosis and cicatrization at multiple sites where exposure

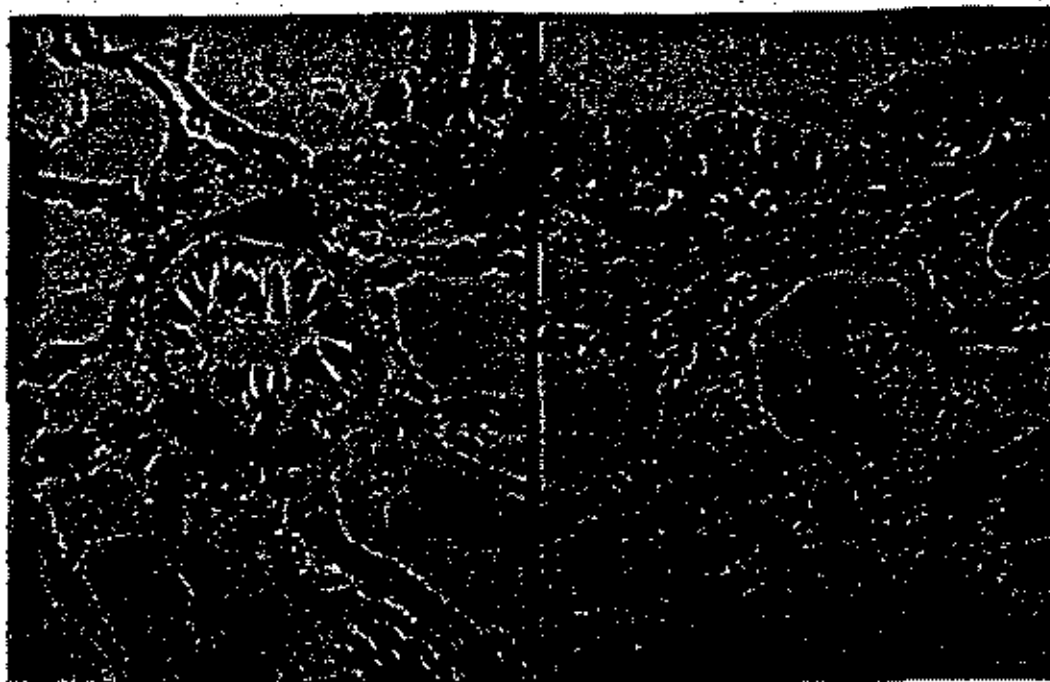
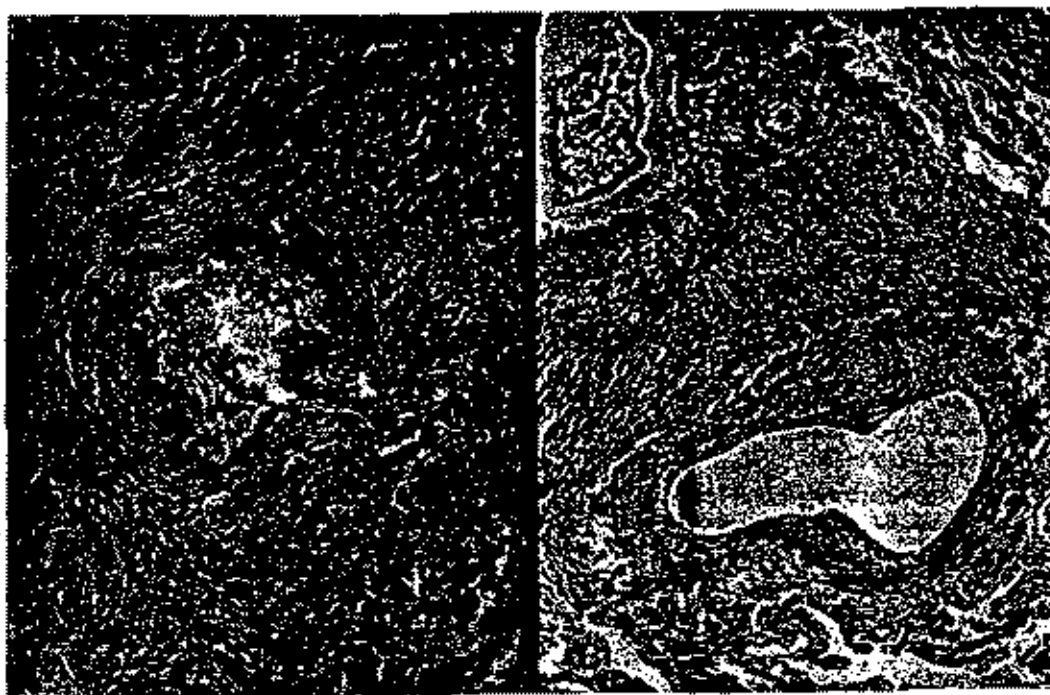


Fig. 9.—Bronchial damage in talcosis. *A*, irregular focal proliferation of muscularis mucosae (low quartz content in lung ash). *B*, submucosal fibrosis, with lymphatic distention but no injury to the epithelium (moderate quartz content in lung ash).

Fig. 10.—Vascular damage in talcosis. *A*, perivascular fibrosis and intimal swelling (high quartz content in lung ash). *B*, talcotic nodules in the walls of blood vessels (low quartz content in lung ash).



to quartz dust was adequate. This combination of chronic hypertrophic bronchitis, obliterative bronchiolitis, and the peripheral bronchiolectasia superimposed on the fibrocellular changes throughout the lungs may lead, on the one hand, to extensive areas of partial atelectasia of the relevant lung fields or, on the other, may be associated with the development of multiple epithelium-lined peripheral cysts. The latter are essentially ballooned-out terminal segments of the respiratory passages and may be readily distinguished from emphysematous bullae by the presence of the epithelial lining, the residual basement membrane, and the irregular presence of supporting muscle fibers. True emphysema is relatively infrequently seen and, when present, consists of the atrophic vesicular variety.

The differential involvement of lymphoid tissue in the reaction to talc dust and to talc dust combined with quartz dust is clearly demonstrated in the present series. Whereas the talc reaction tends sedulously to avoid the lymphoid tissue, the contrary condition prevails when quartz is abundantly present or where there is an associated tuberculosis. Talc bodies are, however, never seen in the lymph nodes, and the reaction present in most instances is limited to medullary macrophage infiltration and pigmentation. Silicotic or tuberculosilicotic nodules are present in but a few instances (Cases 1 and 5). Despite the fact that multiple nodules and necrotic foci are present in the lung substance, the hilar node involvement is not marked. This state of affairs is the reverse of what prevails in the presence of exposure to quartz dust unaccompanied by an exposure to talc dust. One is consequently inclined to infer that the simultaneous presence of talc dust and quartz dust in the lungs militates against the transportation of the quartz dust to the hilar nodes. Alternately, though talc bodies are not seen in the hilar nodes, their liberal transference is not yet precluded, and the inhibitory tendency of the talc on the silicotic reaction, which is manifest in the lung substance of this series, may prevail also in the lymphoid tissue.

Necrotic foci were observed within the areas of cellular proliferation in Cases 2, 4,

5, 6, and 7. In Case 2 histoplasmosis is the obvious answer, while in Cases 4, 5, and 6 the lesions are more suggestive of tuberculosis or tuberculosilicosis. There is some tendency toward inflammatory reaction at the periphery of the lesions in the latter three cases only. On the other hand, the necrosis also involves the stromal elements, favoring histoplasmosis once more. In the majority of other cases, it seems possible that the necrosis may be explicable on an ischemic basis, either because the cellular hyperplasia had outstripped its vascular supply or because the latter had been cut off through regional vascular occlusion. However, as all these cases came from the St. Lawrence Valley area at the time of an epidemic in that region, it is possible that histoplasmosis may be a factor.

The process seen in Cases 4, 5, and 6, if tuberculous, has been modified considerably by the abundance of fibrous tissue and cells. A large thick-walled cavity, without a distinctive fibrous capsule or even components, is present in the latter instance. Atypical tubercles are present within this wall at the edge of the broad inflammatory zone. While the temptation exists to interpret this cavity as tuberculous, it may represent merely a chronic discharging abscess. The lesion is also compatible with a diagnosis of histoplasmosis. Attention may also be drawn to the marked peribronchitis and ulcerative bronchitis in the passage draining this cavity. No tubercles were observed here.

Pneumonic areas were observed in the cases with exposures to both quartz dust and talc dust, especially Cases 2 and 4, but not where only talc dust was the responsible etiological agent. This pneumonic process tends to show healing by organization in various stages of progression, and numerous talc bodies are thus trapped. It seems likely that those present in the formed lesions may have been incorporated in this manner through earlier episodes of inflammation.

COMMENT

The chronic or long-term effects of the inhalation of dusts, such as are generated in talc industries, are thus demonstrated by this

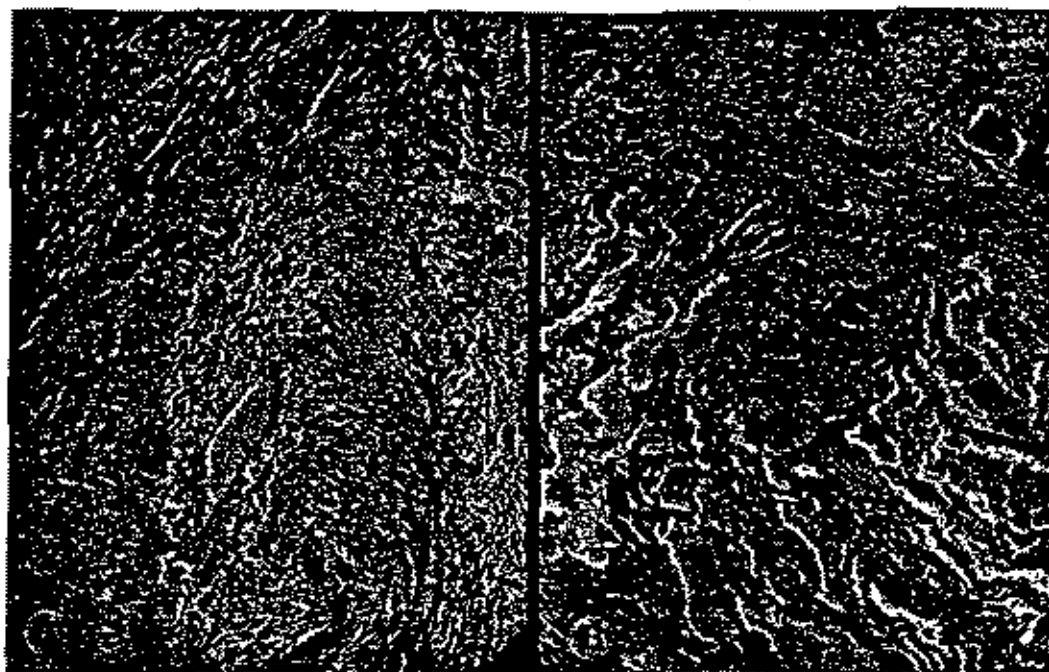
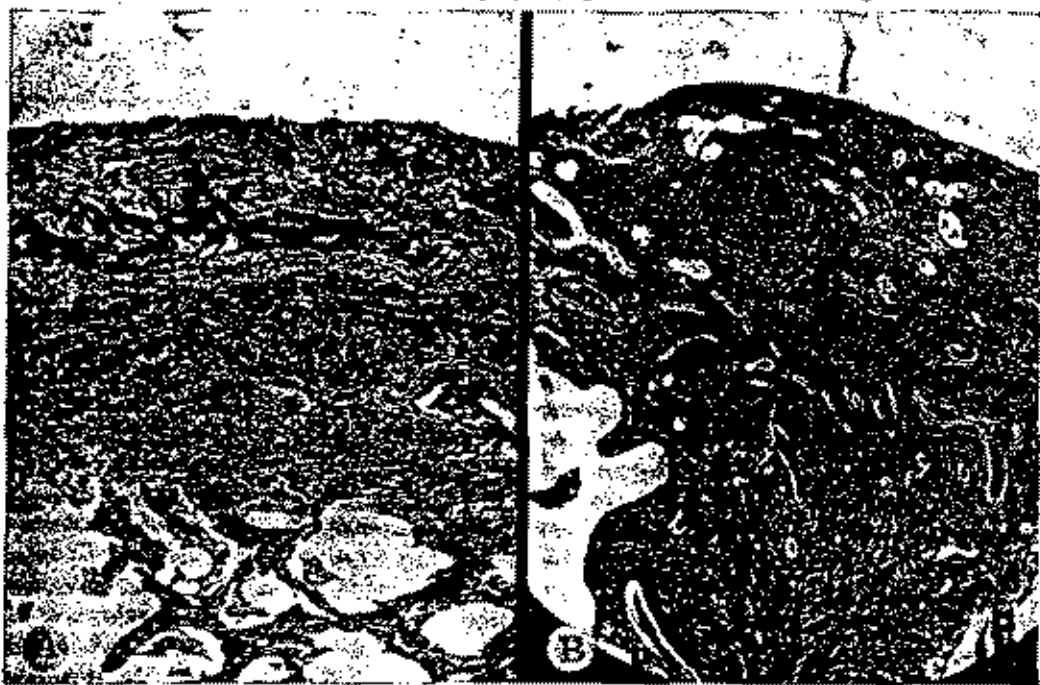


Fig. 11.—Vascular damage in talcosis. *A*, progressive loss of venous lumen through progressive proliferation of intima (moderate quartz in lung ash). *B*, fibroelastic scar in interlobular septum, representing the remains of obliterated blood vessels (moderate quartz in lung ash).

series of cases to vary considerably according to the extent or nature of associated dust in other industries to which the person may have been exposed, either preceding or suc-

Fig. 12.—Pleural damage in talcosis. *A*, diffuse fibrocellular, partly pigmented, and highly vascular reaction (low quartz content of lung ash). *B*, loose fibrous proliferation external to lamina elastica, with whorled nodule; talc plaque (high free-silica content of lung ash).



feeding the period during which talc dust was breathed.

The histopathological features enumerated are almost entirely explicable in terms of the mineralogical analyses of the lung ash presented in Table 4.

It is seen, for instance, that for both of our key cases of pure talc pneumoconiosis (Cases 3 and 7) the quartz content of the lung ash (2.3% and 3.2%) was about the same as the corresponding value for many normal persons never exposed industrially to quartz dust. Among this series, the amount of lung ash of Case 7 is particularly low (4.69% of dried tissue), and so is the total silica content (17.9% of ash) which includes the silica in the silicates present in these tissues.

Quartz was present in Cases 1, 2, 4, 5, and 6 in concentrations compatible with nodular silicosis. Indeed, the average quartz content of the silicosis cases studied at The Saranac Laboratory is 9.3% of the lung ash. Cases 1 and 5, therefore, had unusually large amounts of quartz dust lodged in their lungs. Yet nodular silicosis was conspicuous by its absence in Cases 2, 4, and 6 and only sparsely present in Cases 1 and 5.

Attention is drawn to the demonstrated presence of talc, tremolite, and anthophyllite in the lung ash of Case 7. There is no apparent correlation in this series between the length of exposure and the concentration of these minerals in the lung ash.

The factor which seems most obviously to be responsible for the modification of the essential reaction to talc dust is the abundant amount of quartz dust coexistent with the talc in the pulmonary tissues. Five of the eight deceased talc employees had been miners also of lead, zinc, or pyrites. Attention is drawn to the minor differences in the mineral components of the lung ash. While we do know that quartz is an active pulmonary pathogen, we do not yet know whether the additional substances demonstrated (e. g., feldspar) are capable of playing a material role in modifying the response to either the quartz or the talc or are themselves pathogenic.

It does seem permissible, however, to infer that the presence of talc dust in its turn modi-

fies appreciably the type of reaction to fl quartz dust. Though considerable quantities of free silica were demonstrable in the lung tissue (Table 4) in some instances (Cases 2, 4, 5, and 6), there was not in this series clear-cut tendency to nodular silicosis.

Tuberculosis or histoplasmosis may have been a factor in the pneumoconiotic reaction in some of these cases. While doubt persists as to the diagnosis of a true infective process it does seem certain that if the latter diagnosis has to be accepted the presence of the talc reaction induced an aberrant type of chronic inflammatory process.

While it has been postulated that the foregoing observed deviations from the primary process may all be due to coincidental quartz exposure to tuberculosis or histoplasmosis or to nonspecific pneumonia, reference should be made to the fact that there is insufficient knowledge in the present instances concerning the differences in the talc dusts to which the men were exposed or to the concentration and rate at which the talc dust was deposited in their lungs. The latter factors alone are known to influence the nature of the silicotic reaction which may follow exposure to quartz dust, and the precise composition of the talc may therefore necessarily be a factor too. In this connection it is interesting to note that the majority of talc bodies were in a range of 20μ to 50μ , being somewhat longer and thinner than the asbestos bodies generally found in asbestosis. In rare instances some slender fibers, measuring up to 200μ , were also present. Terminal clubbing was a factor in all but two cases (Cases 2 and 3), and occasionally an intermediate bead could be seen. Segmented forms were but rarely seen. In all cases the mantle of the body showed an intense iron-staining reaction, but degeneration of this coat was demonstrable in most cases where the talc bodies were present in the newly formed fibrocellular tissue.

In addition to the talc bodies and the chemically demonstrable quartz, there were in most instances pigment granules and birefringent particles, spicules, and crystals within the interstitial tissues and in the konoiphores trapped within alveoli. The variable abundant

presence of such elements at sites of maximal fibroid or cellular reaction may undoubtedly bear some relation to the differential pathological effects observed in the present series. The pigmented particles, though present in all cases, were most abundant in Cases 1, 3, 6, and 8. Brilliantly birefringent particles, on the contrary, were conspicuous features mainly in Cases 2, 3, 4, and 8, and in this series large numbers of such particles were dispersed among the fibrocytes comprising the pulmonary lesions. These particles were identified as talc.

The "talc bodies" described may be an indication of the main pathogenic agent in the present series of cases or may be merely incidental features. Were the former to be the case, it would perhaps be advisable to rename them "tremolite bodies."

They were relatively sparsely represented in Cases 1, 6, and 8, and it is interesting to find that in these very three cases the tremolite content of the lung ash was least. They were present in greatest profusion in Cases 3, 4, and 5, and once more the mineralogical analysis confirms the relatively high incidence of tremolite in these three cases (Table 4). The anthophyllite values, on the contrary, do not correspond with the histopathological findings. It may therefore be fairly safely inferred that the "talc" bodies are of tremolite origin.

In view of the fundamental similarity between the talc reaction seen in this series and the histopathological changes present in asbestosis, one is constrained to speculate whether the tremolite component, being an asbestiform mineral, is not after all the main source of mischief. It remains for animal experiments to shed some light on this subject.

SUMMARY

A survey of the talc industry in Northern New York State revealed that the talc mined and processed there consists of a mixture of talc, tremolite, and anthophyllite. Quartz is also present in moderate amounts in the dust generated in mining and processing the commercial talc.

A mineralogical analysis of the lung ash from eight deceased talc-industry employees revealed the presence of appreciable quantities of talc, tremolite, and anthophyllite. Quartz was present in significant amounts only in the cases where the men had been additionally exposed to dust in mining industries other than in the talc industry.

The histological features suggest that tremolite may be the main pathogenic agent in provoking the characteristic "talc" lung lesion. The role of talc and of anthophyllite has not been wholly excluded.

The presence of quartz modifies materially the nature of the "talc" reaction.

The presence of "talc" dust in the lungs modifies both the response to quartz dust and the course of associated infection.

Marked pulmonary vascular damage was present in the cases where the quartz content of the lungs was highest, and this feature is in harmony with the tendency to cardiac deaths.

Bronchitis, bronchiolitis obliterans, and bronchiolectasis are associated major findings in this series.

The chemical analyses presented in Table 4 were made by A. J. Redlin, chemist, Saranac Laboratory, E. S. Larsen, 3d, Ph.D., of the U. S. Geological Survey, formerly petrographer of The Saranac Laboratory, made the petrographic and X-ray diffraction analyses.

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Pulmonary Disability in Asbestos Workers

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Asbestosis has been described in detail in numerous published articles and texts. While it is true that cases of far-advanced asbestosis may have severe pulmonary disability, relatively few of the people exposed to the fiber develop the disease. Therefore, it is the intent in this paper to mention asbestosis only briefly and then to outline various other pulmonary disabilities seen among asbestos workers.

The word "asbestos" is generally used to describe several fibrous magnesium silicates which are different in their chemical composition and physical properties. The most important types of fibers are chrysotile, amosite, crocidolite, anthophyllite, actinolite, and tremolite. Total world production of all fibers last year amounted to slightly more than 1,500,000 tons. Approximately 95% of the fibers produced were of the chrysotile variety, 3% crocidolite, and 2% amosite. Deposits of various types of this mineral are found in many countries, but the largest mines are located in Canada and Africa.

Asbestos fibers are highly resistant to heat and acids. They have great tensile strength and large surface areas. Because of these properties as well as their filamented structure, industrial use of these fibers throughout the world is increasing. The textile industry has used them for many years to produce blankets, clothing, threads, ropes, tapes, braided tubing, and filters. In recent years, however, there has been an increasing use of asbestos in the insulation, building, and friction-material trades. In addition, the

fibers can be found in paper, wallboard, shingles, pipe covering, floor tiles, brake linings and brake blocks, cements, putties, and plastics.

It should be noted that the facts presented here apply to those persons who have been exposed only to asbestos fibers and to no other dusts. As previously indicated, industry today is finding many new uses for the fibers when they are mixed with other dusts. It is an established fact that when asbestos fibers are mixed with silica, diatomaceous earth, or other potentially toxic dusts, the pulmonary changes resulting from the inhalation of these mixtures are not typical of asbestosis. The x-ray pattern may be different, the clinical course changed, or the susceptibility to intercurrent infection increased or decreased. Thus, in making a diagnosis of occupational pulmonary disease, it is highly important to obtain a detailed occupational history, so that asbestosis, silicosis, or mixed pneumoconiosis can be differentiated.

The statements and observations reported here concern several thousand men and women employed in the asbestos industry in Canada and the United States. In this industry the various mining, milling, and manufacturing operations create some dust containing asbestos fibers. If the fibers up to 50 μ in length are inhaled continually in sufficient quantities over a period of several years, a typical pulmonary fibrosis will develop. It has been demonstrated that this fibrosis is due not to the chemical but rather to the mechanical action of the fibers.¹ The asbestos fibers are deposited in the terminal bronchioles, initiating a tissue response which coats the fiber and eventually produces what is known as the asbestos body. This appears to be a defense mechanism of the lung. Numerous asbestos bodies can be found in the

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PULMONARY DISABILITY IN ASBESTOS WORKERS

sputum of persons who have had only short and sporadic exposure to the dust. These persons are healthy and have no demonstrable signs or symptoms of asbestosis. Therefore, it seems more appropriate to use the term "asbestos" bodies rather than "asbestosis" bodies, signifying exposure to the fibers but not necessarily indicating disease.

If increasing quantities of the fibers are continually inhaled, the tissue reaction progresses, and a generalized, diffuse fibrosis gradually appears throughout the lower lobes of the lungs. With additional exposure, this



Fig. 1.—Early asbestosis.

fibrosis will spread to the other lobes, eventually causing respiratory embarrassment and finally cardiac failure.

The pulmonary fibrosis resulting from prolonged inhalation of asbestos fibers will produce a typical x-ray pattern. In early, or first-stage, asbestosis (Fig. 1), the x-ray shows a fine, diffuse, homogeneous infiltration throughout both lower lung fields. It should be noted that this infiltration is bilateral, that it is generalized at both bases, and that the nodular conglomerate patterns of other pneumoconioses, such as silicosis, are not seen in asbestosis. There is a considerable amount of pleural reaction associ-

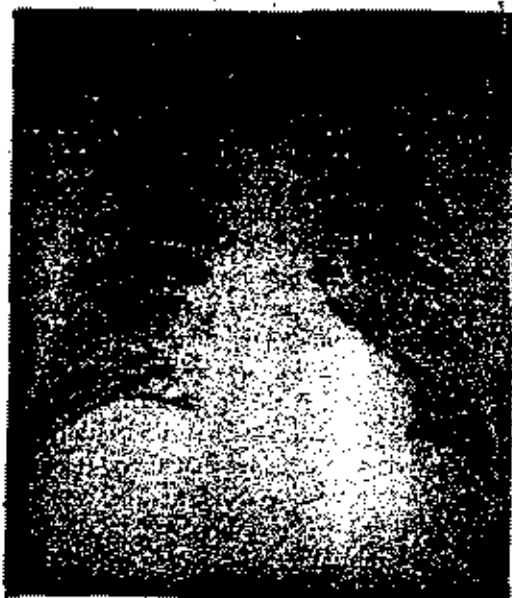
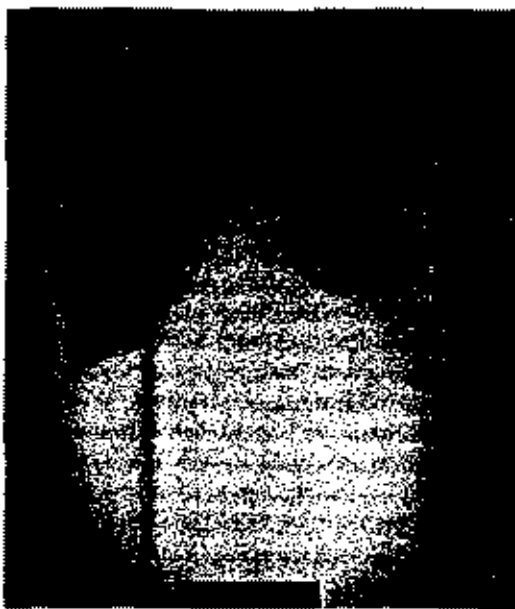


Fig. 2.—Moderately advanced asbestosis.

~~ated with this disease,~~ which may account for the "ground glass" pattern which has been used to describe the typical x-ray picture.

In moderately advanced, or second-stage, asbestosis (Fig. 2), the infiltration has increased but still is confined to the lower lung fields. The "ground glass" pattern is

Fig. 3.—Far-advanced asbestosis.



more apparent, and the heart borders are becoming indistinct or shaggy. There is some irregularity of the diaphragmatic outlines and beginning obliteration of both the cardiophrenic and the costophrenic angles.

In far-advanced, or third-stage, asbestosis (Fig. 3), the infiltration still is homogeneous and bilateral, has spread to the middle and possibly the upper portion of the lung fields, but the apices remain clear. The cardiac outline is almost completely obliterated, as are the domes of the diaphragm and the costophrenic sulci. With this picture in mind, it is advisable to reiterate the observations of many physicians, namely, that the x-ray picture should never be used to estimate the presence or the extent of impaired pulmonary function or disability. Many cases with x-ray evidence of third-stage asbestosis have been known to carry on their usual work and live fairly comfortable lives for several years. On the other hand, no case of definite disability has been seen unless there was the typical x-ray pattern.

There is no typical clinical picture for asbestosis. The disease is insidious in its onset and slowly progressive with continued inhalation of the fiber. There is a gradual increase in cough and expectoration, some anorexia and weight loss, then slowly increasing dyspnea. Cyanosis and clubbing of the fingers are rare findings. There is evidence that asbestosis will not progress after exposure ceases, but this seems to be true only if the worker does not develop an intercurrent pulmonary infection.

It will be shown that asbestos workers are not predisposed to develop more intercurrent pulmonary infections than are found in other workers. However, when an acute pneumonia develops in the presence of an established asbestotic fibrosis, the infection is slow to heal, relapses are frequent, and the patient may be more susceptible to subsequent pulmonary infections. While it is true that the disease is slow and insidious in its onset and that people with advanced asbestosis may lead relatively normal lives, eventually the heart begins to fail, and death from cor pulmonale rapidly follows.

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Gregoire* has reported that pulmonary function studies on asbestos workers have shown that the chief physiological problem is that of a "tight" lung. The vital and maximum breathing capacities are lowered, expansion of the lung is difficult, and arterial oxygen saturation of the blood is diminished in some cases, indicating an impairment of gas transfer through the lung. Diffuse obstructive emphysema, so commonly seen in silicosis, is not apparent in asbestosis. These pulmonary function studies are of importance in the proper diagnosis of pulmonary fibrosis and the estimation of pulmonary disability. Of more importance is the fact that these tests can often help the clinician in directing the treatment of the case. Unfortunately, there are too few persons who are properly qualified today to carry out these tests and interpret the results.

An x-ray survey was made of one group of 708 employees working in an asbestos mill where the ore was dried, crushed, separated and graded, packed, and then shipped. Operations in this plant required the employees to rotate through various jobs; hence it was impossible to relate any x-ray changes to a particular job or to a specified dust concentration. At the same time it could be assumed that all members of the group had been exposed to varying concentrations of the dust. The chest x-rays of these employees were divided into three broad groups: (a) essentially normal lungs; (b) marked linear exaggeration (P-2) but no typical pattern of asbestosis, and (c) definite asbestosis.

Table 1 shows that of the 708 employees studied 649, or 91%, had normal x-rays. This is of interest because 204 employees, or 29% of the total group, had 10 or more years of service, and 2 men actually had worked more than 40 years in the dust.

Table 2 indicates that 52 of the 708 employees showed a marked increase of all peribronchial markings, although none had defi-

* Gregoire, F.: Pulmonary Function Studies in Men Exposed for Ten or More Years to Inhalation of Asbestos Fibers, read before the Seventh Saranac Symposium, 1952 (unpublished).

PULMONARY DISABILITY IN ASBESTOS WORKERS

TABLE 1.—Employees with Normal X-Rays

Exposure, yr.	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49
Employees, no.	224	285	94	40	44	15	5	4	1	1

nite asbestosis. Inasmuch as the majority of these men had essentially normal x-ray films early in their employment history, it is assumed that most of the later increased lung markings were associated with their subsequent dust exposures. Further indication of the length of exposure necessary to develop x-ray changes is seen when it is noted that 69% of this group had 10 or more years of exposure.

Table 3 shows that of the 708 employees 7 had developed definite x-ray evidence of asbestosis. These men exhibited various stages of pulmonary involvement, but all were working steadily at their accustomed jobs with no signs of disability. It is of interest to note that none had developed x-ray evidence of asbestosis with less than 20 years of exposure.

Frequently it has been stated that it takes from 5 to 10 years of exposure to develop asbestosis. The survey reported here concerned mill employees. It is possible that other operations might have different exposures with other disease experience. Factors which might influence this experience are not only the length of exposure or the concentration of dust in the air but also the fact that there is probably an individual susceptibility to the development of pulmonary fibrosis.

Medical literature has given considerable attention to occupational pulmonary disease, but very little has been reported on the occurrence of nonoccupational respiratory disease among those employed in the dusty

trades. The following survey was made in order to determine the incidence of non-occupational respiratory disease in another group, of 1561 men and women, working in the asbestos industry.

A review of absentee records indicated that no valid conclusions could be obtained from this source, because the reason for absence was given by the employee himself. Sickness often was used as an excuse to cover short absences for a variety of personal reasons.

It then was decided to study the claims submitted for sickness and accident insurance. All employees in the survey participated in a plan operated by an independent insurance company. Indemnification was made only after the nature of the illness had been certified by the treating physician.

The study included claims submitted over a three-year period for such illnesses as the common cold, sinusitis, pharyngitis, grippe, bronchitis, pneumonia, asthma, and pleurisy. Occupational respiratory diseases and pulmonary tuberculosis were excluded in the report.

Table 4 shows that of the 1561 employees in the survey group there were approximately equal numbers in dusty and nondusty occupations. Of all claims filed for respiratory diseases, 45% were for employees with dust exposure. Clinical observations for many years had given the impression that a dusty occupation in itself would not predispose a person to more nonoccupational respiratory disease than would a dust-free job. This survey shows that the rate of disease over

TABLE 2.—Employees with P-2 X-Ray Readings

Exposure, yr.	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49
Employees, no.	5	11	2	10	11	4	1	1	0	1

TABLE 3.—Employees with Asbestosis

Exposure, yr.	1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49
Employees, no.	0	0	0	0	5	1	0	1	0	0

a three-year period was approximately the same in the two groups. In addition, there was no appreciable difference in the duration of illness in either group.

Animal experiments and clinical observations have shown that asbestosis does not predispose a person to the development of pulmonary tuberculosis, nor does it aggravate an apparently healed tuberculous lesion. In two isolated one-industry towns in the Province of Quebec where asbestos was mined and processed, the incidence of tuberculosis over a period of many years was no greater than in other isolated towns with comparable populations but without a dusty



Fig. 4.—Electron micrograph, chrysotile asbestos; $\times 4000$.

trade.[†] In addition, the incidence of tuberculosis among asbestos workers was lower

et al., P.: Personal communication to the

4.—Nonoccupational Disease Experience

slaves, total no.	1,661
slaves with dust exposure	807
slaves with no dust exposure	754
days for respiratory disease	27
days for respiratory disease with dust exposure	11
days for respiratory disease with no dust exposure	16
Average length of absence with dust exposure, wk.	12
Average length of absence with no dust exposure, wk.	8.1

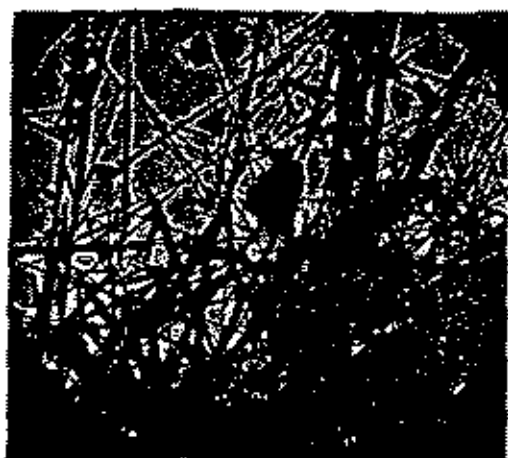
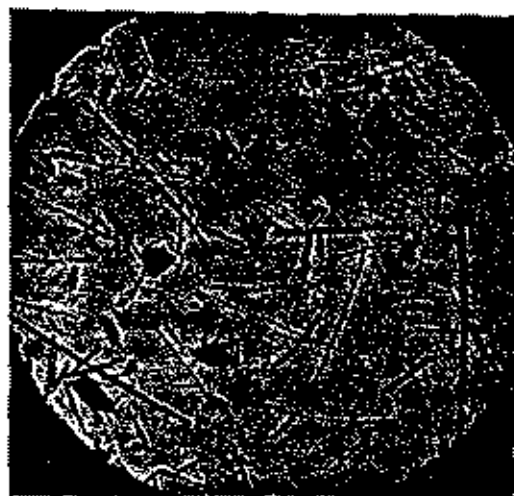


Fig. 5.—Electron micrograph, amosite asbestos; $\times 4000$.

than that among the general population of these mining towns.

Conflicting opinions and different reports make it extremely difficult to confirm or deny conclusively the causal relationship of asbestosis and carcinoma of the lung. Too often a common conclusion is drawn from observations and experiences with different racial groups, living in different parts of the world under variable socioeconomic conditions and working in diverse occupational exposures. To these variables should be added the fact that there are various types of asbestos fibers.

Fig. 6.—Electron micrograph, crocidolite asbestos; $\times 4000$.



PULMONARY DISABILITY IN ASBESTOS WORKERS

Badollet[†] has reported that there are several different types of asbestos fibers used by industry today, and these fibers have different physical and chemical properties. Figures 4, 5, and 6 are enlarged electron micrographs of three types of fibers used most commonly in industrial processes. The long, soft, and silky chrysotile fibers are found chiefly in Canada, while the amosite and crocidolite fibers which are shorter, stiffer, and brittle come from Africa.

Canadian experience with asbestosis has been limited to the chrysotile fiber. The majority of industrial processes in the United States use this fiber, but in recent years there is increased use of the amosite and crocidolite fibers. The British and European industries use greater quantities of these harsher fibers. Therefore, in trying to clarify the causal relationship of asbestosis and bronchogenic carcinoma, many variable facts should be clearly identified, especially the type of fiber used and whether or not other dusts were present in the industrial and environmental atmosphere.

SUMMARY

Respiratory disease experience among several thousand male and female asbestos workers in the United States and Canada is reported. Of all workers exposed to the fibers, very few develop asbestosis.

Asbestosis is insidious in onset and progresses slowly with continued exposure, causing respiratory embarrassment and cardiac failure.

[†]References 2 and 3.

Physiologically, asbestosis is the problem of the "tight" lung. Expansion of the lung is difficult, and there is impaired gas transfer through the lung. Diffuse, obstructive emphysema is not common.

There is a typical x-ray pattern which cannot be confused with other pneumoconioses.

An x-ray survey of 708 employees in a milling operation showed that the majority had normal x-ray patterns, that 10 or more years of exposure were necessary to produce x-ray changes, and that no cases of asbestosis were found who had worked less than 20 years in the dust.

The incidence of nonoccupational respiratory disease was not increased, nor was the illness more prolonged among workers exposed to asbestos dust than among nonexposed workers.

Asbestosis does not predispose to the development of tuberculosis, nor does it aggravate an apparently healed lesion.

There are several reasons for different opinions expressed concerning the relationship of asbestosis and bronchogenic carcinoma. Differences in asbestos fibers are noted.

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Pulmonary Disability Associated with Coal Mining

J. W. G. HANNON, M.D., Washington, Pa.

In the study of pulmonary disability associated with coal mining, one must of necessity give due consideration to the etiological factors that produce abnormal pulmonary conditions in this industry. These abnormalities are both anatomical and physiological. The mining of coal produces dusts that vary from relatively pure carbonaceous material, on the one hand, to relatively pure silica, on the other, with a mixture of coal and silica in between. Because of the many fluctuations that can occur in the aerial dusts of the working atmosphere, the pathological changes in the lungs assume many and bizarre patterns. The quality and the quantity of the dust produced can differ from mine to mine in the same general area, from job to job in the same mine, and even from man to man on the same job. These variations can be accounted for by the following factors.

1. Production methods. The type of production methods has a definite influence on the amount of dust produced. Mechanical mining produces more dust and smaller particle sizes than hand methods.

2. Dust control. The high incidence of coal miners' pneumoconiosis in Welsh pits is best explained by the introduction of mechanization without adequate dust suppression. The patchiness of the incidence in the United Kingdom is best explained by differences in dust concentrations.

3. Geology. The geology is important, as the mines with thin coal seams necessitate a considerable amount of roof drilling, causing dustiness of high silica content. Faulting of the coal seam by siliceous rock also requires drilling of this rock, and the subsequent production of high concentrations of silica dust. The geology can vary greatly from mine to mine in the same general area.

4. Type of work. The specific job of the miner has a definite bearing on his exposure. Men engaged in rock drilling are exposed to high concentrations of silica dust and a small amount of coal dust. Coal-face workers are exposed to relatively pure concentrations of coal dust and develop characteristic lung changes. Coal trimmers who load ships at the dock are also exposed to coal dusts and develop the same lesions as coal-face workers.

The tendency of some coal miners to move from mine to mine, with the associated changes in job types, production methods, dust control, and geology, is of etiological significance. A complicated and somewhat confusing environment can produce an involved pathological pattern in the pneumoconiosis associated with coal mining.

The industrial pulmonary conditions found in coal mining can be grouped into the following etiological classifications:

Silica dust—silicosis

Mixed dusts—anthracosilicosis

Coal dust—anthracosis; emphysema

Any of the above forms may be modified by infection or overwhelming concentrations of the particular dust to produce progressive massive fibrosis.

SILICOSIS

Classical silicosis can be found in coal miners, and its clinical course does not differ

Recorded for publication June 6, 1955.

Medical Director, McIntyre Research Foundation.

ANTHRACOSIS

Anthracosis (Fig. 1), a condition referred to by the British as mixed pneumoconiosis and by others as a modified silicosis, does occur in coal mining. There are some who would discard the term "anthracosis," while others believe that the term adequately and accurately describes a condition which occurs among coal miners. It is contracted by exposure to a mixed dust or by moving from one job to another where the exposures are changed from relatively pure coal to relatively pure silica or vice versa. Anthracosis produces a clinical picture similar to pure silicosis.

ANTHRACOSIS

Anthracosis (Fig. 2), a condition of the lungs due to the retention and subsequent pigmentation of the pulmonary tissues, does not usually present problems of disability.

EMPHYSEMA

Pericardial emphysema (Fig. 3) can occur as a complication of anthracosis, and its incidence and severity are in direct proportion to the concentrations of coal dust and the length of exposure. It does not occur in all coal workers but only in those who have well-

and a lessened capacity for work. dyspnea, cough, tightness in the chest, fatigue, occurs in many stages of severity, and in the advanced stages it is capable of producing from that found in other industries. Silicosis

Fig. 1.—A, anthracosis without silicosis; low-power view, showing stellate carbonaceous deposits with incipient pericardial emphysema. B, silicosis with whorled nodules of silicosis and occasional anthracosis; low-power view, showing circular, eosinophilic nodules; vesicular emphysema occurs in relation to areas where silicotic nodules are most prevalent, and pericardial emphysema in relation to the anthracotic deposits. Courtesy G. W. H. Schepers, M.D., Saranac Laboratory.

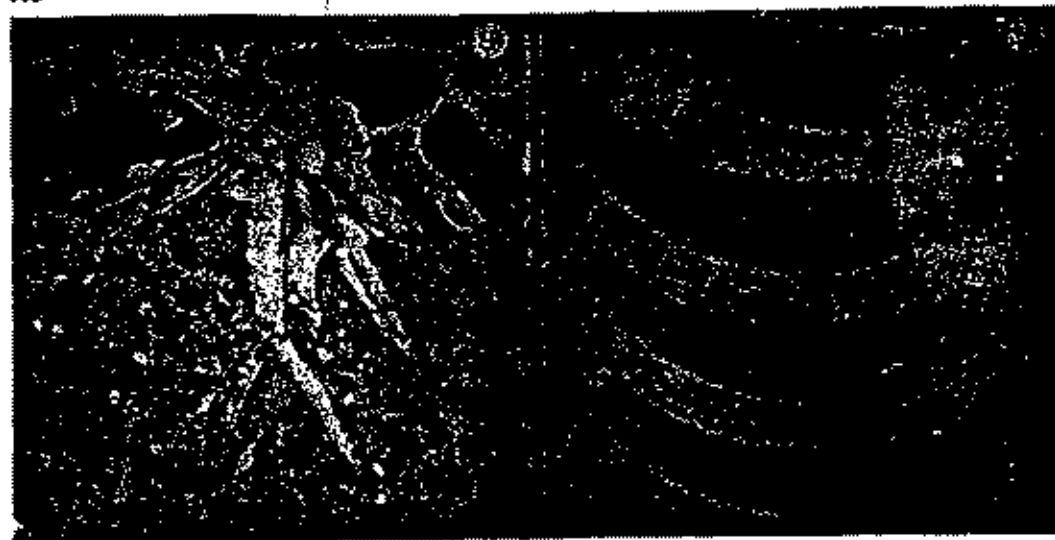
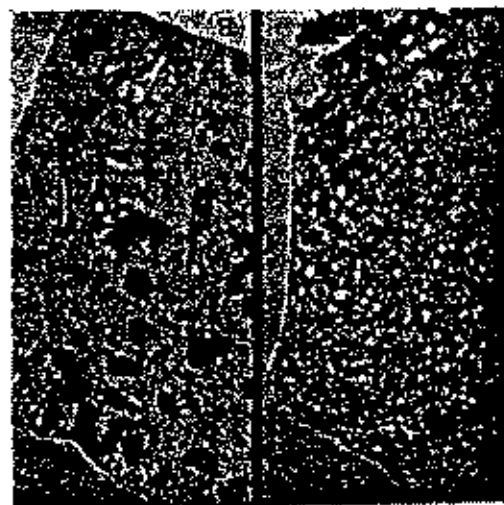


Fig. 2.—A, x-ray of typical well-established nodular anthracosis. B, section of lung, showing pigmented anthracotic deposits. Courtesy Prof. Jethro Gough, Department of Pathology, Welsh National School of Medicine, Cardiff.



Fig. 4—A, x-ray of bilateral massive, apical fibrosis, with compensatory basal emphysema. B, coronal section through the lungs, with massive, apical anthracotic fibrosis. Courtesy, G. W. H. Scheper, M.D., Saranac Laboratory.

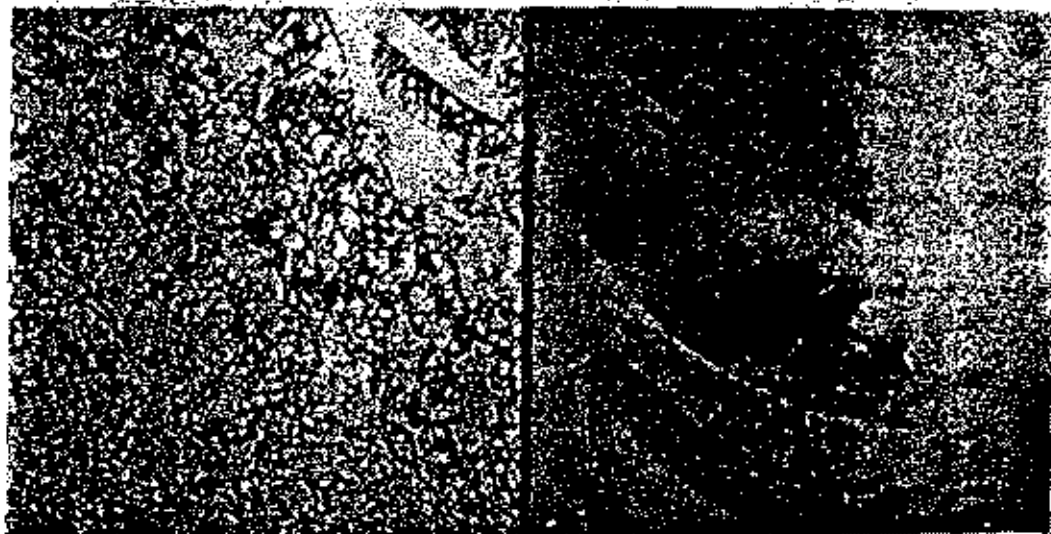
developed areas of coal retention around the respiratory bronchioles. 'Hephestion' has described peribronchovascular emphysema as consisting essentially of a marked dilatation of the respiratory bronchioles. Peribronchovascular emphysema causes disability by increasing the residual air in the lungs as well as by decreasing the velocity and diluting the oxygen content of the inspired air. These conditions result in miners' lungs has not yet been satisfactorily

PROGRESSIVE MASSIVE FIBROSIS

The etiology of massive fibrosis in coal miners' lungs has not yet been satisfactorily

amount of pathological change present. The disability of a grade proportional to the Peribronchovascular emphysema can cause dyspnea and change rather than an anatomical obstruction. functional interference with gaseous ex-

Fig. 3—A, x-ray of anthracosis, with advanced peribronchovascular emphysema. B, section of lung showing anthracosis and associated stress emphysema.



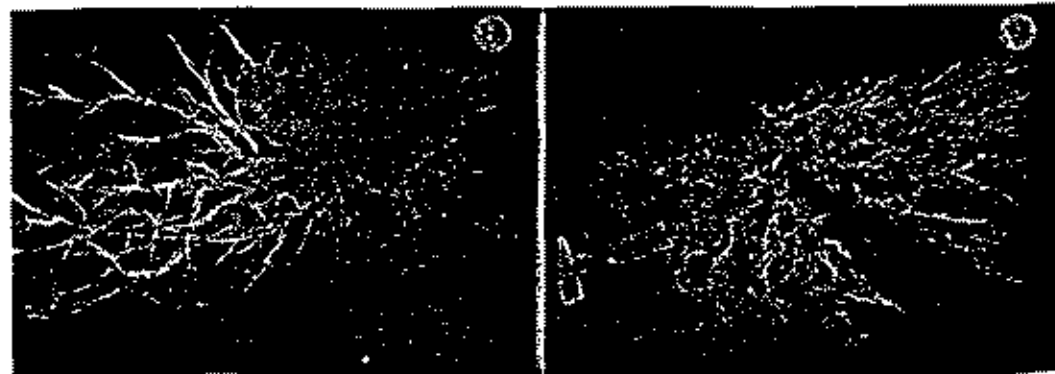


Fig. 5.—A, radiogram of pulmonary arterial pattern in normal excised lung after a radiopaque contrast medium had been introduced. B, progressive massive fibrosis; radiogram of lung, showing advanced degree of loss of ramifications of pulmonary arteries. Courtesy Dr. A. L. Walls, Welsh National School of Medicine, Cardiff.

Fig. 7.—A, horizontal section through heart, showing dilatation of right ventricle due to advanced emphysema. B, coronal section through heart, showing hypertrophy of right ventricular wall due to progressive massive fibrosis.

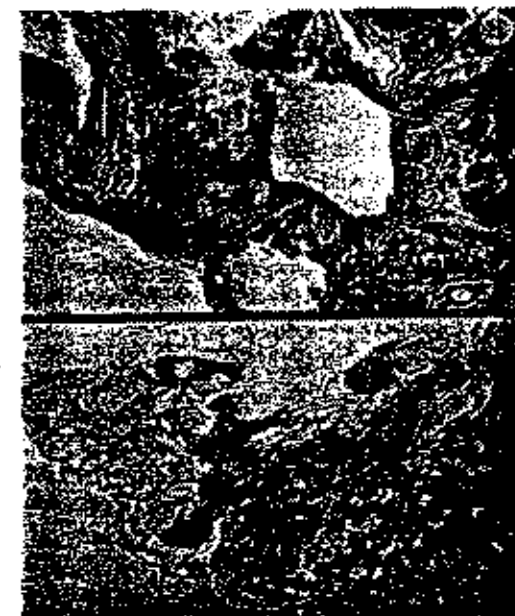


Fig. 6.—A, central liquefaction, with commencing cavity formation in a non-infective focus of massive fibrosis. B, tuberculous cavity in an anthracotic subject. Courtesy G. W. H. Scheper, M.D., Saranac Laboratory.

established. James¹ believes that tuberculosis is an essential factor. Another view is that primary exposure to coal dust and subsequent exposure to high concentrations of silica are the causative factor. Personal observations on workmen who had 8 to 12 years' coal-mining exposures and who later worked in the silica-brick industry showed a precocious rate of development of massive pulmonary disease.

monary lesions without demonstrable evidence of tuberculosis. Massive lesions can result from overwhelming concentrations of dust. Patchy areas of atelectasis, with secondary non-tuberculous infection, can cause localized pneumonitis and/or abscess formation. Progressive massive fibrosis (Fig. 4) can cause severe vascular changes. End-arteritis and thrombotic obliteration are not uncommon. Thrombosis can propagate from an area of massive fibrosis along the branches of the pulmonary artery to the hilus of the lung. The massive forms of arterial obstruction are a major cause of hypertrophy of the right ventricle of the heart. Dilatation often accompanies the hypertrophy. The disturbances in the pulmonary circulation (Fig. 5) as well as the massive fibrosis in the lung bring about disability of a severe form.

TUBERCULOSIS

Tuberculous infection (Fig. 6) can modify any of the pneumoconioses of coal miners. The action of tuberculosis superimposed on silicosis produces progressive massive fibrosis, and the same results can be anticipated in anthracosis with or without complicating emphysema. Clinical evidence of active tuberculosis with pulmonary changes due to coal dust is sufficient evidence of disability.

COAL PULMONARIS

Coal pulmonaris can be present as a direct result of advanced emphysema or massive fibrosis. On the basis of 777 autopsies performed on miners during the years 1947-1949, Gough¹ reports that 53 died of congestive heart failure due to emphysema (Fig. 7A) and 155 of congestive heart failure due

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CONCLUSIONS

1. Exposure to coal-mine dust can produce a complex industrial pulmonary condition.
2. Exposure to coal-mine dust can and does produce pulmonary disability.
3. The distribution of coal miners' pneumoconiosis is world-wide.
4. The incidence rate of coal miners' pneumoconiosis is important enough to warrant an epidemiological survey.

The abnormal pulmonary conditions associated with coal mining are world-wide in their distribution, but little is known about the incidence rate outside of the United Kingdom. Perhaps those who are associated with this type of work could pool their joint resources and clinical data in a study that could be evaluated by some independent research organization. A pathological registry would be of great aid at the present time.

Pathological Study of the Effects of Inhaled Gypsum Dust on Human Lungs

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and
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Recorded for publication June 6, 1955.

Director (Dr. Schepers) and Chief Chemist (Mr. Durkan), The Saranac Laboratory.

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The chief interest in the pulmonary effects of inhaled calcined gypsum dust resides in the fact that exposures to this substance are very widespread and are not confined to industries manufacturing gypsum products. Calined gypsum is often employed, moreover, under excessively dusty conditions. The chemical nature of calcined gypsum and its physical properties as a dust¹ lend further interest to this problem.

The mineral gypsum, which is hydrated calcium sulfate ($\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$) and is an important raw material in the plaster and cement industries, is widely distributed in the United States. When gypsum is calcined at a temperature of 300-400 F, three-fourths of its water content is driven off and the hemihydrate ($\text{CaSO}_4 \cdot \frac{1}{2}\text{H}_2\text{O}$) is formed. On addition of water to the hemihydrate, it recombines with the water, and as the material dries it sets and forms a hard, strong mass. Uncalcined gypsum is used as one of the components of Portland cement, and the calcined product is employed in the manufacture of plaster and of gypsum blocks and wallboard. Ordinarily men engaged in mining gypsum are not exposed to a significant amount of dust. The rock surfaces are usually damp, and the auger drills employed for drilling the rock produce very little atmospheric dust.

After the gypsum has been removed from the mine, it is crushed, then calcined, and finally ground to a fine powder. The finely ground material is transported to a warehouse, where it is mixed with certain substances, such as sand, lime, or wood fiber, and used to make plaster, or it may be employed in the manufacture of gypsum blocks and wallboard. The amount of dust in atmospheric suspension varies somewhat in different parts of a gypsum plant. Where the materials are mixed with water, as in the block plant and board mill, very little dust diffuses into the air. In the crushing and grinding departments some material may escape from the mills, but usually no more than a moderate amount of atmospheric dust is created. Since the air-borne material in those areas is derived from raw or calcined gypsum, the free-silica content of the dust is very low.

Furthermore, the quartz content of the gypsum formation is low and seldom exceeds 1% or 2%. Moderate concentrations of air-borne dust containing more or less free silica may be created in gypsum mines during certain operations, such as extending passages in ways, but men are exposed to conditions of that nature only infrequently and for brief periods.

In spite of admittedly excessive exposures to calcined gypsum dust in the mill and pack house of gypsum plants, and of exposure to some quartz dust in such operations as the chipping of bathstones and the mixing and packing of sanded plaster, studies by The Saranac Laboratory² of men subjected to those exposures failed to reveal evidence of physical disability or mottling in the chest roentgenogram. Not only was the dust of

safe limit by exhaust ventilation or other means. particles is low and usually is held within a quartz, the concentration of the atmospheric ions may contain a substantial amount of Although the dust created by these operations and mining is low, it is not in the dusts found in the atmosphere in gypsum plants, such as chipping of bathstones, packing of sanded plaster, and mixing of gypsum dust.

in performing certain types of work. opportunity to study such material occurs in the report of the features of these cases. The report is presented in somewhat detail in Table I. With one exception, all were middle-aged men who had died of a nonpulmonary cause. Except for Case 2, these men had not presented any chest morbidity or symptoms prior to death, and two were still actively employed at the time of their demise from nonpulmonary causes. The chest symptoms of Case 2 may have been partly linked with exposure to coal-mining dust for an unknown period as a youthful miner in Germany. He was 19 years old when he came to America. At that time there was no barrier against the employment of youths in coal mines. As he had a moderate degree of anthracosis and pericardial

TABLE I.—*Deceased Gypsum Employees General Information*

Case No.	Age at Death	Occupation	Duration of Exposure	Period of Onset of Symptoms	Period of Death	Cause of Death	Other Diseases	Family History	Autopsy	Roentgen	Other
1	47	Mill	10 yrs.	1910	1912	Heart	None	None	Yes	Yes	Yes
2	45	Mill	10 yrs.	1910	1912	Heart	None	None	Yes	Yes	Yes
3	45	Mill	10 yrs.	1910	1912	Heart	None	None	Yes	Yes	Yes
4	45	Mill	10 yrs.	1910	1912	Heart	None	None	Yes	Yes	Yes
5	45	Mill	10 yrs.	1910	1912	Heart	None	None	Yes	Yes	Yes
6	45	Mill	10 yrs.	1910	1912	Heart	None	None	Yes	Yes	Yes
7	45	Mill	10 yrs.	1910	1912	Heart	None	None	Yes	Yes	Yes
8	45	Mill	10 yrs.	1910	1912	Heart	None	None	Yes	Yes	Yes
9	45	Mill	10 yrs.	1910	1912	Heart	None	None	Yes	Yes	Yes
10	45	Mill	10 yrs.	1910	1912	Heart	None	None	Yes	Yes	Yes
11	45	Mill	10 yrs.	1910	1912	Heart	None	None	Yes	Yes	Yes
12	45	Mill	10 yrs.	1910	1912	Heart	None	None	Yes	Yes	Yes
13	45	Mill	10 yrs.	1910	1912	Heart	None	None	Yes	Yes	Yes
14	45	Mill	10 yrs.	1910	1912	Heart	None	None	Yes	Yes	Yes
15	45	Mill	10 yrs.	1910	1912	Heart	None	None	Yes	Yes	Yes
16	45	Mill	10 yrs.	1910	1912	Heart	None	None	Yes	Yes	Yes
17	45	Mill	10 yrs.	1910	1912	Heart	None	None	Yes	Yes	Yes
18	45	Mill	10 yrs.	1910	1912	Heart	None	None	Yes	Yes	Yes
19	45	Mill	10 yrs.	1910	1912	Heart	None	None	Yes	Yes	Yes
20	45	Mill	10 yrs.	1910	1912	Heart	None	None	Yes	Yes	Yes

SCHIEPERS AND DURKAN

about 50% quartz, and yet the air-borne dust created during the packing of that product was found on analysis to have a quartz content of only about 3%. The reason for this striking reduction in the free-silica content appears to lie in the large particle size of the sand used and in the flocculating character of calcined gypsum. The large size of the sand particles prevents them from being dispersed into the atmosphere readily; the flocculating property of the gypsum produces gypsum-quartz aggregates which settle out of the air rapidly.

calined gypsum found to be harmless to human beings, but it also appeared to protect against the harmful action of quartz dust which may be inhaled simultaneously with the gypsum. Both clinical and experimental studies indicate that calcined gypsum dust does not predispose to tuberculosis or reactive arrested or latent tuberculosis. In view of these observations, it is of interest to present the histopathological features of four cases of deceased employees of the gypsum industry who had no significant exposure to silica in any other industry. An

emphysema, it is probable that he had been employed several years as a coal miner.

Exposure to calcined gypsum dust in ware-

houses constituted a significant factor in

Cases 1 and 3. Cases 2 and 4 had considerable

experience as gypsum miners, while Case 3

had additional exposure to gypsum dust in

the mill and as a laborer in the yards of the

gypsum plant.

The presence of areas of organized pneu-

monia in two of these cases and of broncho-

pneumonia in the other two cases at the time

of death appears significant and indicates a

TABLE 2.—Chemical Analysis of Lung Tissue of Deceased Gypsum Workers

The analyses on these four cases are as-sembled in Table 2. Case 1 could not be analyzed in detail, as the tissue had been fixed in Zenker's solution and had undergone some postmortem autolysis before fixation. Attention must finally be focused on the SiO_2 content of the lung ash in Cases 1, 3, and 4. The total silica content in none of these cases significantly exceeded the normal range, and it is remarkable to note that Case 2 showed only 2.75% SiO_2 after 36 years of gypsum mining.

CHEMICAL ANALYSES

Component	1	2	3	4	Normal (approx.)
Ash, %	8.76	6.46	4.46	2.44	0.14-6.23
Total silica, %	0.21	0.24	1.00	0.25	0.05-0.75
Percentage composition of lung ash					
SiO_2	31.35	3.76	16.31	30.20	6.63-14.20
Fe_2O_3		12.06	0.85	1.71	1.19-7.44
Al_2O_3		12.76	2.03	6.10	1.49-11.22
CaO		2.11	4.54	16.50	1.30-10.00
MgO		0.54	0.67	2.06	0.77-4.34
K_2O		14.21	21.18	6.28	0.40-16.30
Na_2O		17.05	1.96	6.70	0.41-26.71
P_2O_5		19.40	14.30	0.78	10.10-21.73
Detected lymph node		5.87	2.61		
Ash, %	30.17				
Total silica, %	11.06				
Lymph node ash					
Total silica, %	14.50				

Parenchymal Lesions.—In the lungs examined, the parenchymal lesions associated with prolonged inhalation of calcined gypsum

HISTOPATHOLOGY

On the whole, these chemical findings are compatible with the normal findings for a per-

son who has not had a significant industrial exposure to siliceous dust.

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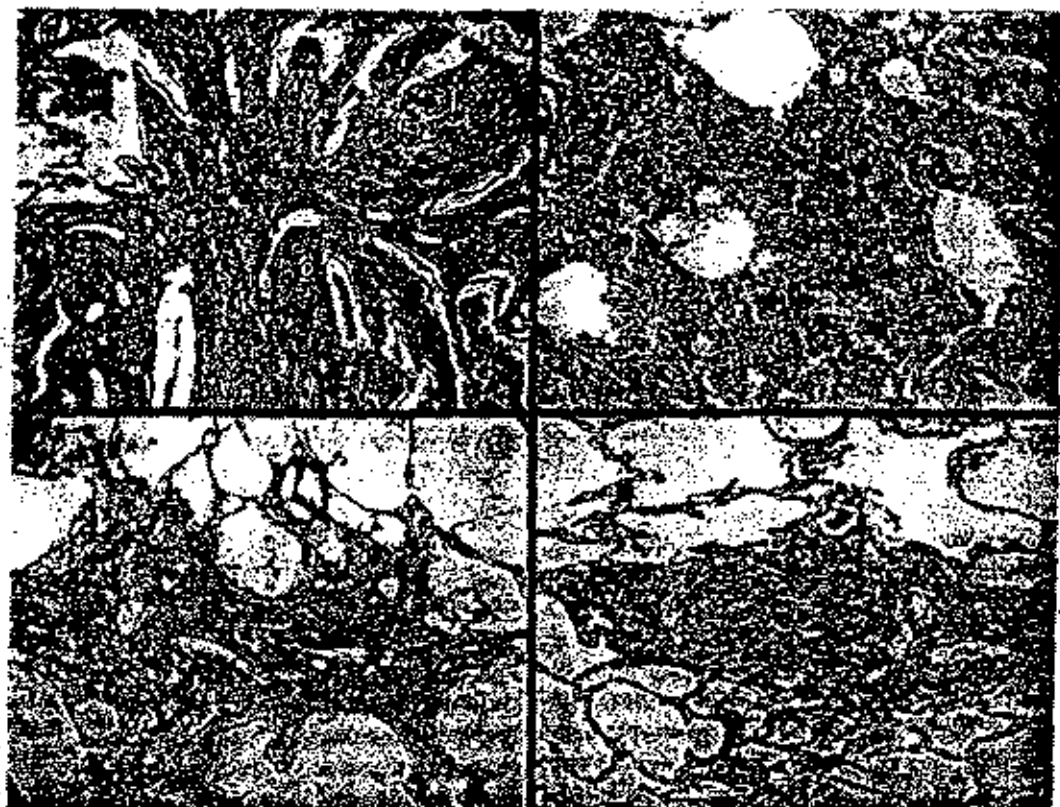


Fig. 1.—Granulomatous lesions in lungs of deceased gypsum workers. A, vascular stromal focus; multiple foci of pigmentation (Case 1). B, fibrocellular stellate nodule; collagen fibers with isolated elastic bundles (Case 1). C, pneumoconiosis nodule; collagen fibers (Case 3). D, organizing pneumonia nodule; collagen fibers, lymphocytes, and fibrocytes (Case 4).

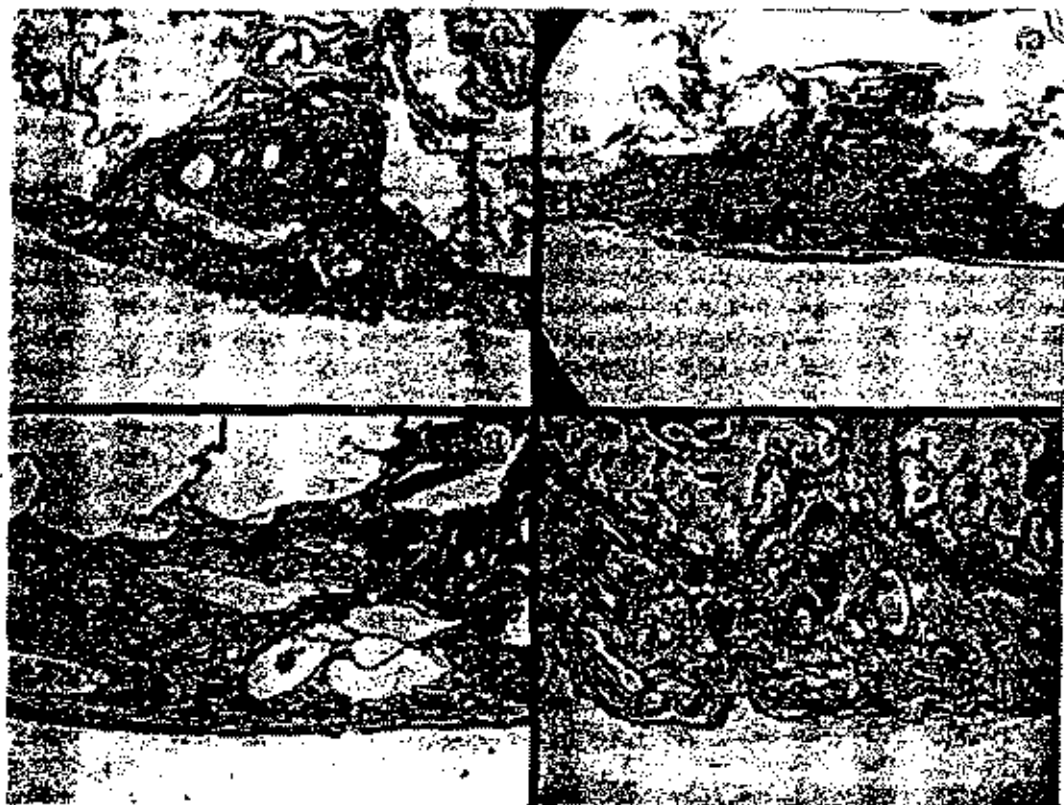
do not assume a pattern which would characterize them as a specific type of pneumoconiosis. In Cases 1 and 2, but particularly in the latter, fibrous nodules were found which resembled silicotic nodules. In Case 2 the nodules were surrounded by a stellate, heavily pigmented, cellular halo resembling the lesions characteristic of siderosis and anthracosis. In this case, however, it is to be noted that the SiO_2 content of the lung ash was remarkably low for an industrial worker. The man had been exposed to coal dust in his youth, and it is to be presumed that these anthracotic nodules had such a remote occupational origin. It seems probable that these fibrous nodules have little if anything to do with the gypsum exposure. Occasionally nodules may be found (Fig. 1A) which may be characterized as vascular granulomas in that they consist of cellular accumulations, supported on a delicate collagenous web surrounding clustered blood capillaries. Some pigment may be present in relation to the collagen. In other instances these small nodules have fewer vascular components and assume a more decisively fibrocellular character and stellate appearance (Fig. 1B). Such nodules are common to several pneumoconioses and may represent a nonspecific type of reaction to inhaled dust particles. They do not exceed 2 mm. in maximum diameter. Some scarring of the interlobular septa is also present. This was found to be most marked in Case 1. A lesion which may perhaps be regarded as primordial to the nodules just described may be found at multiple foci. It consists of stromal foci of pigmentation with some

other areas (Fig. 1D) a delicate degree of collagen deposition and capillary infiltration has taken place. Such areas may be interpreted as foci of organizing pneumonia or pneumonia, but their prevalence in this series of cases poses the question whether they may not represent a specific type of subacute reaction to the gypsum dust. It is to be noted that they are present in men who had succumbed unexpectedly from nonpulmonary causes of death and who had not previously experienced any pulmonary symptoms. The diffuse lesions also have relatively well-defined septal boundaries (Fig. 1D) and in many areas assume the appearance of perivascular granulomata which bulge into the alveolar spaces. It is clear that the nature of these pathological changes requires further inquiry.

and some plasma cells and lymphocytes. In cells are clustered karyophores, macrophages, resemble pneumonitis (Fig. 1C). The main areas there are cellular accumulations which chymal change may also be found. In some More extensive or diffuse types of paren even where they traverse nodules.

tion. The elastic fibers are well preserved, capillary and pericellular reticulum deposition. There is a tendency toward increased periphery poorly developed within these foci, lymphocytes or plasma cells. While collagen nodes are macrophages and occasionally polymorphonuclear leukocytes but almost never seen in Case 2 may perhaps be of anthracotic origin. The dominant cell types in these nodes are macrophages and occasionally polymorphonuclear leukocytes but almost never seen in Case 2 may perhaps be of anthracotic origin. The dominant cell types in these nodes are macrophages and occasionally polymorphonuclear leukocytes but almost never seen in Case 2 may perhaps be of anthracotic origin.

Fig. 2.—Pleural lesions associated with chronic gypsium inhalation. A, chronic pleuritis; epipneural proliferation of blood capillaries and lymphatic plexuses with supporting delicate collagen stroma (Case 1). B, diffuse pleural sclerosis; subpleural dense collagen deposit around pigmented deposits and distended blood capillaries and lymph ducts (Case 2). C, avascular plaque; isolated, collagenous, subpleural focus with peripheral pigmentation (Case 2). D, perivascular plaque; collection of pigment and collagen around pleural veins (Case 3).



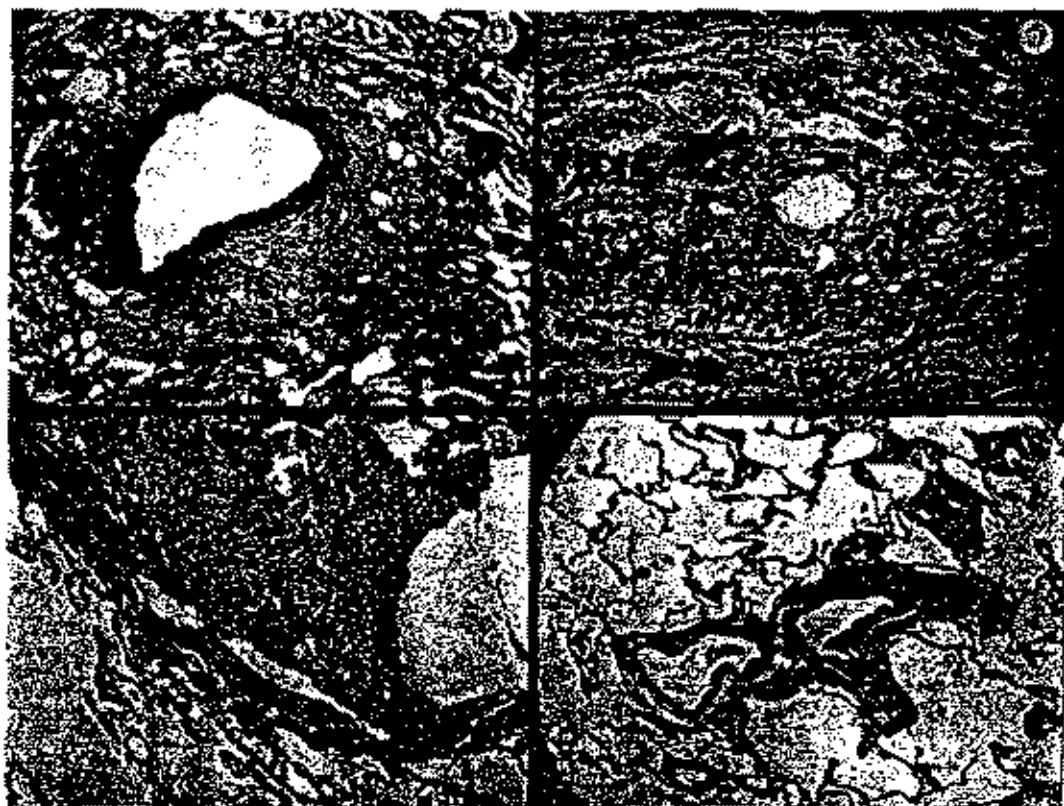
veins pass from interlobular septa to the lung surface.

Bronchial Changes.—

There may be remarkably little bronchial disturbance (Fig. 3A) or relatively pronounced change (Fig. 3B). No evidence of chronic bronchitis with epithelial desquamation could be discerned in sections through the larger bronchi. In air passages of intermediate caliber there is a tendency toward mucosal fibrosis, with a diffuse collagen layer in the plane of transition to the adventitia (Fig. 3C). A layer of round-cell and macrophage infiltration generally intervenes between this zone and the basilar membrane, and this portion tends to be possessed of a generous lymphatic plexus. There is no tendency toward epithelial desquamation or metaplasia at these levels.

The regional lymph nodes are not affected by all these changes, which appear, therefore, associated with this infiltrative change, a tendency toward bronchiolitis may be noted in some areas and in others the lumen may be virtually strangulated. A tendency toward epithelial hyperplasia and small areas of squamous metaplasia may be found. At some sites there is also an associated epithelization of alveolar ducts and proximal alveoli.

Fig. 4.—Perivascular lesions in lungs of deceased gypsum workers. A, minimal perivascular deposit; limited pigmentation around blood vessels which failed to occlude the lumen; almost no collagen (Case 3). B, perivascular fibrosis; irregular collagen sheath around a blood vessel with limited pigment deposition in relation to it (Case 3). C, perivascular collagen; broad dense collar of collagen around medium-sized blood vessel; no narrowing of lumen (Case 2). D, pigment in vascular sheath; iron-staining pigment particles in relation to perivascular lymphatic plexus (Case 2).



to be neither infective in character nor due to any silica present in the dust.

Vascular Damage.—Pervascular fibrosis is present at most sites but is limited generally to a delicate collagenous web found in association with the perivascular lymphatic plexuses (Fig. 3D). The perivascular collar may be minimal (Fig. 4A) or may assume a quite prominent appearance with pigment either embedded in it or at its periphery (Figs. 4B and 4C). The vasa vasorum do not, however, appear to have suffered any

in this instance reacted positively to the Prussian blue stain (Fig. 4D). Iron was demonstrable also in Cases 3 and 4. The latter employee had worked in a foundry for a short period before commencing his duties in the gypsum mine, which may account for the presence of iron dust in his lungs.

It is to be noted, however, that the several pathological deviations thus far described bear no special relationship to the sites of maximal accumulation of the pigment, which may therefore rate as an incidental finding.

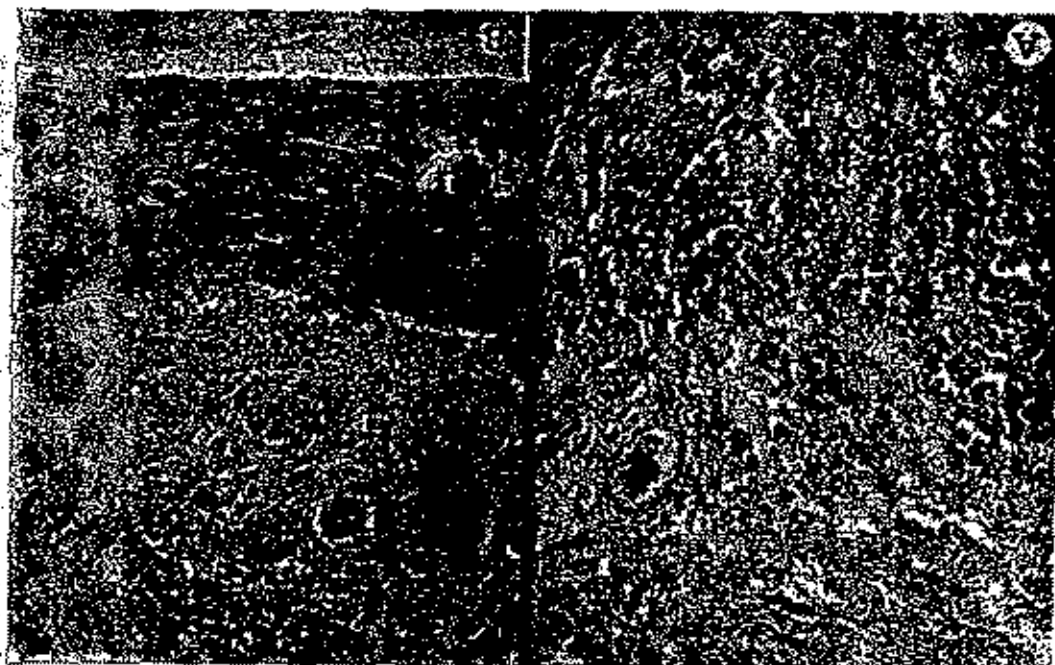


Fig. 5.—Hilar lymphadenopathy in deceased gypsum employees. A, lymph node pigment; B, sclerosing perinodular reaction; dense fibrous capsule around lymph node showing no perinodular reaction (Case 1).

change though embedded in this collagenous layer, and the affected blood vessels themselves generally retain their patency, quite unlike what may occur in the case of the other pneumoconioses.

Pigment.—Throughout these lungs, alveolar mural, perivascular, peribroncholar, and pleural foci of pigmentation are to be found. They are most prominent naturally in Case 2, where a known history of coal mining was on record. Unexpectedly, though, the pigment

Hilar Lymph Nodes.—Pigmentation of the lymph node medullary regions is the most significant histopathological change observed. This pigment reacts positively to Perl's stain in all cases (Fig. 5A), though in Case 2 some of the pigment no doubt is carbonaceous. At no point is any fibrous or hyperplastic reaction demonstrable in relation to the pigment.

Foci of calcification were discovered at autopsy in the root nodes of Cases 1 and 4.

and some atypical focal fibrosis was macroscopically discernible in Case 3. The cause of this calcification has not been determined, though in Case 4 partially healed tuberculous foci are probably to be considered in this connection.

Marked pericarditis may have been present at some time prior to death in Case 1, as there is dense fibrous capsular development around the lymph nodes (Fig. 5B). No vestige of the nature of the cause of this lesion remains, as the adjacent lymphatic tissue shows no corresponding change.

COMMENT

In these four cases we have examples of men who had for relatively long periods been exposed not only to calcined gypsum dust in mills and warehouses but also in two instances to raw gypsum, anhydrite, and argillaceous limestone dusts. Yet the lung tissues show changes which must be classified as minimal dust reactions. The chemical analyses, moreover, reveal that comparatively little dust was retained in the lungs, the maximal amount found, in Case 3, approximating the upper limit of the normal range. In hard rock miners, on the contrary, there may be a tremendous accumulation of mineral matter in the lung within a relatively brief period of exposure.

Only in Case 3 was there more silica in the lung ash than may be found in the normal population in which occupational exposure to dust is absent. In Case 3, however, there was no significant tendency toward more fibrosis than in the other cases. The large quantity of silica found in the lymph nodes may have accounted for some of the hilar fibrosis described at the time of the autopsy, but characteristic silicotic nodules were not demonstrable. It seems possible, therefore, that in the presence of concurrent gypsum exposure the silica had a reduced fibrogenic potentiality.

This study confirms further the clinical fact that exposure to calcined gypsum dust does not facilitate the development of tuberculosis. Caseating foci of tuberculosis were

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All four men had been industrially exposed to gypsum products only and died of non-pulmonary causes.
No specific pneumoconiotic syndrome occurred, though parenchymal pleural, bronchial, and vascular lesions were present which, though indubitably attributable to the gypsum-dust exposure, assumed a nonspecific and minimal character.

SUMMARY

Chemical analyses of pulmonary tissues and histopathological features of four deceased gypsum-industry employees are presented. All four men had been industrially exposed to gypsum products only and died of non-pulmonary causes.
No specific pneumoconiotic syndrome occurred, though parenchymal pleural, bronchial, and vascular lesions were present which, though indubitably attributable to the gypsum-dust exposure, assumed a nonspecific and minimal character.

The Demonstration of Aluminum in Animal Tissues

DOOLEY A. IRWIN, M.D., Pittsburgh

Some years ago, my colleagues, Denny and Robson,¹ observed that the addition of small amounts of finely divided metallic aluminum to an aqueous suspension of finely divided quartz resulted in the insolubilization of the quartz particles by a two-step physicochemical reaction. In the first step, the film of aluminum oxide on the surface of the metal-aluminum particles took on water to form hydrated aluminum oxide. The second step of this reaction was the adsorption of this positively charged hydrated aluminum oxide to the surface of the negatively charged quartz particles. This film, when adsorbed to the surface of the quartz, so interfered with the rate of the solution of quartz in water that for practical purposes the quartz became insoluble.

Further investigation showed that this film of hydrated aluminum oxide when adsorbed to a quartz surface resisted removal by those physical and chemical conditions which probably existed in the tissues of the lung. The next step was obviously to determine whether this test-tube insolubilization of quartz would take place in the lungs of animals and thereby inhibit the usual proliferative fibrotic response. This question had to be answered by animal experimentation.

Control rabbits were exposed to atmospheres containing quartz dust alone, while other rabbits were exposed to admixtures of aluminum and quartz. At the conclusion of

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Medical Director, Aluminum Company of America.

these experiments, the concentration of the quartz and aluminum in the lung tissues was determined quantitatively by suitable analytical methods. Sections of lung tissue were prepared for microscopic observation to permit a study of the response of the lung tissue to the dust retained in the lung. This was facilitated by suitable tissue stains and the technique of microincineration.

Although chemical analysis of the lung tissue quantitated the quartz and aluminum present, it did not indicate the distribution of the aluminum in the lung, the relation of the aluminum to the quartz particles, or whether or not the quartz particles possessed an adsorbed film of hydrated aluminum oxide. As a study of the literature did not disclose a method to demonstrate aluminum in histological preparations, ways were sought to develop such a procedure.

Except in a few instances, methods had not been developed to identify metals in tissue sections suitable for histological study. Ferri's stain for iron was probably not only the best known but was also the most satisfactory stain for any metal. Even this method was found to have limitations in that the staining of iron compounds in tissue required the iron to exist as the ferric ion so that it would react with a solution of aqueous acidulated potassium ferrocyanide to form Prussian blue (potassium ferric ferrocyanide). Any un-ionized iron, such as the iron in the hemoglobin complex, did not stain by this method. Mention is made of this reaction to show the limitations that existed even in this well-known procedure. A start was made by a study of the aluminum powder used in the animal dusting experiments. The collected aluminum powder had the appearance of carbon black rather than a metallic appearance. Analysis of

* D. R. P. 49,970 (German Patent), issued to Joh. Rud. Geigy and Company.

At this stage, attention was paid to the possible application of a complex dye used in the quantitation of aluminum. This dye, ammonium aurintricarboxylate, was first mentioned in 1889 in a German patent based on the work of Sandmeyer. In 1925, Hammett and Sottery² described the use of this dye as a new reagent for aluminum. Shortly after this publication, the dye became available under the name of "aluminon." Lundell and Knowles,³ in 1926, showed the value of this dye in the detection of small amounts of aluminum. Apparently, the preparations of aluminum on the market at that time varied in reaction to such an extent as to make the analytical method unreliable. Scherrer and Mogerma,⁴ in 1938, published their methods to produce an aluminum satisfactory for the colorimetric determination of aluminum. Their improved method of preparation was by the reaction of allylic acid with formaldehyde in a mixture of concentrated sulfuric acid and sodium nitrite. Under certain conditions, aluminum forms a lake with a number of metallic ions. The lake is a complex precipitate formed by the dye molecule reacting with the particular metallic ion. Middleton⁵ reported the formation of lakes formed by aluminum with the hydroxides or basic acetates of aluminum, beryllium, iron, thorium, and the rare earths. Most of these lakes, with the exception of those formed by aluminum and beryllium, are dissolved or decolorized by a solution containing ammonium ion buffered at a pH of 7.2. The beryllium lake is unstable in the absence of excess dye. These reactions indicated a practical approach to the aluminum staining of hydrated aluminum oxide. The aluminum-aluminum lake formation is a complex reaction of at least two stages. One stage of the reaction is believed to comprise adsorption of the dye to the surface of the gelatinous hydrated oxide of aluminum. The other step consists of a chemical reaction between the adsorbed dye and the hydrated aluminum ion to form the cherry-red lake. These reactions occur simultaneously.

The aluminum powder showed it to be composed of 15% metal, while the remaining 85% was in the form of aluminum oxide. Observations by transmitted light and electron microscopy showed the individual particles to be uniform in appearance, spherical in shape, and less than a micron in size. Unstained histological sections of the lung tissue of animals exposed to aluminum powder alone showed a widespread distribution of black particles. The size, shape, and opacity of these individual particles were such that they could not be distinguished from extraneous carbon particles lodged in the lung tissue or the particles so frequently seen in formalin-fixed tissues and referred to as "formalin precipitate." Microscopic observation of a drop of sodium hydroxide solution spreading over such a section showed the rapid disappearance of most of the black particles, with the production of minute bubbles indicative of metallic aluminum and/or aluminum oxide. The black particles that remained after such treatment could not have been aluminum. This reaction offered little practical help in the identification of aluminum particles. However, the sum of these observations indicated that the aluminum particles deposited in the lung tissue of the experimental animals were tiny, spherical masses composed of a centrally placed small nucleus of metal surrounded by hydrated aluminum oxide. It was also established that such lung tissue could be stored in formalin for months without any apparent effect on the aluminum particles and that these particles appeared to be unaltered in frozen or paraffin histological sections.

These observations indicated that the aluminum particles in lung tissue could be identified and demonstrated by a method which would stain the hydrated aluminum oxide covering the metallic nucleus in a characteristic manner. The chemical characteristics of aluminum and its compounds seemed to preclude any hope of a simple staining reaction comparable to Perls's stain for iron.

1. Sections may be made of formalin-fixed tissue cut in paraffin (be sure to remove all para-

TISSUE SECTIONS ALUMINUM OXIDE IN

ALUMINON STAINING OF HYDRATED

solutions are given below.

Detailed instructions for the staining technique and the composition of the necessary

particles.

distinction between quartz and aluminum

this aluminum staining method does make a

bills exposed to quartz dust alone shows that

of staining reaction in the lung tissue of rab-

tissue has been available for study. The lack

aluminum dust and quartz dust. No human

to aluminum dust alone and to a mixture of

lungs of guinea pigs, rats, and rabbits exposed

the presence of aluminum particles in the

The method has effectively demonstrated

cannot be stained by this method.

aluminum oxide. Complex aluminum salts

its use to the demonstration of hydrated

num ion which for practical purposes limits

method requires the presence of an alumi-

It must be realized that this staining

interfering substances.

is that it decolorizes any lakes formed by

varange of treatment with the second solution

long in this buffered solution. Another ad-

lake if the section is allowed to remain too

tion will decolorize the aluminum-aluminum

7.2. Caution must be observed, as the solu-

in a similar solution buffered at a pH of

dye, which was removed quickly by a dip

ments took on a pinkish cast from adsorbed

sections so stained, some of the tissue ele-

ammonium ion buffered at a pH of 5.2. In

aluminum dissolved in a solution containing

tissue sections took place in a 2% solution of

staining of the hydrated aluminum oxide in

water at room temperature.

4. Dip section three or four times in distilled

the tissue to some extent.

aluminum oxide a bright cherry red but also stain

minutes at 75°C. This solution stains the hydrated

1. Immerse in aluminum staining solution for five

through to water in usual way.

2. Mount sections on glass slide and bring

some.

also be prepared by means of the freezing micro-

1926.

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D. A.: Prevention of Silicosis by Metallic Alu-

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to pH 7.2.

Add one or other of these solutions to adjust

—25.5 parts

1.6 M aqueous ammonium carbonate solution

Buffer solution pH 5.2—73.5 parts

Decolorizing Buffer Solution pH 7.2

to stand 48 hours and then filter before use.

solution to make a 2% solution of aluminum. Allow

crystals in an agate mortar and dissolve in buffer

Grind aluminum (ammonium aurintricarboxylate)

Aluminum Staining Solution

parts

6 M aqueous hydrochloric acid solution—11.6

parts

5 M aqueous ammonium acetate solution—44.2

parts

5 M aqueous ammonium chloride solution—44.2

Buffer Solution pH 5.2

7. Mount in the usual manner.

the tissue.

6. Wash in distilled water at room temperature.

disturb or remove color of aluminum lake.

color of the aluminum lake. Longer treatment may

the pinkish-stained tissue, with little effect on the

three seconds at room temperature. This decolorizes

5. Dip slide in decolorizing buffer solution for

water at room temperature.

4. Dip section three or four times in distilled

the tissue to some extent.

aluminum oxide a bright cherry red but also stain

minutes at 75°C. This solution stains the hydrated

1. Immerse in aluminum staining solution for five

through to water in usual way.

2. Mount sections on glass slide and bring

some.

also be prepared by means of the freezing micro-

Experiences with the Control of Silicosis in a Foundry

LESLIE H. OSMOND, M.D., Homestead, Pa.

THE DUST HAZARD

In the foundry described large castings in the range of $\frac{1}{4}$ ton to 350 tons are manufactured. Because of a multiplicity of mechanical factors involved in the process of cleaning castings, the silicosis hazard in a foundry increases proportionally with the size of the castings. The present foundry provided no exception to this rule. Repeated appraisals of the dust in the plant made by competent engineers revealed a material and continuing dust hazard. The company introduced every recommended or possible hygienic measure but failed to bring the hazard under complete control. Realizing that it was not possible to prevent entirely the release of quartz and cristobalite dust, the company instructed me to study the aluminum method of prophylaxis. This was done over a period of four years in an adjoining silica-brick manufacturing plant. The observations derived from this study were sufficiently favorable to decide the company to apply the method to its foundry in 1948. At the time of introduction of the aluminum method dust counts continued to be higher than desirable.

The dust concentrations and the percentage of free silica in the dust varied from job to job and from man to man on the same job, especially in the case of the larger castings. Because of the inability to clean the larger castings prior to the chipping operation, the chippers received the highest exposures. The large castings, which sometimes took weeks

to cool after being poured, showed a considerable amount of conversion of the quartzite sand particles to cristobalite. According to Hannon,¹ cristobalite tends to fracture into extremely small particles when subjected to shock owing to a difference in the molecular structure.

THE SILICOSIS PROBLEM

I have been continuously associated with this company for 19 years. The men who developed silicosis were not different from men in other plants, and silicosis occurred in many stages of severity. Many of these cases were of simple silicosis and detectable by x-ray only. The silicosis was classified as severe when there were associated symptoms of shortness of breath, tightness in the chest, weakness, cough, and a decrease in the pulmonary reserve. The fact that these were cases of genuine silicosis rather than siderosis was confirmed by periodic x-ray and sporadic autopsy studies.

The pathological picture of silicosis was found to be not unlike the classical silicosis found in comparable steel plants which manufacture large castings.

The roentgenographic findings have likewise conformed to silicosis in other steel foundries. The time required for the development of radiologically detectable silicosis varied considerably. The rate of progression of the disease also varied, but in most cases progression to the advanced stages was found to be relatively slow. The earliest roentgenographic signs included linear thickening of major and minor lung markings, a widespread small nodulation without preceding changes, and focal nodulation usually confined to about the midupper lobe region on

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Medical Consultant, Mesta Machine Company.

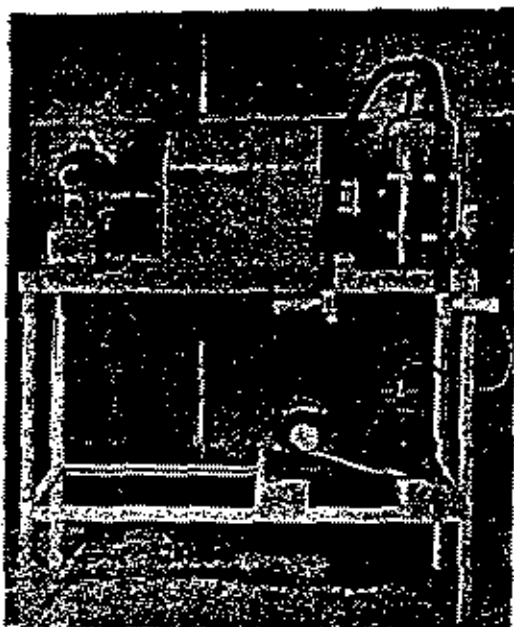


Fig. 1.—Mill used for the production of pulverized aluminum.

either the right or the left side but more commonly on the right. Some cases developed massive conglomeration without much or any apparent preceding nodulation.

In the established case of foundry silicosis the nodular pattern with and without areas of "pockmarking," as described by Cole,² was by far the commonest lesion. Conglomerate reactions, almost entirely confined to the upper lobe regions, were late manifestations. Emphysema in varying degrees was a constant accompaniment of the silicotic process. When this foundry was first studied, in 1936, there was a high tuberculosis rate among the silicotics. The rate has fallen off remarkably, and only one active case was found in the past three years. During the latter years there have, however, been a fair number of cases in which radiological lesions, thought to be tuberculous, developed in the interim, with regression, scarring, and stability.

ALUMINUM PROPHYLAXIS AND TREATMENT

In order to evaluate the effect of aluminum prophylaxis and therapy on silicosis in this foundry, changes in the pulmonary function were used as the essential criterion. Cognizance was also taken of the x-ray changes and physical condition of the men. The men

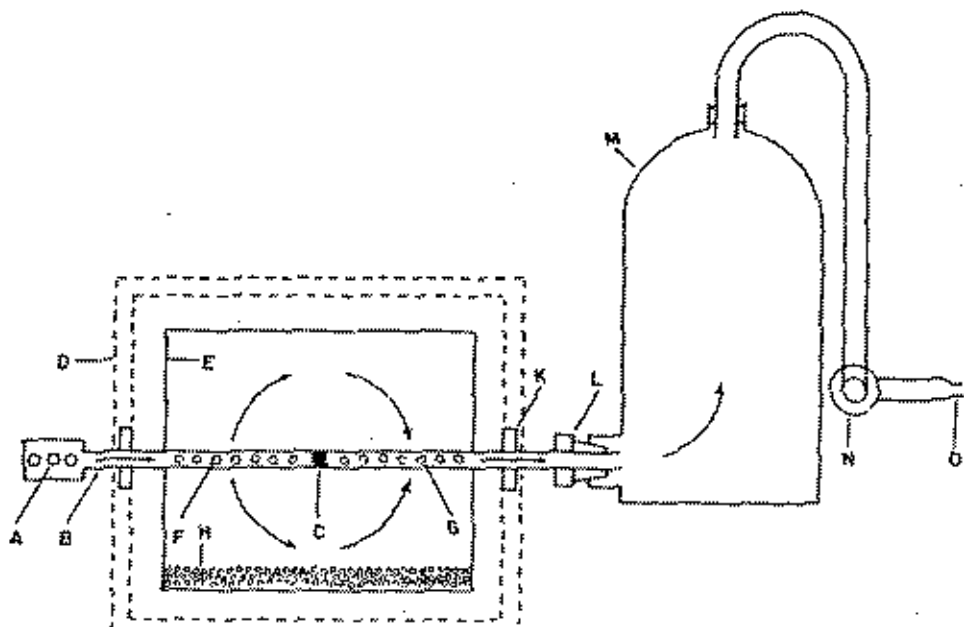


Fig. 2.—Diagram showing manner of action of aluminum powder mill: (A) air inlet; (B) shaft; (C) shaft block; (D) sound insulation housing; (E) ball mill; (F) air inlets to mill; (G) air exits from mill to mill shaft; (H) aluminum pellets; (K) mill bearings; (L) inlet to bottle; (M) bottle; (N) one-way breathing valve, and (O) breathing valve orifice.

CONTROL OF SILICOSIS

were divided into three groups, namely, the chippers, the molders, and the miscellaneous employees, respectively. There was a total of 62 chippers, 39 molders, and 188 in the miscellaneous group.

Aluminum was administered in the following way. A small McIntyre aluminum mill (Figs. 1 and 2), which produced 3.2 mg. of pulverized aluminum per liter of air at an air flow of 10 liters per minute, was used. Owing to impingement in the settling flask, breathing tubes, and breathing valves, the amount of powder released for inspiration was reduced to approximately 50% of the amount generated at the mill outlet. Two men received treatment simultaneously, as shown in Figure 3. Each such employee received on an average 230 minutes' inhalation therapy each year in the form of weekly sessions, lasting an average of 5 minutes each. This aluminum regimen was varied in proportion to the estimated severity of the quartz exposure to which the men had been subjected previously and to which they still were exposed.

The pulmonary function was determined by using the criteria listed below and evaluated with reference to standard normals established in the literature. In this connection, the observation may be made that standards of normality vary considerably between different laboratories, and average values published by separate investigators were relied on. The following were the criteria on which most reliance was placed:

Criteria	Normal Range
Vital capacity, cc.	(U. S. A. $\times 25$) - (25 $\times$ (age-20))
Maximal breathing capacity, liters	145-160 liters
Maximal tidal volume, cc.	1500 - (25 $\times$ (age-20))
Pulmonary reserve, cc.	2000 - (25 $\times$ (age-20))

RESULTS

The status of the men during 1954 is compared with their condition during 1948 and is summarized in Tables 1 to 4.

The result obtained with respect to the chippers is most remarkable, having regard to the fact that their lesions were more advanced and that they continued to receive the same significant degree of dust exposure. It will be observed that only about 9% of these men who commenced the aluminum therapy in 1948 with a normal functional reserve showed any deterioration by the end of 1954.

Of those chippers who were functionally impaired at the commencement of their period of treatment during 1948, only about

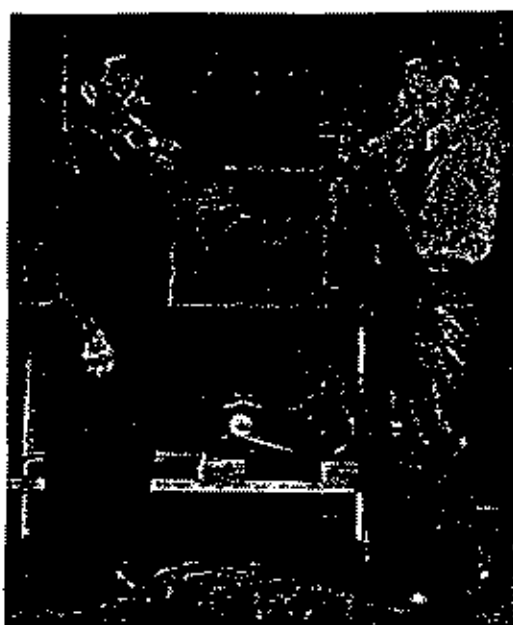


Fig. 3.—Demonstrating manner of administering aluminum powder.

10% deteriorated further despite aluminum therapy. The balance of these men (89%) showed a remarkable degree of improvement. Indeed the lung function figures obtained in

78% of the cases could be classified as normal (Table 1).

The dust hazard—and the consequent severity of the disease—was next highest in

TABLE 1.—Changes in the Functional Lung Capacity of Foundry Chippers (Sixty-Two Workmen) Subjected to Period of Aluminum Therapy—1948-1954

Year	Lung Function Status	Men, No.
1948	Normal	24
1954	Unaltered	21
	Worse	3
1948	Subnormal	26
1954	Unaltered	0
	Aggravated	3
	Improved*	23

* Of the 26 who improved, 22 were normal at the time of the period of assessment in 1954.

TABLE 2.—Changes in the Functional Lung Capacity of Foundry Molders (Thirty-Nine Workmen) Subjected to Period of Aluminum Therapy—1948-1954

Year	Lung Function Status	Men, No.
1948.....	Normal	24
1954.....	Unchanged	22
	Aggravated	2
1948.....	Subnormal	15
1954.....	Unchanged	1
	Deteriorated	2
	Improved*	12

* Of the 12 who improved, 11 were normal at the time of final assessment in 1954.

the molders, and the results obtained with these men after six years of aluminum therapy consequently also appear to be significant. Of those that started off normal in 1948, only about 8% had deteriorated. Of the 15 commencing aluminum therapy with a measurable degree of functional incapacitation, about 7% showed no progression of their condition, about 13% became aggravated, while the balance (80%) improved, with 73% reverting to normality (Table 2).

The remaining cases in the miscellaneous group showed much the same range of response to aluminum therapy. Three out of one hundred six normal cases deteriorated despite therapy, but the balance showed no progression. This result may seem excellent, but it must be recalled that this is the group of foundry employees for whom a six-year period is less critical in respect of the rate at which they develop silicosis or advance to disability.

Of those 82 employees in the miscellaneous group who started off their period of

TABLE 3.—Changes in the Functional Lung Capacity of Foundry Miscellaneous Group (188 Workmen) Subjected to Period of Aluminum Therapy—1948-1954

Year	Lung Function Status	Men, No.
1948.....	Normal	106
1954.....	Unaltered	106
	Worse	3
1948.....	Subnormal	82
1954.....	Aggravated	6
	Improved*	76

* Of the 76 who improved, 54 were normal at the time of final assessment in 1954.

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aluminum therapy with demonstrable functional impairment, 7% showed no favorable response and became aggravated. The balance (93%), however, improved, and of this group 78% reached normality at the end of the six-year period (Table 3).

The totals for the three groups, namely, chippers, molders, and miscellaneous employees, are shown in Table 4.

X-Ray Studies.—Roentgen-ray studies were made on each employee studied in this series at periodic intervals, and each employee was x-rayed at least once each year. It may be significant that during 1953 and 1954 no new cases of silicosis developed in this group, in spite of the fact that the men

TABLE 4.—Changes in the Functional Lung Capacity of All Foundry Workmen (289 Workmen) Subjected to Period of Aluminum Therapy 1948-1954

Year	Lung Function Status	Men, No.
1948.....	Normal	164
1954.....	Unaltered	136
	Worse	2
1948.....	Subnormal	125
1954.....	Unimproved	1
	Aggravated	11
	Improved*	113

* Of the 113 who improved, 81 were normal at the time of final assessment in 1954.

reported on had work exposures of significance prior to 1948 when aluminum therapy was started. A similar observation was never recorded in any prealuminum year in this foundry.

SUMMARY

1. Two hundred eighty-nine foundry employees were subjected to aluminum therapy for a six-year period.
2. The average exposure to aluminum was 230 minutes per person per year.
3. It is estimated that each employee received approximately 1650 mg. of pulverized aluminum per annum.
4. Of the 164 men commencing aluminum exposures with normal functional status, 95% were unchanged and 5% had deteriorated at the end of six years.

CONTROL OF SILICOSIS

5. Of the 125 men starting with a measurable degree of functional incapacitation before aluminum treatment was instituted, 9% deteriorated further, while 90% improved, and of the latter group 77% reached normality at the end of this period.

6. The incidence of new cases of radiological silicosis dropped to zero during the years

1953 and 1954, which is the first time this has happened in the history of this foundry.

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Prophylaxis and Treatment of Experimental Silicosis by Means of Aluminum

An Experimental Study

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The studies presented herewith, which were a major interest of the late Leroy U. Gardner, M.D., and occupied much of his time during the last eight years of his life, comprise a total of 41 systematic experiments, some of which terminated after his death.

In May, 1944, Dr. Gardner delivered the Donald E. Cummings Memorial Lecture,¹ entitled "Aluminum Therapy in Silicosis," at the Annual Meeting of the American Industrial Hygiene Association. He presented some of the essential findings of the studies which had already been completed and described the experiments which were still in progress. He concluded from experimental evidence then available that "aluminum agents in proper form constitute an effective inhibitor of quartz in a living host."

With the establishment of the fact that silicosis can be produced in the experimental

animal, the desire to discover the cause of the toxicity of quartz and to find a means to prevent the disease became a major objective of the research program of The Saranac Laboratory. There was, however, an even bigger stake involved than the development of a method to prevent silicosis, for it was hoped that, in determining the cause of the toxicity of quartz, an answer might be found to explain the increased susceptibility to tuberculosis in the silicotic host.

Before describing the experiments, it may be of historical interest to explain how it happened that The Saranac Laboratory discovered that colloidal aluminum hydroxide exerts a protective effect against the toxic reaction of silica in tissue. When, in 1932, Kettle² reported that particles of quartz coated with iron would not produce a silicotic reaction following injection into animals, an attempt was made at The Saranac Laboratory to repeat his experiment. Kettle did not describe his method. In a personal communication to Dr. Gardner, he stated that the chemist who prepared his coated quartz was no longer accessible, but he suggested that the quartz particles be boiled in a solution of colloidal ferric hydroxide. Dr. Gardner found, however, that quartz particles treated in that manner still produced fibrosis on injection into guinea pigs and rabbits, although the tissue reaction was somewhat delayed.

For a number of years thereafter, experiments were conducted at the Laboratory employing various agents in the hope of pre-

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For the design and conduct of the experiments on which this paper is based, all credit goes to the late Leroy U. Gardner, M.D. Recognition should be given also to A. J. Vorwald, M.D., A. B. Delahant, E. L. Gockeler, A. J. Redlin, and F. T. Creodon for assistance in many technical phases of the work and to T. M. Durkan, M.E., and G. W. H. Schepers, M.D., D.Sc., for assistance in the preparation of the paper.

venting the silicotic reaction, either by neutralizing the charge or by coating the silica particles. Among the substances tested were acacia, sodium oleate, various forms of charcoal, precipitated ferric hydroxide, night blue dye, aluminum phosphate, and colloidal aluminum hydroxide. Of these, colloidal aluminum hydroxide was discovered to prevent the toxic effect of quartz. It was found that when quartz particles, 1μ to 3μ in diameter, were suspended in colloidal aluminum hydroxide and injected intracardially into guinea pigs the silicotic reaction in the liver and spleen, where quartz particles of this size are retained, was completely inhibited. Publication of the findings at that time was considered, but, because of the uncertainty of the permanence of the protective effect, it was decided to follow the observations for a year or more. Other experiments were started at once in order to verify and supplement these initial findings and to define the conditions under which colloidal aluminum hydroxide would be most effective.

It was with great interest that the staff of The Saranac Laboratory read, in 1937, the report of Denny, Robson, and Irwin* in which they stated that they were able to prevent the silicotic reaction in rabbits by means of powdered metallic aluminum. In November, 1937, Dr. Irwin visited The Saranac Laboratory and described their work. In turn, Dr. Gardner demonstrated to him that quartz particles suspended in colloidal aluminum hydroxide and injected into guinea pigs produced a reaction limited to simple phagocytosis. Dr. Irwin sent to The Saranac Laboratory some of the metallic aluminum powder he used so that the relative effectiveness of the metal and of the colloidal hydroxide in protective experiments could be compared.

TECHNICAL PROCEDURES

1. DESCRIPTION AND METHOD OF PREPARATION OF VARIOUS FORMS OF ALUMINUM EMPLOYED IN THE EXPERIMENTAL WORK IN THE SARANAC LABORATORY

The aluminum compounds used are summarized in Table I and deserve the following further comment.

(a) *Colloidal Aluminum Hydroxide.*—This is the colloid that was first used in our experimental investigations. Except for a brief description contained in the paper by Gardner and associates,¹ no detailed account of its preparation has been published. Originally the colloidal hydroxide was prepared as follows.

A 3% solution of aluminum chloride ($\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$) was heated to boiling, and concentrated ammonium hydroxide (NH_4OH) was slowly added, with continuous stirring, until a very faint odor of ammonia

TABLE I.—Aluminum Compounds Used

- | |
|--|
| (1) Colloidal aluminum hydroxide. This compound was prepared in The Saranac Laboratory from $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ by precipitation with NH_4OH . |
| (2) Powdered aluminum hydrate. This compound, designated as H-1010, was especially prepared by the Aluminum Company of America from sodium aluminate; the x-ray diffraction pattern of H-1010 is similar to the pattern obtained from the colloidal aluminum hydroxide prepared in The Saranac Laboratory; H-1010 was used in inhalation experiments. |
| (3) Metallic aluminum powder. The metallic aluminum powder used in the injection experiments was furnished by Dr. D. A. Irwin, formerly of the Medical Research Department of the University of Toronto; the metallic aluminum powder for the inhalation experiments was freshly prepared from pellets of aluminum ground in a rotating aluminum-lined drum and was blown into the dusting room by compressed air. |

persisted. This produced a voluminous gelatinous precipitate represented by the following reaction:



The suspension was filtered through paper, and the precipitate washed with hot water to remove most of the soluble ammonium chloride. A faint trace of the chloride was allowed to persist, because otherwise, as we discovered, no stable colloid would form. The moist precipitate was removed from the filter paper, resuspended in distilled water, and placed in a 500 ml. or larger graduate. After settling overnight at room temperature, the supernatant fluid, which was a viscous milky colloid, was decanted off and reserved, and the gelatinous precipitated aluminum hydroxide in the sediment was discarded. Later, the method was modified by substituting centrifugation for filtration. The hot, freshly precipitated aluminum hydroxide was centrifuged for 10-minute intervals at 2000 rpm. As long as the supernatant fluid remained

clear, it was discarded, and the sediment was resuspended in hot distilled water and recentrifuged. Four or five centrifugations were necessary to remove sufficient ammonium chloride in order to convert a portion of the gelatinous precipitate to a stable colloid. At this point the supernatant fluid assumed a milky viscous appearance similar to the colloid obtained by the overnight sedimentation obtained in the first method of preparation. The milky supernatants were collected in a flask. The pH of the collected supernatants tended to range from 5.8 to 6.4, indicating that the colloidal aluminum hydroxide prepared in this manner was acidic and that its formula may be expressed as H_2AlO_3 to emphasize its acidic nature. It remained stable as long as its reaction remained acid but did not pass through a cellophane or collodion membrane. X-ray diffraction examination of the colloidal aluminum hydroxide after evaporation to dryness in the open air revealed a weak pattern of aluminum β -trihydrate. When the colloid, after evaporation, was dried in a vacuum, an extremely fine-grained aluminum α -monohydrate was formed. The absence of any distinct lines in the pattern of the vacuum-dried material indicated that the product was chiefly amorphous in character. Chemical analysis of the dried colloid showed that it contained 3.40% chlorine. The water loss after ignition was 25.31%.

The colloidal content of the fluid was determined by converting aliquots into aluminum oxide (Al_2O_3) and calculating the aluminum hydroxide content by the factor 1.53. This was done by evaporating 10 ml. quantities of the colloidal aluminum hydroxide on a water bath in a weighed crucible. The crucible was then heated over an open flame to a constant weight, thus converting the colloidal aluminum hydroxide ($Al(OH)_3$) to aluminum oxide (Al_2O_3).

(b) *Powdered Aluminum Hydrate.*—Powdered colloidal aluminum hydroxide was prepared from the colloidal aluminum hydroxide described under (a). The precipitate, after being washed free of most of the chlorides,

was allowed to dry on the filter paper. It was then removed from the paper, placed in an evaporating dish, and dehydrated over sulfuric acid *in vacuo*. When thoroughly dry, the small clumps were ground to a fine powder in an agate mortar. It was resuspended in distilled water as needed for use. Such a suspension does not become as viscous as the original colloidal aluminum hydroxide. It is also nondialyzable and has the same pH as the colloid. When suspensions of this powder and quartz were tested in animals, it was found that the drying did not destroy the inhibitory action.

After it was demonstrated that a powdered form of aluminum hydroxide was an effective inhibitor of silicosis, the Laboratory was confronted with the problem of producing the powdered aluminum hydroxide in sufficient quantity for long-term inhalation experiments. Dr. Francis C. Frary, Director of the Research Laboratories of the Aluminum Company of America, was consulted, and he expressed his willingness to cooperate. After submitting several different forms of powdered aluminum hydroxide (C-730, C-732, C-730 activated), which were tested and found unsatisfactory, the Aluminum Company of America prepared a powdered aluminum hydrate designated as H-1010. This product, when tested by injection methods, proved as effective an inhibitor as our colloid and powdered aluminum hydroxide. It is this product—H-1010—which has been studied exhaustively in a series of inhalation tests involving normal, silicotic, and tuberculous animals. The x-ray diffraction pattern of H-1010 is similar to the pattern of the vacuum-dried compound made in The Saranac Laboratory. The product H-1010 is principally aluminum hydrate, which is possibly to a large extent amorphous and contains at least some of the α -monohydrate. The effects of these different forms of aluminum compounds suggest that their amorphous component may be the active substance that inhibits the quartz and prevents the development of fibrous tissue reaction.

TREATMENT OF SILICOSIS BY MEANS OF ALUMINUM

(c) *Metallic Aluminum Powder.*—The metallic aluminum powder employed in all injection experiments was furnished by Dr. D. A. Irwin, then of the Medical Research Department of the University of Toronto. It was acetone-washed and finely divided. More than 90% of the particles were less than 1μ in size. The metallic aluminum powder for the inhalation experiments was freshly prepared from pellets of aluminum ground in a rotating aluminum-lined drum and was blown into the dusting room by compressed air. The powder prepared in this manner was finely divided, and more than 90% of the particles were less than 2μ in diameter. Occasional clumps, varying from 20μ to 50μ , were present.

The x-ray diffraction pattern of the metallic aluminum powder was the same as that of the standard pattern of crystalline metallic aluminum. When the metallic aluminum powder was suspended in distilled water and allowed to remain in an incubator overnight at 37°C , the hydrate was formed, which yielded an x-ray pattern similar to that of the other aluminum compounds. Denny, Robson, and Irwin⁴ assert that the metallic aluminum hydrolyzes when it comes in contact with the body fluids. Examination of the x-ray diffraction patterns of the vacuum-dried colloidal aluminum hydroxide, the H-1010 powder, and the hydrolyzed metallic aluminum powder revealed that the materials were to a large extent amorphous but contained small amounts of α -monohydrate and β -trihydrate of aluminum.

The three aluminum compounds—colloidal hydroxide, H-1010 powder, and metallic powder—have the faculty of depressing markedly the solubility of quartz as determined by the molybdate method; in fact, the aluminum compound reduced the amount of silica in solution to 1% of the value before the aluminum was added. This observation formed the basis for the theory that the toxicity of silica is due to the release of minute amounts of soluble silica in tissue. The assumption, however, that the soluble silica demonstrated colorimetrically *in vitro* is responsible for the silicotic reaction in tissue has not received

experimental support from studies made in The Saranac Laboratory. Repeated tests made on carefully sized particles, 1μ to 3μ in diameter, have shown that many physiologically inert silicates yield more "soluble silica" than does the very pure quartz which produces the silicotic reaction in tissue. From work done by Gardner and Redlin⁵ and by Filley and his associates,⁶ the hypothesis has been suggested that the toxic effect of finely divided quartz is confined to the surface of the particles where a layer of highly toxic colloidal silica is liberated. Scheel and his associates⁷ have demonstrated that a film of protein is adsorbed from solution by quartz particles 1μ to 3μ in diameter, and Schepers⁸ has shown that the presence of this protein film radically modifies the cellular reaction to quartz. Regardless of whether the toxicity is due to liberated colloidal or soluble silica or to the adsorption of protein on the surface of the quartz particles, the protective effect of the active aluminum compounds may be interpreted on the basis of the inference that quartz particles are rendered inert by an insoluble and impermeable coating.

2. PREPARATION OF QUARTZ PARTICLES FOR INJECTION AND INHALATION

All the quartz used in the various experiments to be discussed was prepared from a finely ground commercial product. The SiO_2 content of the material was 99.7%, and x-ray diffraction examination disclosed nothing but normal quartz. For injection tests, the commercial product was reground in a steel ball mill and elutriated in water. Particles measuring between 1μ and 3μ were separated and used in the injection experiments. The particles were routinely suspended in 0.85% saline solution or in colloidal aluminum hydroxide and sterilized in an Arnold sterilizer for one hour.

In the first group of experiments, injection techniques were employed to produce the silicotic reaction for the quantitative assessment of the inhibitor effects of the aluminum compounds. Later, when the powdered aluminum hydrate H-1010 and the mill for producing metallic aluminum powder became availa-

ble, inhalation methods were employed, both as a procedure for causing silicosis and as a means of introducing the aluminum compounds into the experimental animal. The intravenous injection of quartz particles into guinea pigs and rabbits produces marked silicotic reaction in the liver and spleen. The prevention exerted by the aluminum compound against the fibrotic reaction, particularly in the liver, demonstrated the principle that the inhibitor and the silica particle must localize in the same phagocytic cell.

Injection Methods.—The quartz employed in the injection experiments was the specially prepared powder composed of particles 1 μ to 3 μ in diameter. It was suspended in isotonic saline solution or in a suspension of the aluminum substance to form the desired concentration. The injection techniques included the intraperitoneal, the intravascular, and the intratracheal methods. In the intraperitoneal method, a single dose of 2 ml. of a 10% suspension of quartz particles (200 mg.) was injected into the abdominal cavity of a guinea pig. When the intravascular technique was used for guinea pigs, 1 ml. of a 1% suspension of the quartz particles was injected directly into the left ventricle of the heart twice a week for eight weeks, until 150 mg. of the dust had been given. For rabbits, 5 ml. of a 1% suspension of the dust was injected into the ear vein twice a week for 10 weeks. The intratracheal technique made use of a tracheal catheter through which the dust suspension was introduced into the trachea of guinea pigs, rats, or rabbits and subsequently passed into the lung. The dose was 0.5 ml. of a 10% suspension, and it was given once a week for three weeks.

Inhalation Methods.—The methods for exposing animals to silica dust inhalation have been described in detail in other publications.⁴ Briefly, the technique consisted of the exposure of animals to a cloud of fine silica particles disseminated in the air of a room by means of mechanical devices designed to produce the desired dispersion and concentration of particles in the atmosphere. Samples of the atmospheric dust were collected from time to time by means of a Greenburg-Smith impinger apparatus. In the experiments reported, a concentration of silica particles ranging from 500,000,000 to 700,000,000 particles per cubic foot of air was maintained. An analysis of the size distribution of the particles showed that more than 99% were less than 10 μ in diameter. Chemical analysis showed a total silica content greater than 99%. Atmospheric concentrations ranging from 1 to 3 mg. per cubic foot of air were maintained in the rooms in which either aluminum

TABLE 2.—*Studies of the Prophylaxis and Treatment of Experimental Silicosis by Means of Aluminum*

(1) Effect of aluminum compounds on normal animals
(2) Prophylactic action of aluminum compounds against quartz
(3) Therapeutic effect of aluminum compounds on pre-established silicotic lesions
(4) Effect of aluminum compounds on the course of tuberculous infection in animals not exposed to quartz dust

hydrate H-1010 or metallic aluminum powder was dispersed.

EXPERIMENTAL FINDINGS

The experimental findings will be presented in the order shown in Table 2.

1. EFFECT OF ALUMINUM COMPOUNDS ON NORMAL ANIMALS

(a) *Colloidal Aluminum Hydroxide.*—The results of a series of experiments showed that normal guinea pigs and rabbits receiving repeated injections of large amounts of colloidal aluminum hydroxide remained apparently healthy.

The reaction to intraperitoneal injections of the colloidal hydroxide consisted of the formation of flat white plaques on the omentum and peritoneal surfaces. Throughout a period of one year of observation, the only change observed in these plaques was the formation of a capsule composed of a thin layer of connective tissue, while there was no reaction in the adjacent tissues. The occurrence of increased numbers of phagocytes in the lungs, liver, and tracheobronchial lymph nodes suggested that small amounts of the aluminum agent had been transported to these organs.

One of Gardner's experiments led to the observation that aluminum-containing phagocytes entered the lung from the peritoneal site. This experiment was executed before a powdered aluminum hydrate suitable for inhalation had been prepared. The attempt to introduce the colloid into the lungs from an atomized spray proved ineffective. A group of 20 guinea pigs was, therefore, exposed by inhalation to a concentration of 800,000,000 particles of pure quartz per cubic foot of air through the course of one year. One-half of the animals received in addition biweekly

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intraperitoneal injections of 2 ml. of a 0.2% suspension of colloidal aluminum hydroxide, and the other half served as the quartz control. Two animals of each group were killed at intervals during the year. In the groups of animals killed at the end of 10 months, gross and microscopic examination showed that the silicotic reaction was definitely inhibited by the hydroxide which reached the lungs from the peritoneal cavity. The lungs of the control animals showed widespread fibrosis with nodulation, some with necrotic centers and beginning hyalinization. The silicotic reaction in the treated animals was limited to proliferation of macrophages and infiltration of lymphocytes (Fig. 1). The definite inhibition of inhalation silicosis by intraperitoneal in-



Fig. 1.—Protection against inhalation silicosis by means of colloidal aluminum hydroxide introduced by intraperitoneal injection. Experiment 790.—guinea pigs killed after 10 months. Whole lung sections. *A*, lung of animal exposed to quartz inhalation, with simultaneous treatment by means of bi-weekly intraperitoneal injection of 2 ml. of 0.2% suspension of colloidal aluminum hydroxide. *B*, lung of quartz control without aluminum treatment; nodulation and necrosis and incipient hyalinization contrast with complete absence of silicosis in the aluminum-treated animal.

jection of the colloidal hydroxide intensified the efforts to prepare a powdered aluminum hydroxide which could be suspended in air and inhaled as dust.

It was found that after intracardial injection of colloidal aluminum hydroxide the greatest accumulation of the colloid occurred in cells of the reticuloendothelial system of the spleen and liver. Isolated giant cells, clumps of mononuclear cells, grayish blue in color, were seen in the pulp and follicles of the spleen. In the portal area of the liver,

similar cells were present. A similar localization of the colloid occurred following intravenous injections in a rabbit.

From these observations it was concluded that normal guinea pigs and rabbits are not seriously affected by repeated injections of large amounts of colloidal aluminum hydroxide. The phagocytes apparently retain much of it for at least one year.

(b) *Powdered Aluminum Hydrate H-1010*.—The results of experiments by injection and inhalation showed no evidence of any toxicity or any chronic change which appeared to affect the health of the animals. The aluminum was apparently also retained for at least a year.

An inhalation experiment in which healthy guinea pigs were exposed eight hours daily for one year to an average concentration of 1.57 mg. of powdered aluminum hydrate H-1010 per cubic foot of air demonstrated that there was progressive accumulation of the aluminum compound in the lung. Gross inspection of the lung at the end of the year showed a slight diffuse tan pigmentation anteriorly. Microscopic examination revealed localized peribronchiolar foci of alveolar phagocytes sometimes surrounded by slight infiltrations of lymphocytes in adjacent walls. The phagocytes were markedly bluish gray and often swollen, and aluminum particles could be seen in their cytoplasm. The tracheobronchial lymph nodes showed heavy diffuse mononuclear infiltration with no evidence of fibrosis.

(c) *Metallic Aluminum Powder*.—Difficulty was encountered in preparing suspensions of metallic aluminum powder for intravenous injection into animals. In an inhalation experiment with powdered metallic aluminum, in which guinea pigs were exposed for one-half hour daily to an atmosphere containing an average of 0.88 mg. of metallic aluminum per cubic foot of air, no gross change was noted in the lungs until the expiration of one year, when a few small discrete foci of black dust appeared. The size of the foci had increased by the end of two years to 2 mm. diameter, but the number of foci did

not materially increase. Chemical analysis of the lung for aluminum showed no additional accumulation of the metal after the first year of exposure. The tracheobronchial lymph nodes were slightly firmer, with little pigmentation at the end of one year and with increased pigmentation at the end of two years. There were no gross changes in the spleen, liver, kidney, and hepatic lymph nodes. Denny, Robson, and Irwin⁸ exposed rabbits 12 hours daily for 14 months to an atmosphere containing freshly ground particulate metallic aluminum powder. Although the lungs contained 270 to 1200 mg. of aluminum per 100 gm. of dried tissue, the authors reported no evidence of toxicity or damage to the tissues.

2. PROPHYLACTIC ACTION OF ALUMINUM COMPOUNDS AGAINST QUARTZ

The prophylactic effects of aluminum compounds have been studied in different experiments involving guinea pigs, rats, and rabbits. The aluminum agents were administered by injection or by inhalation, either prior to the exposure of the animals to quartz dust or simultaneously with the exposure to the quartz dust as a mixture or as separate components.

A group of experiments employing the injection of colloidal aluminum hydroxide demonstrated most conclusively the inhibitor effect of the hydroxide. Though the reaction took place in the liver and spleen, the results are considered valid, because it has been shown that free silica has the same effect upon connective tissue regardless of the organ in which it is located. The connective tissue of

TABLE 3.—Degrees of Tissue Reaction Produced by Quartz as a Measure of the Protective Effect of Aluminum Compounds

Degree of Experimental Silicosis	Characteristic Features of the Reaction	Degree of Protection by Aluminum
E. S. 0	Simple phagocytosis; this is minimal silicotic reaction, indicating complete protection by aluminum compound	A. P. 4
E. S. 1	Slightly increased numbers of phagocytes usually appearing in small compact clumps, indicating that quartz particles may be slightly irritating without exerting any appreciable effects upon surrounding tissues	A. P. 4
E. S. 2	There is now an additional infiltration of lymphocytes in the immediate vicinity of the clumps of phagocytes; this indicates evidence of chronic inflammation	A. P. 3
E. S. 3	Proliferation of phagocytes and infiltration of lymphocytes; this stage indicates that aluminum is only partially protective	A. P. 2
E. S. 4	Widespread fibrosis with necrosis; silicotic reaction is only slightly retarded	A. P. 1
E. S. 5	Mature hyaline silicotic nodules; this lesion represents standard terminal reaction to quartz particles, indicating no protective effect from aluminum	A. P. 0

the liver which reacts to the silica is composed of the same cytological elements as the connective tissue of the lungs, although the tissue assumes different forms in the two organs.

The capacity of the different aluminum compounds to inhibit the silicotic reaction has been determined by the cellular response of the tissue to quartz particles, and the results are presented in a series of tables. The scale or severity of the silicotic reaction and the degree of protection afforded by aluminum are summarized in Table 3.

Table 4 lists the results of a series of experiments with colloidal aluminum hydroxide. The control guinea pigs receiving quartz particles suspended in isotonic saline de-

TABLE 4.—Protective Effect of Aluminum Hydroxide Against Quartz Injection Experiments—Quartz and Aluminum Hydroxide Mixed

Exp. No.	Species of Animal	Animal No.	Injection Route	Aluminum Agent Employed	Quantity of Alum. Mg.	Quantity of Quartz, Mg.	Duration of Observation, Mo.	Silicotic Tissue Reaction	Protection by Aluminum
746-A	Guinea pig	5	Intraperitoneal	Al(OH) ₃	4.0	300	12	E. S. 0	A. P. 5
747	Guinea pig	5	Intracardial	Al(OH) ₃	40	200	12	E. S. 0	A. P. 4
879	Guinea pig	5	Intracardial	Al(OH) ₃	30	150	12	E. S. 0	A. P. 4
928	Guinea pig	5	Intracardial	Al(OH) ₃	30	150	12	E. S. 0	A. P. 4
778	Rabbit	4	Intravenous	Al(OH) ₃	300	500	12	E. S. 0	A. P. 4

* Quartz particles used were 1 μ to 2 μ in diameter.

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veloped characteristic silicotic lesions in the spleen, liver, lymph nodes, and bone marrow. During the first four months there was rapid proliferation of mononuclear cells in focal areas associated with degeneration of the contiguous parenchymal elements. Eight months after completing the injections, most of the silicotic reaction in all these viscera had attained maturity and was composed of more or less hyaline fibrous tissue.

The guinea pigs receiving the same amount of quartz particles suspended in colloidal aluminum hydroxide showed no nodule formation or fibrosis. The primary phagocytes ingesting both the quartz particles and

the hydroxide did not proliferate but remained widely scattered throughout the tissue. There was no evidence of injury to the cells. The histological picture remained unchanged 12 months after completing the injection, as it had been in the animals killed at one month (Fig. 2). In order to be certain that the associated aluminum substances had not altered the distribution of the injected quartz particles so that they no longer accumulated in the usual viscera, the livers of all animals in this experiment were analyzed chemically. The analysis demonstrated that in all groups there were sufficient quantities of silica to have produced reaction (Table 5).

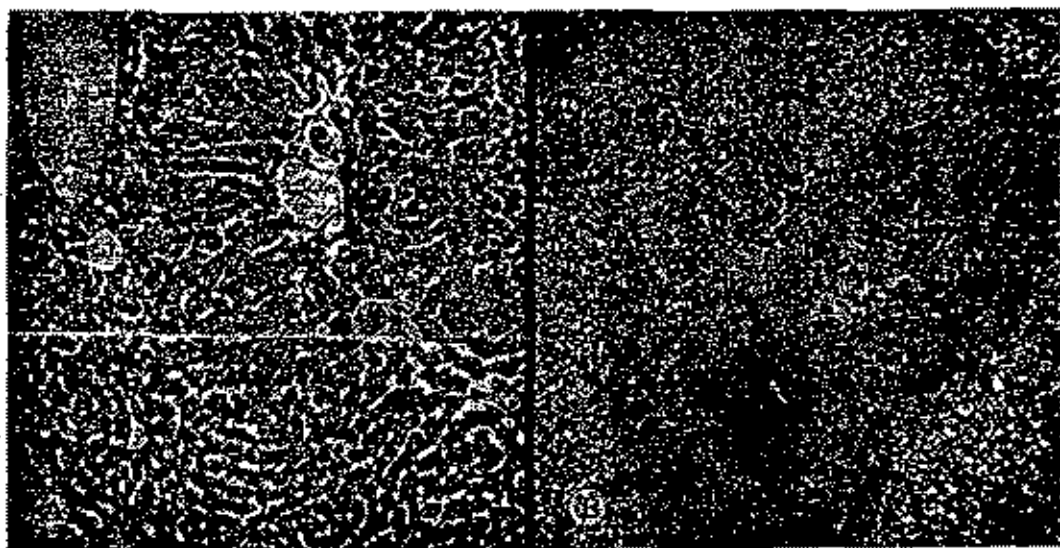


Fig. 2.—Complete protection afforded by colloidal aluminum hydroxide against hepatic sclerosis from quartz dust. Experiment 747—guinea pigs; result at end of one year. Microscopic sections. A, liver of treated animal, showing no cellular multiplication or colloid. B, liver of untreated control, showing hyalinizing nodules.

TABLE 5.—Silica Content of Desiccated Livers of Guinea Pigs That Had Received by Injection Quartz Particles Alone and Quartz Particles in an Aluminum Suspension *

Duration of Exposure, Mo.	Quartz Particles Suspended in Isotonic Saline Controls, %	Quartz Particles Suspended in 0.85% Al(OH) ₃ , %	Quartz Particles Suspended in 0.07% Metallic Al Powder, %
1	1.45	1.29	1.80
4	1.96	1.51	2.40
8	0.96	0.81	1.42
12	1.80	0.83	1.37

* A total dose of 200 mg. of quartz particles, 1 μ to 3 μ in diameter, was introduced into the circulation of each animal.

In all experiments employing the injection of colloidal aluminum hydroxide and powdered aluminum hydrate H-1010, the silicotic reaction was inhibited. On the other hand, animals treated with powdered metallic aluminum showed only a slight inhibitory effect of the aluminum agent on the silicotic reaction. Seven different injection experiments were performed, and the results were invariably poor. When the metallic aluminum was suspended in 0.85% saline solution or in distilled water, the suspensions flocculated, and no dispersing agent that we tried could

prevent the formation of large clumps of the powder at the point of contact with body fluids. On injecting the suspension of metallic aluminum powder and quartz particles into the guinea pig heart, most of the metallic aluminum powder remained in the cardiac ventricles, while the quartz particles were carried to the spleen, liver, and lymph nodes where they produced silicotic fibrosis.

There was correspondence and consultation between Dr. Irwin and Dr. Gardner regarding the difficulties with the metallic aluminum. Dr. Irwin held the view that, if the metallic powder depressed the solubility of quartz in the test tube, it should possess the property of inhibiting the toxicity of silica. Tests showed that the solubility of the quartz was reduced 95% by the aluminum powder. Dr. Irwin suggested that the tissues be examined for soluble aluminum by the aurin-staining method, but the sections of tissue so stained showed no aluminum. Chemical analysis of the tissues for aluminum disclosed that very little metallic aluminum was present in the tissues, in comparison with the amount of aluminum found in the hydroxide-treated animals. In an intracardial injection experiment employing both the metal and the hydroxide, in which equivalent quantities of aluminum were given, 25 times more aluminum was found in the tissues of the guinea pigs receiving the colloidal aluminum hydroxide than in the animals into which the metallic aluminum suspension had been injected (Table 6). Two other experiments

TABLE 6.—Amount of Aluminum Retained in Liver and in Spleen of Guinea Pigs After Intracardial Injection of Suspension of Colloidal Aluminum Hydroxide and of Powdered Metallic Aluminum*

Time After Injection, Mo.	Liver		Spleen	
	Colloidal Al(OH) ₃ , Mg.	Metallic Al, Mg.	Colloidal Al(OH) ₃ , Mg.	Metallic Al, Mg.
1		8.7		4.8
2	16.5		145.2	...
4	27.4	0.36	174.5	8.1
8		0.20		4.8
12	16.1	0.05	184.7	6.0
Normal controls	0.024		0 to 0.58	

* The two suspensions contained equivalent amounts of aluminum; values given are milligrams of Al component per 100 gm. of dried tissue.

confirmed these findings. Apparently our inability to prevent the flocculation of the metallic aluminum was responsible for the absence of the protective effect of the metal. Further injection experiments with metallic aluminum powder should be planned, utilizing the newer dispersing agents now available. If the metallic aluminum can be localized in the liver and spleen, a protective effect against quartz particles in these tissues similar to that observed with colloidal aluminum hydroxide should occur.

Experiments in which groups of rats were exposed by inhalation to an atmospheric suspension of H-1010 for varying periods of time prior to exposure by inhalation to quartz particles are listed in Table 7. At the end of a year there was evidence of some inhibition of the reaction to the silica, but in none of the animals was the protection complete. The degree of protection was in proportion to the

TABLE 7.—Protective Effect of Aluminum Compounds Against Quartz*

Exp. No.	Species of Animal	Animals, No.	Aluminum Agent Employed	Duration of Exposure to Aluminum	Duration of Exposure to Quartz	Silicotic Tissue Reaction	Protection by Aluminum
964-I	Rat	25	H-1010	8 hr. daily for 4 mo.	8 hr. daily for 1 yr.	E.S.-3	A.P.-1
964-II	Rat	25	H-1010	8 hr. daily for 2 mo.	8 hr. daily for 1 yr.	E.S.-4	A.T.-2
964-III	Rat	25	H-1010	8 hr. daily for 1 mo.	8 hr. daily for 1 yr.	E.S.-3	A.P.-1
964-IV	Rat	25	H-1010	8 hr. daily for 2 wk.	8 hr. daily for 1 yr.	E.S.-6	A.P.-0
965	Rat	40	H-1010	1/4 hr. daily for 12 mo.	7 1/2 hr. daily for 1 yr.	E.S.-4	A.P.-1
961a	Guinea pig	25	Metallic Al	1/4 hr. daily for 20 mo.	7 1/2 hr. daily for 20 mo.	E.S.-3	A.P.-0

* Inhalation of H-1010 powder and of metallic aluminum powder followed by inhalation of quartz dust. Concentration of H-1010 powder: 25 to 50 mg. per cubic foot of air. Concentration of quartz dust: 700,000,000 particles per cubic foot of air.

TREATMENT OF SILICOSIS BY MEANS OF ALUMINUM

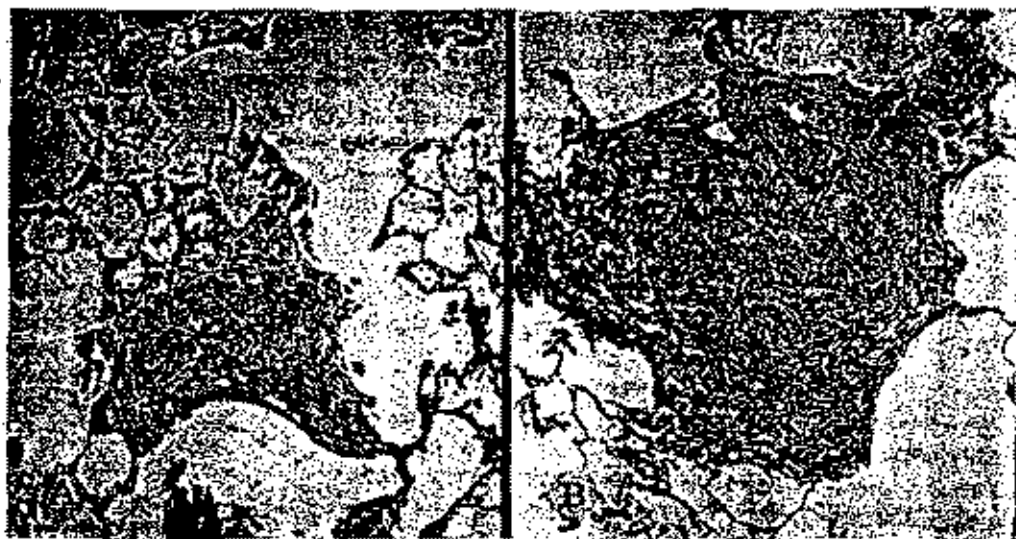


Fig. 3.—Prophylaxis against experimental silicosis. Experiment 984-I—administration of H-1010 aluminum agent to rats preceding exposure to quartz dust. Microscopic sections. *A*, lung of aluminum-treated animal; reaction limited to focal cellular reaction without collagen formation. *B*, lung of quartz control; fully formed hyalinizing nodules have developed.

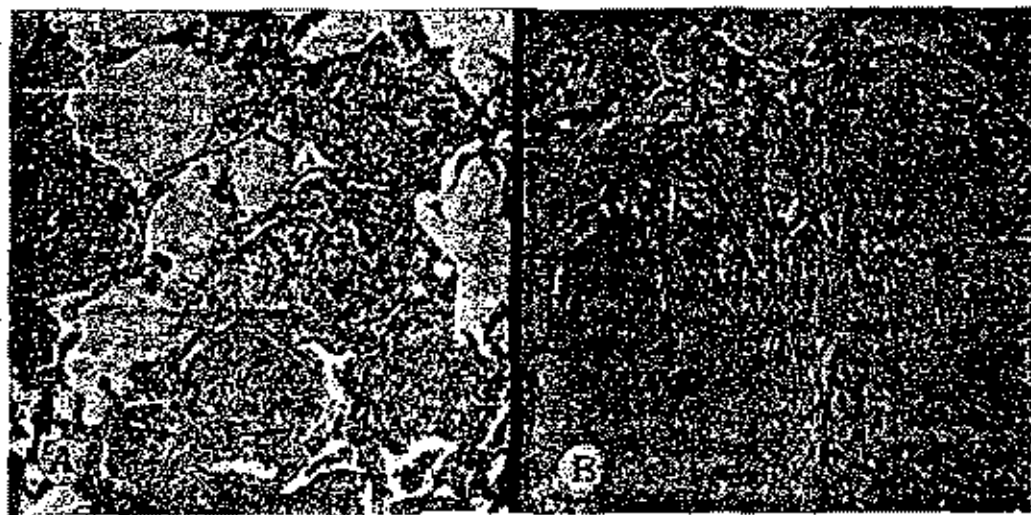


Fig. 4.—Partially effective prophylaxis against experimental silicosis by means of H-1010 aluminum agent. Experiment 985—rats. Microscopic sections. *A*, lung of aluminum-treated animal at end of one year of exposure to quartz dust for seven and one-half hours daily, preceded by one-half-hour exposure to H-1010 aluminum agent; small cellular nodules only have developed. *B*, lung of quartz control without aluminum treatment; at end of eight months there is diffuse fibrosis.

duration of prophylactic treatment with H-1010 and to the amount of H-1010 found in the lungs by chemical analysis. In those animals which inhaled the aluminum agent for eight hours a day, the lung showed 42.3 mg. of aluminum per 100 gm. of dried lung at

the end of four months, compared with 7.5 mg. of aluminum at the end of two weeks.

In the groups of animals treated for one, two, and four months, respectively, by means of the inhalation of H-1010 before exposure by inhalation to quartz particles, evidence of

inhibition of the silicotic reaction was demonstrated. The lungs of an animal killed one year after exposure to the quartz particles showed a histological picture of widespread focal cellular proliferation, with no necrosis or hyalinization. The lungs of the untreated animal showed large hyaline nodules (Fig. 3).

An experiment in which 40 rats were exposed by inhalation to H-1010 for half an hour daily, and then were transferred to another room and exposed to quartz dust for seven and one-half hours daily, demonstrated some inhibitory capacity of the aluminum agent, but the protection was not complete. The rats were observed for a period of one year, and the nodules did not become large enough to be recognized on gross inspection of sections. On microscopic examination, rare nodules were seen to have necrotic centers in some animals. There was incomplete protection in the lymph nodes. In the control animals, however, fibrous nodules were macroscopically visible after 8 months, and the animals died before the 12th month. In the treated group, six animals were killed at the end of 12 months in order to terminate the experiment, but none died spontaneously (Fig. 4).

An experiment in which 25 guinea pigs were exposed to 0.88 mg. of powdered metallic aluminum per cubic foot of air for half an hour daily, followed by exposure to a high concentration of quartz dust for seven and one-half hours daily, showed less pro-

tection than was found in the rats exposed to H-1010 on the same daily routine. At the end of one year, microscopic examination of the lung showed extensive dust reaction, with marked proliferation of macrophages in all sites of localization (Fig. 5). A distinct nodular pattern with small central hyaline fibrosis was observed in many lungs. Observations were continued for 20 months, but intercurrent infections interfered with the study in the latter part of this experiment. Chemical analysis, however, showed that some metallic aluminum had accumulated in the lung.

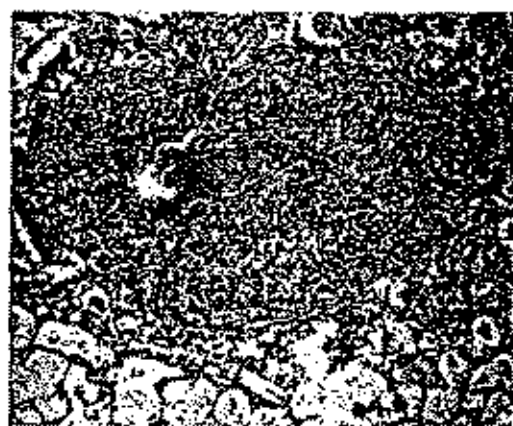


Fig. 5.—Incomplete protection against silicosis by means of powdered metallic aluminum. Experiment 1018—guinea pigs exposed daily for half an hour to powdered metallic aluminum, followed by exposure for seven and one-half hours to quartz dust. Microscopic section. At end of 12 months there are nodular foci of extensive cellular reaction with central hyaline formation in the lung.

TABLE 2.—Therapeutic Effect of Aluminum Compounds on Preestablished Silicotic Lesions

Exp. No.	Species of Animal	Animals, No.	Method of Producing Silicotic Lesion	Time of Exposure to Quartz Dust Before Treatment	Aluminum Agent Employed	Method of Treatment	Time of Exposure After Treatment, Mo.	Silicotic Lesion Reaction	Protection by Aluminum
778	Rabbit	4	Intravenous	5 wk.	Al(OH) ₃	Intravenous	12	E.S.-3 to 0	A.P.-1 to 5
806	Rabbit	4	Intravenous	6 mo.	Al(OH) ₃	Intravenous	12	E.S.-3 to 5	A.P.-2 to 0
804-I	Guinea pig	6	Inhalation	8 hr. daily for 6 mo.*	Al(OH) ₃	Intracardial	12	E.S.-3	A.P.-2
804-III	Guinea pig	6	Inhalation	8 hr. daily for 6 mo.	Al(OH) ₃	Intracardial	12	E.S.-3	A.P.-2
806-VII	Guinea pig	25	Inhalation	8 hr. daily for 12 mo.	H-1010	Inhalation 8 hr. daily	12	E.S.-4	A.P.-2
1030-I	Guinea pig	25	Inhalation	8 hr. daily for 6 mo.	Metallic Al	Inhalation 1/2 hr. daily	6	E.S.-5	A.P.-0
1030-III	Rat	25	Inhalation	8 hr. daily for 6 mo.	Metallic Al	Inhalation 1/2 hr. daily	6	E.S.-5	A.P.-0

*The exposure by inhalation to quartz dust was continued for another six months during treatment with aluminum agent.

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3. THERAPEUTIC EFFECT OF ALUMINUM AGENTS ON PREESTABLISHED SILICOTIC LESIONS

The next group of seven experiments, listed in Table 8, was concerned with the protective effect of aluminum agents administered either by injection or by inhalation to animals which had silicotic lesions in various stages of development.

A group of rabbits was injected intravenously with 500 mg. of quartz particles over a period of five weeks and then was given colloidal aluminum hydroxide by intravenous injection. The treatment halted an extensive active proliferation. At the end of three months the silicotic reaction had retrogressed to a simple phagocytic reaction re-

hyaline fibrous silicotic nodules and the diffuse fibrosis replacing all normal structures except the bile ducts. The microscopic appearance of the section from the treated liver was normal except for a localized collection of large phagocytic cells in the connective tissue between lobules and a few isolated phagocytes in the blood spaces (Fig. 6).

In another experiment with rabbits, the treatment was delayed until six months after the introduction of the quartz particles. In these animals it was observed that the hydroxide had no effect on mature fibrous nodules present at the beginning of treatment, but immature cellular nodules re-

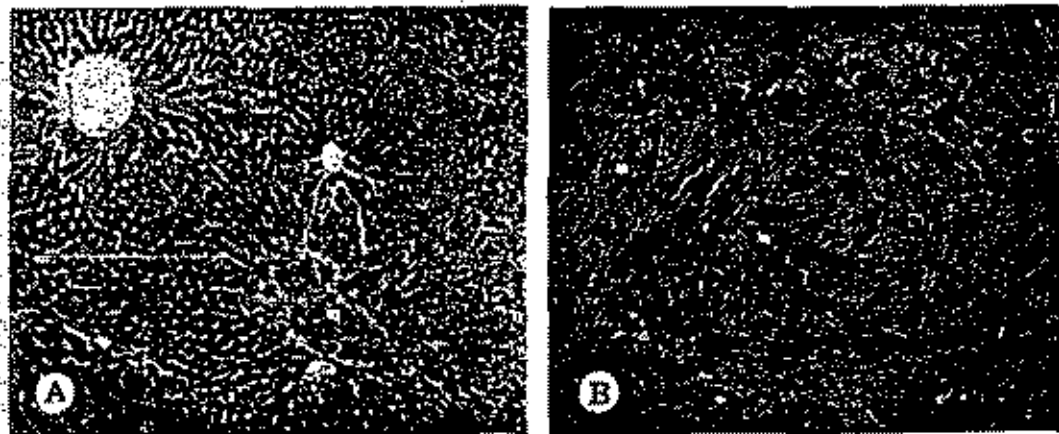


Fig. 6.—Protection against intravenously administered quartz dust by means of intravenous injection of colloidal aluminum hydroxide. Experiment 773—rabbits received 500 mg. of quartz particles for five weeks, followed by 50 ml. of 0.2% $\text{Al}(\text{OH})_3$ for five weeks; result at end of 12 months. Microscopic sections. A, liver of aluminum-treated animal; normal except for small interlobular foci of macrophages. B, liver of quartz control, with confluent hyaline silicotic nodules replacing all liver cells; bile ducts survive.

sembling the effect of a mild irritating silicate, such as that of the clay materials. The protection was maintained for at least one year after completion of the quartz injection. The livers of the control animals showed massive silicotic cirrhosis at the end of a year, with marked destruction of liver tissue and replacement by dense leather-like fibrosis. The liver from the rabbits which received the same amount of quartz particles with colloidal aluminum hydroxide appeared normal except for small areas of pigmentation beneath the capsule. Microscopic examination of sections from the control liver showed the large

progressed and disappeared. Microscopic evidence proved regression of immature cellular nodules. The mature fibrous nodules remained unaltered. The liver of the control rabbit was completely fibrosed at the end of a year (Fig. 7).

In a further experiment to determine the protective effect of colloidal aluminum hydroxide on a preestablished silicosis, the hydroxide was introduced intracardially. Fourteen guinea pigs were exposed for six months to a high concentration of quartz dust (800,000,000 particles per cubic foot of air). Thereafter they were divided into two

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groups. Eight animals received weekly intracardial injections of 2 ml. of 0.2% aluminum hydroxide without further dust exposure, and six animals received the same treatment but with continued quartz exposure. There were appropriate controls. Four control animals were killed at six months to observe the degree of quartz reaction before treatment was initiated. Their lungs showed bronchiolitis, i. e., the stage of dust reaction before nodulation or fibrosis. The control animals which were exposed for six months and then removed to a normal atmosphere for another six months showed progressive silicosis. Microscopic nodules with hyaline necrotic

junction caused retrogression of silicotic lesions that had not yet reached the stage of maturity, but tissue already fibrous was not affected. The inhibiting effect apparently depended on the colloid reaching the tissue in the early stages of the silicotic reaction and being retained either by the same cells that had phagocytosed the quartz particles or by other cells in the immediate vicinity. Chemical analysis of the tissue of the liver and spleen of animals which had received colloidal aluminum hydroxide showed an accumulation of the silica in these organs.

When powdered aluminum hydrate H-1010 became available, it was possible to

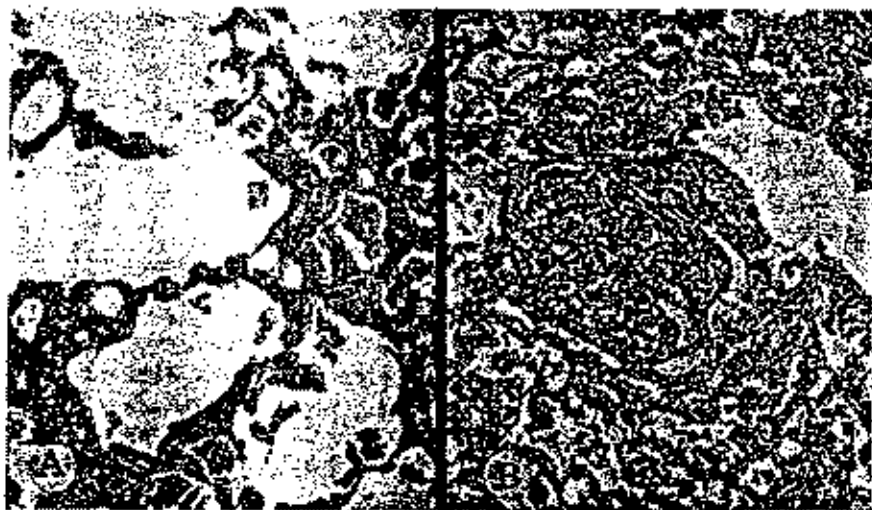


Fig. 9.—Capacity of inhaled H-1010 aluminum agent to arrest silicosis if treatment is continued long enough. Experiment 950—guinea pigs exposed for 11 months to inhalation of quartz dust for eight hours each day, followed by treatment with H-1010 for 13 months. Microscopic sections. *A*, lung parenchyma of a guinea pig treated with H-1010. *B*, lung of untreated quartz control, killed after six months, in which histological reaction shows unintentional protection (see text).

centers were seen throughout the lungs. In the treated animals, nodule formation was inhibited. The pulmonary lesions (Fig. 8) still consisted of localized areas of interstitial proliferation, and there were no metastatic foci of silicosis in the liver or spleen. The hydroxide had not prevented all tissue reaction but had reduced it to a mild and apparently non-progressive interstitial proliferation. Typical silicotic reactions occurred in the tracheo-bronchial lymph nodes.

These experiments demonstrated that colloidal aluminum hydroxide introduced by in-

introduce the aluminum agent directly into the lung by inhalation. Twenty-five guinea pigs in which immature silicotic lesions had been produced by previous exposure to a high concentration of quartz dust for 11 months were exposed for eight hours daily over a period of 13 months to an atmosphere containing an average of 1.57 mg. of H-1010 per cubic foot of air. The treatment was most effective in halting the progress of the silicotic lesions. Microscopic examination of the lungs of the four guinea pigs killed at 13 months after treatment showed focal proliferation of

mononuclear cells only. There was no evidence of fibrosis (Fig. 9). Analysis of portions of the guinea pig lung shown in Figure 9 for aluminum showed the accumulation of 125 mg. of aluminum per 100 gm. of dried lung tissue.

The untreated quartz control animals that had been kept in a normal atmosphere after their removal from the dust room gave some unexpected evidence of the protective effect of aluminum. Some of the animals failed to develop a degree of disease commensurate with their exposure. Gross examination of the lungs of such an animal killed six months after removal to a normal atmosphere re-

vealed multiple areas of reaction, but on microscopic examination these foci were not fibrous (Fig. 9). These lesions suggested a partially inhibited silicotic reaction. On analyzing the portion of the lung of this animal, it was found to contain 38.6 mg. of aluminum per 100 gm. of dried lung. The upper limit for the aluminum content of a normal lung is 2 mg. per 100 gm. of dried lung tissue. On investigation it was discovered that the quartz dusting room had been contaminated by moving racks of cages from the aluminum room into the quartz room without first attempting to remove the aluminum dust that had accumulated upon the cages. Though this development constituted an unintentional inhibitory effect, the incident demonstrated

4. EFFECT OF ALUMINUM COMPOUNDS ON THE COURSE OF TUBERCULOUS INFECTION IN ANIMALS NOT EXPOSED TO QUARTZ DUST

Since silicosis is frequently associated with tuberculosis, experiments were planned to determine (a) whether aluminum compounds would modify in any way the course of a tuberculous process in normal animals infected at the same time that the treatment with the aluminum was initiated, (b) whether the aluminum compounds would reactivate a

TABLE 9.—Effect of the Inhalation of Aluminum Compounds on the Course of Tuberculous Infection in Animals Not Exposed to Quartz Dust*

Exp. No.	Species of Animal	Animals, No.	Aluminum Agent Employed	Interval Between Infection and Exposure to Aluminum	Duration of Exposure to Aluminum	Results
260-II	Guinea pig	25	H-1010	Simultaneous	8 hr. daily for 12 mo.	Spreading tuberculosis in lungs, with no deaths
266	Guinea pig	25	H-1010	Simultaneous	1/4 hr. daily for 12 mo.	Does not alter the course of R1 inhalation infection
1018-II	Guinea pig	25	MetaBis Al	Simultaneous	1/4 hr. daily for 24 mo.	10 animals showed spreading tuberculosis at time of autopsy, with no deaths
260-IV	Guinea pig	18	H-1010	4 1/2 mo.	8 hr. daily for 6 mo.	Healing proceeded typically; no reactivation
260-V	Guinea pig	9	H-1010	8 mo.	8 hr. daily for 6 mo.	Healing proceeded typically; no reactivation
1018-VIIA	Guinea pig	10	MetaBis Al	2 mo.	1/4 hr. daily for 12 mo.	Healing proceeded typically; no reactivation
1018-VIIB	Guinea pig	6	MetaBis Al	4 mo.	1/4 hr. daily for 12 mo.	Healing proceeded typically; no reactivation
1018-VIIC	Guinea pig	8	MetaBis Al	6 mo.	1/4 hr. daily for 12 mo.	Healing proceeded typically; no reactivation

* Organism used, attenuated human tubercle bacillus, Strain R1; method of infection, by inhalation.

vealed multiple areas of reaction, but on microscopic examination these foci were not fibrous (Fig. 9). These lesions suggested a partially inhibited silicotic reaction. On analyzing the portion of the lung of this animal, it was found to contain 38.6 mg. of aluminum per 100 gm. of dried lung. The upper limit for the aluminum content of a normal lung is 2 mg. per 100 gm. of dried lung tissue. On investigation it was discovered that the quartz dusting room had been contaminated by moving racks of cages from the aluminum room into the quartz room without first attempting to remove the aluminum dust that had accumulated upon the cages. Though this development constituted an unintentional inhibitory effect, the incident demonstrated

partially healed or a healed tuberculous infection, and (c) whether treatment with aluminum compounds would alter the usual increased susceptibility to tuberculosis created by silicosis. In Table 9 are listed the experiments which will be briefly discussed.

In the first experiment 50 guinea pigs were infected by inhalation of attenuated human tubercle bacilli, Strain R1. As is well known, this organism causes in the guinea pig a self-limiting tuberculous reaction which heals by resolution or calcification. The group was equally divided. Twenty-five animals were exposed for eight hours daily, six days a week, for one year in an atmosphere containing 1.57 mg. of H-1010 per cubic foot of air. The other 25 infected guinea pigs were kept

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Fig. 10.—Harmful effect of massive aluminum therapy on the course of experimental tuberculosis. Experiment 958-II—simultaneous infection of guinea pigs by means of R1 tubercle bacilli and exposure by inhalation to H-1010 aluminum agent eight hours daily for one year. Whole lung sections. *A*, lung of infected animal in which one year of exposure to H-1010 has resulted in massive fibro-calcious tuberculosis. *B*, lung of R1 infection control without exposure to H-1010; standard reaction at end of one year, with minute, isolated, healed tubercles.

in normal air as infection controls. In the controls the infection ran a normal course, healing by resolution, with the disappearance of most of the tubercles by 12 months. The findings in the infected animals exposed by inhalation to H-1010 showed, up to six months, results similar to the controls. In the 14 animals killed during the 8th, 10th, and 12th month after the inhalation of H-1010, however, all but one showed some spreading

Fig. 11.—Transitory stimulatory effect of minimal aluminum therapy on R1 tuberculosis. Experiment 998—guinea pigs infected with R1 tubercle bacilli and exposed to H-1010 for half an hour daily. Whole lung sections. *A*, lung at end of one month, showing a few small gelatinous tubercles and associated lymph node enlargement. *B*, lung at end of one year; a few calcific scars only may be found (multiple dark foci are lymphoid aggregates).



cellular tubercles in the lung (Fig. 10). In a few animals the lesions were confluent. No necrosis or cavitation occurred.

The results of this experiment indicated that excessive concentrations of the aluminum agent exerted an unfavorable influence upon guinea pig susceptibility to tuberculosis. Analyses showed as much as 156 mg. of aluminum per 100 gm. of dried lung tissue. Exposures to this compound in such concentrations for eight hours daily were far in excess of any that would be contemplated for human therapy. Another experiment was similar to the one just described, except that the infected animals were exposed by inhalation to H-1010 for half an hour daily instead



Fig. 12.—Transitory tuberculogenic effect of metallic aluminum dust. Experiment 1018—guinea pigs infected with R1 tubercle bacilli by inhalation and exposed to metallic aluminum dust half an hour daily for 25 months. Whole lung sections. *A*, lung at end of nine months, showing multiple spreading tubercles. *B*, lung at end of 12 months, showing partial regression of pulmonary lesions but persisting lymph node enlargement.

of eight hours daily. Groups of animals were killed at intervals extending over a period of 15 months. In the 50 animals killed the tuberculous lesions resolved and behaved in the same manner as seen in the lungs of the controls (Fig. 11). This experiment proved that exposure to the H-1010 aluminum hydrate for half an hour daily did not retard the healing of tuberculosis provoked in guinea pigs by the attenuated human tubercle bacillus, Strain R1.

Twenty-five guinea pigs were next infected with the attenuated human tubercle bacillus, Strain R1, and exposed to metallic aluminum powder by inhalation for half an hour daily. Of the 25 infected guinea pigs, 10 showed evidence of spreading tubercles in the lung. The spreading disease was observed in 5 of the 16 animals killed during the first 12 months and in 5 of 9 animals killed during the last 12 months of the experiment (Fig. 12). Though the spreading disease was not marked and the features of the tubercles suggested that they would have healed if the animals had been allowed to survive longer, this finding contrasted with the favorable results obtained when exposure was to H-1010 for half an hour daily.

The next experiments to be mentioned are also listed in Table 9 and concern attempts to reactivate a partially healed tuberculosis by the inhalation of H-1010 and of powdered metallic aluminum.

The animals exposed by inhalation to H-1010 for eight hours daily for six months were divided into two groups. One group had been infected with the R1 strain by inhalation four and one-half months previous to the exposure to H-1010, and the other group had been infected six months prior to the exposure to H-1010. Over the period of six months autopsies of the animals revealed no evidence of reactivation or spread of the tuberculosis.

Since it was observed that guinea pigs infected with the R1 strain by inhalation showed some spreading tuberculosis when they were exposed half an hour daily by inhalation to powdered metallic aluminum, an experiment to determine whether the metallic aluminum would be able to reactivate an R1 infection was planned as follows. A batch of 30 guinea pigs was infected with the attenuated human tubercle bacillus, Strain R1. The animals were divided into three groups. In the first group the infection was allowed to proceed for two months, in the second group for four months, and in the third group for six months before the infected animals were exposed half an hour daily by inhalation to powdered metallic aluminum. The animals in all groups were

killed over a period of one year. There was no evidence of reactivation. Healing of the tubercles proceeded in a normal manner.

CONCLUSIONS

The experimental data presented in this paper warrant the following statements.

1. By injecting into animals a suspension containing both quartz particles and colloidal aluminum hydroxide or powdered aluminum hydrate H-1010, it has been demonstrated that the aluminum agent specifically inhibits the characteristic fibrogenic reaction to quartz. Each aluminum agent has been found capable of completely inhibiting the silicotic reaction for over a year, and there is no indication that it would not have continued to do so indefinitely.

2. The injection of the aluminum agent causes resolution and healing of immature silicotic tissue reactions, but fibrous nodules do not disappear. However, further enlargement of the fibrous nodules ceases after the institution of aluminum treatment.

3. The silicotic reaction may be prevented by introducing into the body the aluminum agent and the quartz particles, together or in separate suspensions and by the same or different pathways, provided that the inhibitor agent and the quartz particle localize in the same phagocytic cell. Unless such intimate contact is established, protection is slight or absent. This evidence indicates that the successful prevention and treatment of silicosis can be expected only when the aluminum agent is administered by inhalation.

4. Prophylactically, the inhalation of powdered aluminum hydrate H-1010 limits the silicotic reaction to the innocuous proliferation of macrophages in the lung parenchyma, and no fibrous reaction follows. As a treatment for established disease, the inhalation of H-1010 causes regression of immature silicotic lesions, but its only effect upon fully developed fibrous nodules is to prevent their further enlargement and their confluence.

5. Normal animals, repeatedly receiving the aluminum agent by injection or by inhalation, show no evidence of any toxicity or

TREATMENT OF SILICOSIS BY MEANS OF ALUMINUM

of any chronic change that appears to affect their health. The agent is ingested and retained for at least one year by connective tissue phagocytes. The metallic aluminum agent elicited the least cellular response.

6. The inhalation of excessive amounts of powdered aluminum hydrate H-1010 for eight hours daily for one year transiently causes extension of the tuberculous process in some animals infected with attenuated human tubercle bacilli Strain R1. The spreading infection does not, however, cause death. When the animals are exposed to H-1010 for only half an hour daily over a period of fifteen months, the hydroxide appears to have no stimulatory effect on the benign course of this type of tuberculous infection.

7. The transitory stimulatory effect of inhaled powdered metallic aluminum on the tuberculous process lasts somewhat longer in comparison with that caused by colloidal aluminum hydroxide under the same experimental conditions.

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Experiences with the Control of Silicosis in the Ceramic Industry

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Silicosis of varying degrees of severity has been encountered sporadically in the ceramics industry. I have been associated for about 12 years with such a plant which has been manufacturing bathroom fixtures since 1907. A study of the influence of aluminum therapy on the course of silicosis was facilitated by the fact that there was a very low turnover in workers. During the first 25 years of the existence of the plant, no connection between the ceramics industry and silicosis was recognized by management. Consequently no attempt was made to keep the plant dust-free. Silicosis first became recognized in Pennsylvania as a compensable disease during 1937. Since that time strenuous efforts have been made to clean up the plant. Dust levels averaging less than 5,000,000 particles per cubic foot (ppcf) have been achieved in the casting rooms, with a range of 800,000 to 4,100,000 ppcf. It has not been possible to maintain such levels in the mixing rooms, where limited numbers of personnel have been obliged to handle raw clays, flints, and feldspars.

Because of the fact that the majority of employees work in the casting department, the greatest hazard, from the point of view of statistics, remains here, even though there is excellent ventilation and at points where dust is generated respirators are provided for the men. The respirators are not always in use. Soda ash is employed as a deflocculent. An incidental effect of this is that the soda ash increases the solubility of free silica

in the raw materials, and this fact may have significance, because experimental work has shown¹ that soda ash increases the solubility and subsequent toxicity of quartz.

Clinical studies of casting department employees in the ceramics industry, as a whole, have demonstrated that, in spite of dust counts averaging below 5,000,000 ppcf, from 40% to 50% of the casters have radiological silicosis after 12 to 15 years of exposure. As the dust counts are low, the statistical finger of guilt points to the soda ash that is admixed with the silica.

In my experience and that of other physicians* concerned with the ceramics industry, the radiograms in ceramics workers are best classified as follows:

Class I: Normal chest

Class IIA: Increased lung markings but still within normal limits

Class IIB: Compatible with incipient silicosis

Class III: Nodular silicosis

Class IV: Coalescent silicosis

Class V: Complication

In grading the various cases, several groupings of the above five classes are possible, e. g., IIA + V or III + V. The classes do not necessarily correspond to the degrees of associated disability.

I have dealt with 139 ceramics workers continually during the past 12 years. Among these, 36 cases of indisputable silicosis were identified, the dominant lesions being those graded as Classes III and IV above. Two cases only of active tuberculosis were isolated. Thirty-two men were in Class IIB.

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Medical Director, Universal Rundle Corp.

* Hannon, J. W. G., and Bovard, P.: Personal communications to the author.

CONTROL OF SILICOSIS IN CERAMICS INDUSTRY

In 1944, after two successful claims for occupational disease brought against the company, it was decided to treat the men by aluminum therapy. At this time dust counts over the entire plant were found to be below the legal occupational hazard level, except in the clay-mixing departments, and have been kept so during the whole past decade. All employees were given the opportunity to take treatment at regular intervals and indeed were strongly urged to do so. No one was discharged because of failure to use treatment. The method of administering aluminum was technically identical with that described by Osmond.² The regimen of therapy, however, deviated from his method in minor respects, owing to special environmental circumstances. Sixty-five per cent of all the men in the plant received constant aluminum therapy for the past 10 years, i. e., they received five to six minutes of aluminum powder inhalation once a week during the whole year. A total of about 1650 mg. of aluminum oxide powder per man per year was used. Another 25% of the men received sporadic treatment; i. e., owing to illness, absences, and lack of enthusiasm, they missed many of their scheduled treatments. When the company first started to administer aluminum therapy, the men were put on frequent intensive courses of therapy, with intervening rest periods. After one year, however, it was deemed advisable to institute constant therapy at weekly intervals. All the men with a silicosis classification in Grades 3 and 4 received two or three treatments per week, totalling 600 to 700 minutes of therapy per annum as against an average of 230 minutes for those without silicosis or with incipient lesions only. As an additional aid in selected cases, I have, since 1950, used intermittent positive-pressure breathing administered by means of the MSA Pneumophor. Phenylephrine (Neo-Synephrine) hydrochloride and Alevaire were introduced into the patient's respiratory passages by this means immediately prior to each aluminum treatment session. This method was resorted to in all men with advanced silicosis or with marked symptoms.

To assess the influence of aluminum in the control of silicosis in this ceramics industry, the following criteria were applied: (a) symptomatic improvement, aggravation, or stasis; (b) radiological progression, arrest, or regression.

Of a total of 139 men who received aluminum therapy for a period of 10 years, the results were as follows:

	No. Cases
(a) Symptomatic Response.....	73
Unchanged.....	25
Improved.....	45
Worse.....	3
(b) Radiological Response.....	139
Unchanged.....	117
Improved.....	20
Progressed.....	2

Thus it appears that aluminum has a markedly beneficial effect in suppressing symptoms and in arresting radiographic advance of the lesions of the men subjected to study. For instance, of 73 men who had symptoms at the start of their course of therapy, 62% were improved at the end of 10 years, while only 34% showed no amelioration and 4% became worse in spite of therapy.

Radiologically the following results were obtained: Of 139 men who started aluminum therapy in 1944, 84% remained unchanged, 14% improved, while 2% progressed.

COMMENT

It was not possible to have adequate controls in this study because of management's desire that all employees should undergo aluminum therapy. The untreated group represents the employees of less than 10 years' work history and does not constitute a control group for the 10-year period. Many of these men entered the service of the company during the last eight years and hence do not fulfill the requirements of this study. Others left the industry during this period, and thus their cases have no statistical importance. The only control resides in the experience of the company management in

respect of the numbers of key and skilled men that were conserved after the period of aluminum therapy had been instituted as compared with the disturbing personnel losses annually experienced prior to this period. This improvement was also reflected in reduced disbursements for disability compensation. Another corroboration of the value of the method comes in the form of sustained enthusiasm by the men during the whole 10-year period and insistence on the part of the labor union that therapy must be continued.

SUMMARY

One hundred thirty-nine employees of a ceramics plant with a known silicosis hazard were subjected to aluminum therapy for a period of 10 years. The average amount of

aluminum used annually for the employees without advanced silicosis approximated 1650 mg. per case. Silicotics in the more advanced stages received up to three times this amount at the start of treatments.

The aluminum therapy appears to have an indisputably beneficial influence in suppressing symptoms, in arresting radiological advance, and in improving the functional reserve of ceramic workers.

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Some Experiences with Silicosis Control in Gold Mining

J. K. GODIN, M.E., Belleterre, Que., Canada

This paper deals with silicosis control measures and experiences in the gold-mining industry of the Province of Quebec where there are 16 straight gold-producing mines. All are located in the northwestern section, in the counties of Temiskaming, Rouyn-Noranda, Abitibi-East, and Abitibi-West. These mines handle a minimum of 4,500,000 tons of ore annually. The free silica content of this ore averages 70%. Of a total of 4150 employees, about 2900 are exposed to siliceous dust.

CONTROL MEASURES

In general, the control of silicosis has received in the gold mines of Quebec the attention which it warrants. The principal control measures are the following: medical supervision; ventilation; dust control, and aluminum powder prophylaxis.

Medical Supervision.—As required by the Quebec Mining Act, every employee in the industry must have a medical certificate, issued by medical officers appointed by the Workmen's Compensation Commission, which certifies that the applicant is free from diseases of the respiratory organs. Annual control examinations are also mandatory and necessitate issuance of a certificate which is renewed only if the employee is free from tuberculosis of the respiratory organs.

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The results of the annual examinations are made available to the employer concerned. This is a great help in prevention work in that any employee who shows a predisposition to a lung disease may be placed in a nondusty occupation.

Many of the mines required pre-employment and annual control examinations with chest x-rays even before such examinations with the accompanying certificates were required by law. When medical control became compulsory, workmen already employed whose chest x-rays revealed some abnormal condition, varying from slight fibrosis to some degree of silicosis, were given restricted certificates which enabled them to continue working at the mine where they were employed at the time of the certification. These men either were advised to leave the industry or were transferred to nondusty occupations. The solutions to some of the problems encountered were described at the 1952 Conference of the McIntyre Research Foundation by Fisher.*

Ventilation (Consult also Appendix A).—Adequate ventilation and dust suppression are primary factors in the prevention and control of silicosis. Ten of our sixteen gold mines have mechanical ventilation systems, while the other six are ventilated naturally. Most main fans are placed on surface, and special permission from the Department of Mines is necessary for the underground installation of a main fan. A shaft usually provides the return air circuit, especially at the smaller mines. In development headings and isolated sections, auxiliary ventilation is

* Fisher, R. S. M.: Examination, Practice, and Experiences Regarding Compensation and Certification, read before the McIntyre Research Foundation Conference, Noranda, Que., Jan. 28-30, 1952.

supplied by small compressed air or electric fans, exhausting or blowing through metal or rubberized tubing.

In the mechanically ventilated mines, the air circulated in one day averages 50 cu. ft. per minute per ton of ore mined. Air circulation through stoping areas varies between 600 and 4000 c. f. m., the average being 1500 to 2000 c. f. m.

The Department of Mines employs two ventilation engineers, one stationed in Quebec City and the other in Noranda. Their duties include conducting periodic surveys of the ventilation and dust-control systems in underground workings and crushing plants, making recommendations following these surveys, and conducting follow-up surveys. They are available also to assist in solving specific ventilation problems.

Some of the larger mines employ their own ventilation engineers. In such cases the government engineers verify the surveys and systems to the satisfaction of the Department of Mines.

Dust Control.—Primary crushing is done underground at many mines. This operation produces the largest dust concentrations that underground men must breathe. For maximum protection, good exhaust systems must be used and the dust-laden air removed to return air currents and not recirculated.

Large and dangerous amounts of dust are produced in underground scraping and slashing operations.† To keep dust counts at a minimum, the muck is continually wetted down during the working shift. This is complemented, especially in scram drifts,‡ by a good ventilation system.

† Slushing is a method of mechanical loading of ores. The scraper or slusher carries the load. It is pulled by a single drum hoist, operated by one man. Another man guides the slusher and pulls it back to the face.

Scraper loading employs a two-drum hoist, the scraper being pulled back to the face by a cable through a fixed tail sheave. Only one man is needed.

‡ A scam drift is an opening in a stope above the main haulage drift, generally at a right angle to it, whose purpose is to provide a passageway for ore from the stope to the haulage drift.

Great concentrations of injurious dusts are generated by blasting operations. Danger from this source is minimized by the fact that before men are allowed to return to the scene of a blast much of the dust is suppressed or removed. Water sprays are used for such purposes throughout the industry. A mist-like spray is produced through a combination of compressed air and water. The sprays are turned on at blasting time and are left in operation throughout the interval between working shifts, a period of from three to eight hours. The water spray minimizes the dust produced by the blast, wets the walls and muck pile, dissolves nitrous fumes, and humidifies the air. Miners are required to further wet the working face, walls, and muck pile with a standard water hose before beginning work in a freshly blasted area.

Drilling operations underground are further sources of dangerous dust concentrations. Although the concentrations are ordinarily not so high as in some other underground jobs, more miners are subjected to the dust during the whole drilling shift. Wet drilling is universal practice. Most mines require the automatic air-and-water throttle, which makes it practically impossible to start or drill a hole dry. The vented front head and oversized water tube are also in common use on present-day drills.

Ore pass dumps and drawpoints are further dust-producing locations. Most dumps have doors that are kept closed except when a train of cars is being dumped. This keeps the dust out of travelways. Water sprays have been tried at drawpoints but proved unsatisfactory. Ore drawn from stopes is ordinarily moist.

Underground samplers wear dust masks while cutting samples.§

§ Cutting samples is a procedure for taking a representative portion from a whole material for assay purposes. Underground, a sample is cut across a vein or ore face using a moil and single jack-hammer or more simply by means of a small hand pick. In a laboratory or assay-office cutting, a sample would entail putting crushed material through a sample splitter, which mechanically cuts a representative sample of the whole.

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Surface crushing plants are also sources of large quantities of dust. Most plants have satisfactory exhaust systems which remove the dust-laden air from discharge ends of crushers, from screening floors, and from ore transfer points.

Assay-office grinding rooms are equipped with exhaust systems. The operations which produce undesirable dust concentrations are crushing, riffing, pulverizing, and screening.

tains a high percentage of free silica, the average is below 5,000,000 ppcf. Dust concentrations increase with the rate of mining in a given area and the tonnage of ore and waste handled. The dust counts that have been most frequently met during mining operations are given in Table 1. For purposes of comparison, the base metal mines of northwestern Quebec are included in these figures, showing that some of these ores

TABLE 1.—Average Dust Counts in Metal Mines of Northwest Quebec

Operation	Machine	Dust Count, Mpcf	Comments
Drilling	Leyners and air-leg drills	1.0 to 4.0	Holes collared wet and drilled wet in drifts and stopes
Drilling	Leyners and air-leg drills	5.0 to 20.0	Holes collared dry for a few seconds; lack of adequate water pressure
Drilling	Stopers	10.0	Holes generally collared dry; samples taken in raises
Mucking	Rocker shovel	2.0 to 4.0	Muck wet; samples taken in drift headings and drawpoints
Mucking	Rocker shovel	5.0 to 10.0	Dry ore or waste
Scraping or shuffling	Air slusher	2.0 to 5.0	Ore or waste kept wet
Scraping or shuffling	Air slusher	5.0 to 15.0	Dry muck
Scraping or shuffling	Electric slusher	2.0 to 10.0	Ore moist; stopes well ventilated
Scraping or shuffling	Electric slusher	5.0 to 40.0	Dry ore or waste; high counts produced in spite of good ventilation
Chute pulling	Hand-operated gates	1.0 to 4.0	Ore moist
Chute pulling	Arr-gate or chain-gate chutes	1.0 to 5.0	Ore moist
Chute pulling	Arr-gate or chain-gate chutes	Up to 20.0	Very dry ore
Chute blasting		2.0 to 5.0	Samples taken about 5 min. after blast
Secondary breaking	.. (sand blasts)	5.0 to 10.0	In well-ventilated grizzly drifts and screen drifts after smoke had cleared away
Secondary breaking	.. (sand blasts)	20 to 40.0	In smoke cloud exhausted from grizzly or screen drifts
Underground crushing	Jaw crusher	3.0	In crushing room; good dust-collecting system; exhaust piped to shaft; exhausted air being replaced by fresh air
Underground crushing	Jaw crusher	10.0 to 15.0	Dust-collecting system but exhaust air re-circulated
Underground crushing	Jaw crusher	Over 25.0 to 80.0	Without any dust-collecting system; lower count obtained with very wet ore
Ship loading	Measuring pocket	2.0 to 10.0	Lower count obtained with wet ore and good draft through loading station

In taking dust samples, the Department of Mines engineers use the midjet impinger. The samples are counted on a microprojector at a magnification of $\times 1000$. There is no acid treatment given to the dust samples; so all the dust particles are counted. The maximum allowable concentrations are 5,000,000 particles per cubic foot (ppcf) of air for dust with more than 50% of free silica and 10,000,000 ppcf of air for dust with less than 50% of free silica.

Underground dust concentrations have varied from a low of 600,000 ppcf to a high of 75,500,000 ppcf, the average being about 7,300,000 ppcf. In mines where the ore con-

have as high a free silica content as the gold ores. Mining methods used are much the same.

The dust counts in naturally ventilated mines were not higher than in the mechanically ventilated ones, probably because mining is done at a slower pace. However, traces of carbon monoxide can often be detected in the general atmosphere of the naturally ventilated mines, especially during the summer months when natural ventilating pressures are often negative.

In crushing plants the lowest dust count was 600,000 ppcf of air, and the highest

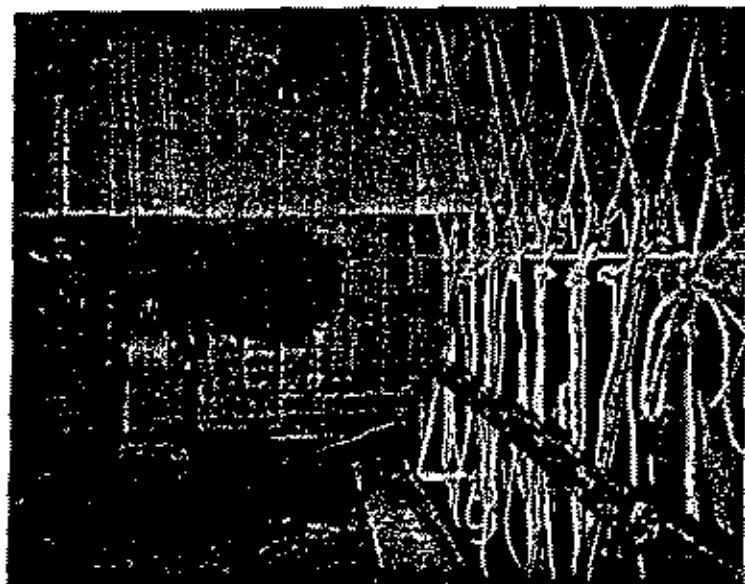


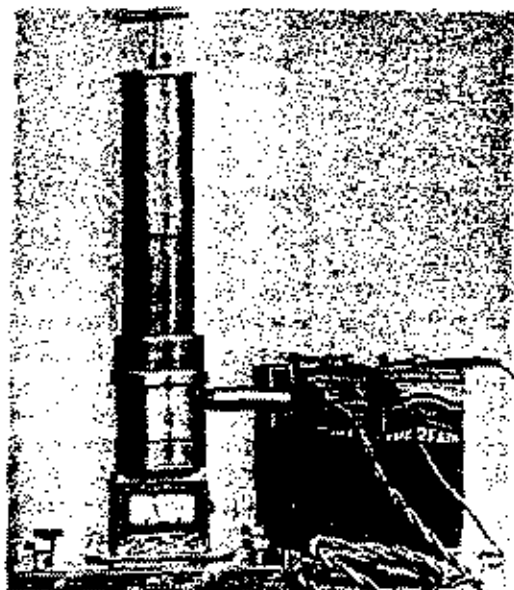
Fig. 1.—Dispersal of aluminum powder by compressed air ejectors in mine-clothes section of change-house.

was 106,000,000 ppcf. Crushing plants with very good exhaust systems have less than 3,000,000 ppcf of air in the general atmosphere of the plant during the summer months and less than 5,000,000 ppcf during the winter months. Dust counts are always higher during the winter months because windows and doors are kept closed. They are higher too when the crushing machinery is first started and vary according to whether the ore is wet or dry. Crushing plants with poor exhaust systems have counts ranging from 10,000,000 to 20,000,000 ppcf of air in the summer to 40,000,000 ppcf or more in winter. In these plants the employees are required to wear dust masks until recommended improvements are made.

In mills dust concentrations are usually well below 5,000,000 ppcf of air and do not present any hazard. In assay-office crushing rooms well-designed exhaust systems keep the dust counts below 5,000,000 ppcf of air. However, if the employee is careless in cleaning pulverizers by means of compressed air jet, the count may be raised to 10,000,000 ppcf of air. Since the dust-producing work lasts for only an hour or two, the employees wear dust masks.

Aluminum Powder Treatment.—Even with good ventilation and dust-control systems, not all harmful dust is removed from the air that mine workmen must breathe. For this reason, 12 of the 16 gold mines are today using aluminum powder as a prophylactic measure. A minimum of 2900

Fig. 2.—Device for measuring powder concentrations used in aluminum powder treatments.



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TABLE 2.—Silicosis Cases Compensated by the Quebec Workmen's Compensation Commission 1931-1953

Industry	Cases, No.	Per Cent of Total
Gold mining.....	10	9
Base-metal mining.....	9	8
Diamond drilling.....	4	3.6
Others.....	166	88

men are employed by these 12 mines, and all who are exposed to siliceous dust in their work receive the aluminum powder treatments.

The aluminum powder is dispersed by compressed air ejectors in the mine-clothes section of the change-house, as shown in Figure 1. A discharge pressure of about 40 lb. per square inch is used, corresponding to a line pressure of 100 lb. Windows and doors are kept closed during the dispersal phase. The powder concentration recommended is a minimum of 20,000 particles per cubic centimeter for a 10-minute inhalation period or 10,000 particles per cubic centimeter for a 20-minute session. The powder concentrations are measured by means of a filter-paper sampler calibrated against the thermal precipitator (Fig. 2). The basis of dispersal is 1 gm. of powder for each 1000 cu. ft. of room content where the average period of exposure to the powder is 10 minutes. If the exposure period is to be 20 minutes, the amount of aluminum to be used is halved. Treatments are usually given when the workmen are coming on shift, but in some cases it has been found more satisfactory to administer the aluminum as the men come off shift.

SILICOSIS RATES

From 1931, when silicosis was first recognized as an industrial disease in Quebec, until 1953, the Quebec Workmen's Compensation Commission compensated 230 cases, 116 cases being complicated silicosis (tuberculosis present) and 114 cases being uncomplicated silicosis (Consult also Appendix B). The distribution is shown in Table 2. Nine of the twenty gold mine compensation

TABLE 4.—Gold-Mining Silicosis Compensation Cases: Living Miners

Stage of Silicosis	Cases, No.	Average Age When Compensated, Yr.	Average Exposure, Yr.
Primary silicosis.....	7	47.7	19.0
Secondary silicosis.....	2	43.5	12.0
Complicated silicosis.....	2	43.5	11.0

cases are now deceased; particulars are given in Table 3. Particulars of the 11 living cases are given in Table 4. Table 5 shows the years in which 20 cases were recognized as claims.

Disability in these cases has varied from 15% to 100%. Applicants for pension are referred to the Silicosis Referee Board of the Workmen's Compensation Commission by the local examining physicians. The procedures of this Board in examining claimants and establishing the degree of disability were described at the Noranda Conference of the McIntyre Research Foundation by Dr. Vidal,|| the Chairman of this Board.

ROLE OF ALUMINUM IN SILICOSIS PREVENTION

Because of the policy of management to attempt to suppress dust by every known or possible means, it is somewhat difficult to formulate a statistically valid indication of the specific role of aluminum in the control over the silicosis hazard.

The working force is over 4000 men, and about 2900 of these are exposed to siliceous

|| Vidal, J. A.: Examination Procedures for Silicosis as Practiced by the Workmen's Compensation Commission of Quebec, Canada, read before the McIntyre Research Foundation Conference, Noranda, Que., Jan. 28-30, 1952.

TABLE 5.—Years When Gold-Mining Compensation Cases Were Recognized

Year	Cases, No.	Year	Cases, No.
1941.....	1	1948.....	0
1942.....	1	1949.....	2
1943.....	1	1950.....	2
1944.....	4	1951.....	0
1945.....	3	1952.....	0
1946.....	4	1953.....	0
1947.....	2		

TABLE 3.—Gold-Mining Silicosis Compensation Cases: Deceased Miners

Stage of Silicosis	Cases, No.	Average Age at Death, Yr.	Average Exposure, Yr.
Uncomplicated silicosis.....	2	51.0	17.0
Complicated silicosis.....	7	50.8	13.4

dust. To date we have had 20 compensation cases of silicosis. It is impossible to estimate how many men working under restricted certificates will eventually become claims. Undoubtedly some will; many will not. However, from the results to the present time, it is evident that the control effort has been worth-while.

Since 1947, the sharp decline in new cases of the disease in Quebec gold mines has been intriguingly coincident with the general adoption of aluminum powder prophylaxis in this industry. No other method of control was introduced at that time which can satisfactorily account for this change. A review of the problem at a later date may clarify the whole issue. Meanwhile, however, personal conversations and correspondence with the other gold mine managers in Quebec have confirmed the general conviction that the beneficial influence of aluminum powder has been sufficiently impressive to continue its use. No ill effects have, moreover, been recorded from the aluminum exposures.

For assistance received in the preparation of this paper, I express my sincere thanks to the following: Mr. Eugene Larochelle, Secretary-General of the Quebec Metal Mining Association; Mr. M. O. Lafontaine, Assistant Chief Inspector of Mines for the Province of Quebec; Dr. J. E. McArthur, Medical Officer for the Quebec Workmen's Compensation Commission, and the mine managers of the gold and base-metal mines of northwestern Quebec.

APPENDIX A

EXTRACTS FROM REGULATIONS FOR THE SAFETY AND PROTECTION OF WORKMEN IN MINES AND QUARRIES, ESTABLISHED BY ORDERS-IN-COUNCIL IN VIRTUE OF THE QUEBEC MINING ACT

Ventilating Fans

All fans except auxiliary fans shall be above ground and shall be reversible and all fans and structures containing the same shall be fireproof.

Ventilation of Workings

The ventilation in every mine shall be such that the air in all its workings that are in use or are to be used by workmen shall be free from dangerous amounts of noxious impurities and shall contain sufficient oxygen to insure the health of anyone employed in any such mine. In any mine workings where such conditions cannot be obtained by natural ventilation, means for mechanical ventilation shall

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be provided and kept in operation until such workings have been abandoned or until satisfactory natural ventilation shall have been brought about therein.

Safety and Sanitary Precautions

All buildings must be built and kept in such a manner as to secure the safety of employees and shall be well lighted and ventilated. The operator shall take necessary measures to insure removal of noxious gases and dusts.

Masks

The operator must supply to workers masks of a type approved by the Minister and designed to protect workers who are exposed to dust, gas, and irritating and dangerous fumes.

APPENDIX B

EXTRACTS FROM THE QUEBEC WORKMEN'S COMPENSATION ACT

106. In this act,

1.) the word "pneumoconiosis" shall mean a pathological condition of the lungs, due to breathing air containing siliceous dust and characterized anatomically by generalized fibrous changes in both lungs; such word includes, especially, the diseases known under the names of "silicosis" and "asbestosis."

2.) the expression "siliceous dust" shall mean silica dust or other compounds of silicon, including asbestos. [21 Geo. V, c. 100, s. 105a; 2 Geo. VI, c. 89, s. 1; 7 Geo. VI, c. 27, s. 6.]

107. In order that "pneumoconiosis" may be considered an industrial disease within the meaning of this act, the workman must have been actually exposed to the inhalation of siliceous dust in the course of his employment in the Province, during periods the total duration whereof amounts to at least five years. [21 Geo. V, c. 100, s. 105b; 2 Geo. VI, c. 89, s. 1; 7 Geo. VI, c. 27, s. 5.]

DISCUSSION

ON PAPERS BY MR. DWORSKI, DR. IRWIN, DR. OSMOND, DR. PERRY, AND MR. GODIN

Prophylaxis and Therapy of Silicosis by Means of Aluminum

DR. PAUL G. BOYARD: I have been particularly interested in silicosis for three decades and became interested in aluminum therapy about 1944. During the past 10 years, I have thus had an opportunity of watching x-ray films of some 4000 or 5000 persons exposed to quartz dust, some of whom have also been under treatment by means of aluminum therapy. I have found a decrease in the rate of progression of silicosis among those who have been treated with aluminum powder. I think that this is an interesting and a prophetic thing to find after such a brief study, as it takes from 25 to 30 years to pro-

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duce silicosis. The statement from Morris Dworski's discussion which impressed me most particularly was that possibly aluminum compounds are good for more than prophylaxis, since they help to eliminate the immature nodules in the established case of experimental silicosis.

DR. T. L. SKIRMAN: Have there been any studies in which a group of men receiving aluminum therapy were paralleled by a control group in the same industry?

DR. L. M. D. OSMOND: I do not know of any such studies. We have a potential control group in this plant, and I tried very hard to get five or six men in for lung function studies. They were not available.

DR. JOHN SUMMERS: What type of pulmonary function apparatus did you use for your lung function studies, and what kind of intermittent positive-pressure machine?

DR. F. GREGOIRE: We followed the standard methods evolved by Dr. George Wright, of Saranac Lake, in his studies on the pulmonary disability of the pneumoconiosis and placed greatest reliance on the blood gas levels at rest and on exercise. We also studied the limits of the capacities of the men to work and compared this capacity with the predictable capacities of normal men. We also evaluated the percentage improvement of the vital capacity, maximum breathing capacity, and also arteriolar blood gas changes when the subjects breathed oxygen while performing work.

DR. KELLER JOSEPH: What does aluminum and prevention therapy cost a company, and under what conditions may one use the method?

DR. J. W. G. HANNON: There are one or two requirements that must be fulfilled before a company can use aluminum. First, it must be proved that management is making every effort to reduce the dust of the plant to the practical working minimum. Second, there must be a medical control program. Third, there is a licensing fee of \$1.00 per year per each man who is exposed to quartz. These dollars are paid to defray the expenses of the McIntyre Research Foundation in administering the patent, and any surplus must be dedicated to further research in industrial pulmonary diseases, chief of which is silicosis.

MR. T. C. WATERS: I'd like to ask Dr. Schepers whether or not in his opinion as of this time the use of aluminum therapy either inhibits or retards the development of silicosis, whether it is safe to employ, and whether this type of expedient may be the ultimate solution of the problem of silicosis.

DR. G. W. H. SCHEPERS: The Saranac Laboratory has already produced conclusive experimental proof that in some forms aluminum is an effective prophylactic against silicosis. The issue that re-

mains in doubt is whether the results of experiments with guinea pigs may be extrapolated to man. The clinical reports by the McIntyre Foundation on the prophylactic use of aluminum have all been favorable. They have, however, had the flaw that no proper controls were set up, and there are some who reason that the simultaneous improvement in industrial hygiene in the plants where aluminum was introduced was the cause of the improved silicosis statistics. This confusion of issues is regrettable. The problem could have been solved in South Africa, where excellent control facilities could have been established, but South African authorities were prejudiced against the method by the premature criticism which emanated from Canada and the United States. Two of the main objections which have been raised against the employment of aluminum have been that it might facilitate the development of tuberculosis and that the aluminum dust may itself cause a pneumoconiosis.

There is no clinical proof that aluminum provokes tuberculosis when used as a prophylactic. Tuberculosis rates in Canada have gone down, not up, in spite of the use of aluminum. Those who use the method would surely not be so callous as to continue to use it if they suspected that it provokes tuberculosis. The Saranac Laboratory has shown that overwhelming exposures to aluminum hydroxide and metal powder, probably by lowering tissue resistance, mildly activate tubercle bacilli of the attenuated R₁ human strain found eminently suitable to probe the capacity of inhaled dust to facilitate the development of progressive tuberculosis. The lesions resulting from such concurrent exposure to aluminum dust and infection by R₁ bacilli are transient and probably amenable to present-day therapy and therefore very different from the tuberculosis which complicates quartz exposures. Moreover, the tuberculogenic propensity only showed itself when experimental exposures to aluminum were excessive. When used in amounts comparable to the quantities to which the men are exposed for purposes of prophylaxis, the aluminum does not activate tuberculosis.

We do not know much about the so-called clinical cases of aluminosis. Their occurrence has been limited to but a few German wartime industries. The pulmonary lesions may have been due to contaminants of aluminum, as, for instance, stearin. No disease of comparable nature has been caused in animals.

I could not say whether aluminum is going to be the ultimate answer to the problem of silicosis. The first and most important method of prevention remains dust control combined with proper medical supervision. But there are certain circumstances in which quartz inhalation cannot be avoided. As we have prima-facie evidence that aluminum can protect animals from the effects of quartz and as we

have no adequate reason to suspect that aluminum in the recommended dosage can cause harm, why not at least try it in cases of silicosis, while we know of nothing else that can serve as a certain prophylactic? Certain exceedingly dangerous quartz derivatives and amorphous silicas have also found their way into the modern industrial environment. Means must be found to protect personnel against their deleterious effects, and, if engineering cannot but aluminum will do so, we have at least one method to try.

MR. T. C. WATERS: Are the benefits reported by patients on aluminum therapy not merely psychological?

DR. G. W. H. SCHREKES: Psychological support is a most valuable adjunct to any form of medical treatment; indeed, it is an objective of medical therapy. Men who have been exposed to aluminum report rapid and marked improvement in well-being. It is possible that this improvement may be imaginary. It is equally possible that the aluminum helps to counteract the toxic action of the accumulated quartz. The experiments of Berry and Christie

purporting to show that psychological improvement constitutes the only benefit to be derived from aluminum therapy are not conclusive, as they did not prove that their control substances were themselves pharmacologically inert. The resistance to the concept that aluminum may help as a therapeutic agent stems naturally from the apparent permanence of the mature nodule. I do not believe aluminum can take away collagenous nodules. There is, however, much more to silicosis than the mere development of nodules. Prolonged quartz inhalation leads to bronchitis, emphysema, and pulmonary vascular disease. Even though aluminum cannot resolve collagenous nodules which have already formed, if it can but alleviate bronchitis and emphysema or prevent the superposition of cor pulmonale, while retarding the formation of new nodules, its introduction will have been of great benefit to the employee. After all, except in the more advanced stages, the silicotic is not disabled by the nodules in his lung but rather by the above-mentioned functional mechanisms, which are in a measure reversible and therefore amenable to therapy.

Reaction of Chromium Compounds with Body Tissues and Their Constituents

A. M. BAETJER, Sc.D.
C. M. DAMRON, Ph.D.
J. H. CLARK, Ph.D.
and
V. BUDACZ, Ph.D., Baltimore

Epidemiological studies * have shown that the rate of bronchogenic carcinoma is significantly higher in men who had been exposed to high concentrations of chromium compounds in the chromate-chemical manufacturing industry than in comparable control groups. In order to study the possible role of chromium compounds in lung cancer, two types of investigations were undertaken in this laboratory: (a) studies of the incidence of lung tumors and other pathological changes in several species of laboratory animals upon exposure to chromium compounds and (b) chemical studies on the distribution of chromium in men and animals following exposure to these chemicals and the reaction of these compounds with body tissues and their constituents. The preliminary results from the lung tumor studies were presented at the Sixth Saranac Symposium. The preliminary results of the biochemical studies will be reviewed in this presentation. The data are not complete because the experiments are still in progress.

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Department of Environmental Medicine, School of Hygiene and Public Health, The Johns Hopkins University.

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* References 1 to 5.

The cancers which have occurred in the chromate workers have been located entirely in the respiratory tract. As far as is known, cancers have not occurred in the skin or nasal septal membrane of these workers, although skin ulcers and perforation of the septum are very common in persons exposed to chromates. Cancer of the gastrointestinal tract also has not been reported, although these workers must have swallowed a considerable amount of inhaled dust. Another characteristic exhibited by some of these cases was a relatively long latent period between the end of exposure and the appearance of the cancers. In view of these facts, experiments were undertaken to determine the following: (a) whether chromium would be retained in the lungs or would be distributed to other tissues after introduction into the respiratory tract by inhalation or injection; (b) whether the presence or absence of cancer is related to the concentration of soluble and/or insoluble chromium in the lungs; (c) whether the lungs have a special affinity for chromium as compared with other body tissues, and (d) what part of the cell is affected by chromium and what reaction chromium compounds have with the cell constituents. The biochemical studies were planned to elucidate these various problems.

DISTRIBUTION OF CHROMIUM IN BODY TISSUES FOLLOWING EXPOSURE TO CHROMIUM COMPOUNDS

The first series of experiments included analyses of tissues from chromate workers who had died with and without lung cancer and analyses of tissues from animals which

had been exposed to chromium through intratracheal, intraperitoneal, or intravenous injection of hexavalent and trivalent chromium salts.

Human Cases.—Lung tissue and, in some cases, other tissues were obtained at the time of pneumonectomy or autopsy from 10 men who had worked in the chromate chemical manufacturing industry. Of these cases, six had bronchogenic carcinoma, whereas four had no signs of any malignant neoplasms. The tissues were analyzed for both soluble and insoluble chromium.† Lung tissue from two persons with no known exposure to chromium also was analyzed.

Although the data from these human cases are meager and variable, certain general conclusions appear to be valid.

1. The presence or absence of cancer did not appear to be related to the average concentration of the acid-soluble or acid-insoluble chromium found in the lungs at the time the cancer became evident. This conclusion was based on a comparison of the cancer cases with the noncancer cases and a comparison of the portions of the lungs where the cancers were located with the noncancerous areas in the individual cases. However, the concentration in different areas of the lungs varied greatly, and the concentration in the area at the time of onset of the cancer was not known. The concentration of chromium in the bronchi was lower than that in the lungs.

2. The average concentration of acid-soluble chromium in the lungs varied approximately with the duration and extent of exposure. On the other hand, the concentration of the acid-insoluble chromium did not show any very definite relation to either of these factors. The most significant finding was the presence of considerable water- or acid-soluble chromium in the lungs many years after the end of exposure.

† The micromethod used for the analysis of chromium in these experiments was a modification of the diphenyl carbazide method developed in this laboratory by Budacz.

3. The concentration of chromium in the tumors varied greatly both in different areas of the same tumor and in the different cases but was lower than that in the lung tissue.

4. In all the chromate cases, the concentration of soluble chromium per gram of wet or dry tissue or ash was greatest in the lungs. The concentration of soluble chromium in the other organs analyzed was variable and relatively low. Acid-insoluble chromium was not found in any organs except the lungs, tracheobronchial lymph nodes, and nasal cartilage.

Animal Experiments.—In order to study the fate and distribution of chromium compounds introduced into the lungs, a number of guinea pigs were injected intratracheally with solutions of sodium chromate or potassium dichromate. One or two animals were killed immediately after injection and thereafter at intervals up to 140 days. The urine, blood, and soft tissues were analyzed for chromium.

During the first few hours following the injection of the soluble hexavalent chromates, some of the chromium passed rapidly from the lungs into the red blood cells and into the urine. After this initial period, the rate of elimination of chromium from the lungs decreased, and the excretion in the urine ceased. A considerable amount of chromium remained in the lung tissue for some weeks.

The total amount of chromium in the blood cells decreased rapidly in the period between 30 and 60 days after injection as the blood cells were destroyed. Although the total amount in the spleen was small, the concentration per unit weight increased rapidly during the first 30 days after injection and remained high for some weeks, undoubtedly owing to the destruction of the red cells.

In the analyses completed up to the present time, no measurable amount of chromium has been found in the bones.

Experiments are now in progress to study the retention in the lungs and distribution to other tissues of trivalent chromic chloride when injected intratracheally.

REACTION OF CHROMIUM COMPOUNDS WITH BODY TISSUES

AFFINITY OF LUNG TISSUE FOR CHROMIUM

In order to determine whether lung tissue has a special affinity for chromium, sodium chromate and chromic chloride were injected intravenously and intraperitoneally into guinea pigs. The animals were killed 24 and 72 hours after injection, and the tissues analyzed for chromium. The lungs did not remove more than a very small fraction of the total amount of chromium which reached this organ through the blood, and the concentration of chromium in the lungs was no higher than that in the liver or spleen. The amount of chromium taken up by the lung tissue from the blood was approximately the same as that which remained fixed in the lungs four months after intratracheal injection of soluble chromates.

Since bronchogenic carcinoma has occurred in man in response to chromium chemicals but has not been produced in animals, it seemed likely that the lung and bronchial tissue of man might have a greater affinity for chromium than that of other species. This possibility was investigated by suspending fresh slices of human, rat, and guinea pig lungs in dilute solutions of Na_2CrO_4 , $\text{K}_2\text{Cr}_2\text{O}_7$, and CrCl_3 . Liver slices were similarly treated. Preliminary results indicate little quantitative difference in the behavior of lung tissue as compared with liver or in the behavior of lung tissue from different species toward CrCl_3 . Human lung tissue seems, however, to bind hexavalent chromium to a less extent than does the lung tissue of guinea pigs and rats. Further experiments will be necessary to see whether this difference is significant.

These experiments indicate that the lungs do not contain any component which binds chromium to a greater extent than other tissues and that lung tissue of man does not bind trivalent cationic chromium differently from the manner in which lung tissue of the animals tested binds such chromium. There may, however, be a real difference in the manner in which the lung tissues of the various species react with hexavalent anionic chromium.

REACTION OF CHROMIUM WITH PROTEINS AND NUCLEIC ACIDS

Combination of Chromium with Nucleic Acids.—A study of the chemical reaction of hexavalent and trivalent chromium compounds with pure deoxyribonucleic acid and ribonucleic acid was made. At a pH of 7, an immediate precipitate was formed when CrCl_3 was added to either of the nucleic acid solutions, but no reaction was observable with the hexavalent chromates at this pH, and no precipitate formed until the pH was lowered to the point where the nucleic acids themselves precipitate. Analysis of the reaction product of CrCl_3 with the nucleic acids indicated that two moles of chromium combined with one mole of acid.

Reaction of Chromium Chemicals with Proteins.—The reaction of the hexavalent chromium salts, sodium chromate and potassium dichromate, and the trivalent salt, chromic chloride, with bovine plasma albumin has been studied. Aqueous solutions of this albumin have their isoionic point at pH 5.4. When these hexavalent chromates (1%-3%) were added to protein solutions at a pH above 5.4, the solutions remained clear even after the chromate was removed by dialysis, showing that the protein was not denatured by contact with hexavalent chromates at a pH above 5.4. However, the hexavalent chromates were partially reduced to the trivalent state by contact with the protein, as some trivalent chromium was found in the dialysate. On the other hand, when hexavalent chromates were added to the albumin and the pH adjusted to a value below pH 5.4, a heavy white precipitate was formed. When the chromium was removed as completely as possible by prolonged dialysis, the residual precipitate contained approximately 1 mole of chromium per mole of albumin, was stable over a wide pH range, and was presumably denatured.

When trivalent CrCl_3 was added to the albumin solution at a pH greater than 5.4, a precipitate was formed containing protein as well as chromic hydroxide. At a pH below 5.4, the solutions remained clear, but when

the chromium was removed by dialysis, a precipitate was formed, indicating denaturation of the protein. This precipitate contained 16 to 18 moles of chromium per mole of albumin. Although such a reaction would not occur at the normal pH of the body, it might occur under some local conditions of reduced pH, such as in inflammatory areas.

Dr. Baetjer is indebted to members of the Department of Pathology of the Johns Hopkins Hospital, to Dr. Russell S. Fisher, Chief Medical Examiner of Maryland, and to others for providing the tissues included in this study.

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Study of Surface Properties of Quartz Dust

A Biochemical Contribution

LESTER D. SCHEEL, Ph.D., Saranac Lake, N. Y.

The demonstration by Gye and Purdy* in 1922 that colloidal silica was toxic led to the theory that the fine particles of silica dust dissolve in tissue fluids and cause precipitation of a toxic colloidal silica. The first reaction which must occur at the surface of quartz particles to bring about such a result would be one of hydration.



Scheel, Fleischer, Klemperer, Smith, and Van Riper† found that if quartz particles 1μ to 3μ in size are exposed to distilled water for 15 days continuously, 0.18 mg. of silica is dissolved. If, however, the solvent is changed each day, 0.22 mg. of silica is dissolved in 15 days. If instead of distilled water a salt or a protein solution is used as the solvent, the amount of silica dissolved is much larger. To test the possibility that the rate of solution of silica may be inversely proportional to the silicic acid concentration in the solvent, the following experiment was performed.

Pyrex glass was fractured in a mortar and sieved to remove the fine and coarse particles. The fragments, about 1 mm. in diameter, were placed in a glass tube and washed alternately with 2% sodium carbonate solution and 1% hydrochloric acid until the amount of glass dissolved by exposure for five minutes to the 2% sodium carbonate solution became constant. Small amounts of sodium silicate were then added to the 2% sodium carbonate solution, and the amount of silica dissolved in five minutes was determined.

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The Saranac Laboratory.

*References 1 and 2.

†References 3 and 4.

The results of these experiments are given in Figure 1. These results show that the rate of solution of the glass particles is decreased by the addition of the sodium silicate, even though the solution is alkaline and the rate of solubility of the glass is greater than the rate of solubility of quartz.

The "soluble silica" theory may be a possible one if in the living tissue the silicic acid were to combine with some constituent and accumulate until gel formation took place. To test this idea, protein solutions contained in a dialysis bag were exposed to silica solutions and samples of the silica solution were analyzed at intervals until no further change in silica concentration took place. In these experiments it was found that there was no demonstrable interaction of protein molecules with monomolecular silicic acid. However, it could be demonstrated that if colloidal silicic acid formed in the protein solution protein precipitation took place after about two days.

It then became necessary to determine the solubility of silica gel.

To do this, dry silica gel was suspended in water, and the solvent analyzed at intervals for silica content by the molybdate blue method. In another bottle a solution of sodium silicate which had been titrated to pH 7 was allowed to gel and come to equilibrium. The colloidal silicic acid was removed by filtration through a dialysis membrane in a centrifuge and the filtrate analyzed.

The results of this study are presented in Figure 2. The equilibrium value of 166 mg. per liter of soluble silicic acid in equilibrium with silica gel exceeds the values reported by King* for the solubility of silica in body fluids.

Animal experiments conducted by The Saranac Laboratory have failed to reveal any toxicity due to silica gel or molecularly dispersed silicic acid, because the silicic acid is rapidly eliminated from the body

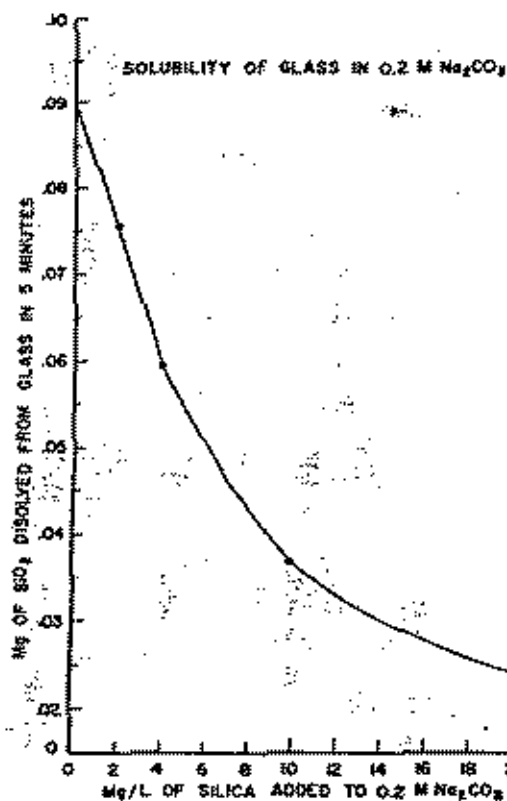


FIGURE 1

fluids by the kidney. The transformation of silicic acid solution into colloidal silica gel is inhibited by the presence of alkali salts and protein in the solution. It is extremely unlikely that solution of particulate silica could produce a concentration of silicic acid sufficient to form colloidal silica at any point within the animal body. It became necessary, therefore, to study the surface reactions of quartz particles to determine the toxic action of this material when trapped in animal tissue. The nature of the pathologic lesion, a nodular growth limited to an area containing particles, suggests that the tissue stimulation is limited to the area containing the particles.

In considering the experimental approach to a study of the surface reactions of quartz particles, definition of the nature of the surface of the quartz is pertinent. The crystalline structure provides a uniform surface pattern in all particles. Further, each oxygen atom is linked to two silicon atoms, and when the crystal is fractured, the new surface created must undergo a readjustment of forces within the surface. This readjustment of forces within the particle surface results in a certain residual state which is called surface

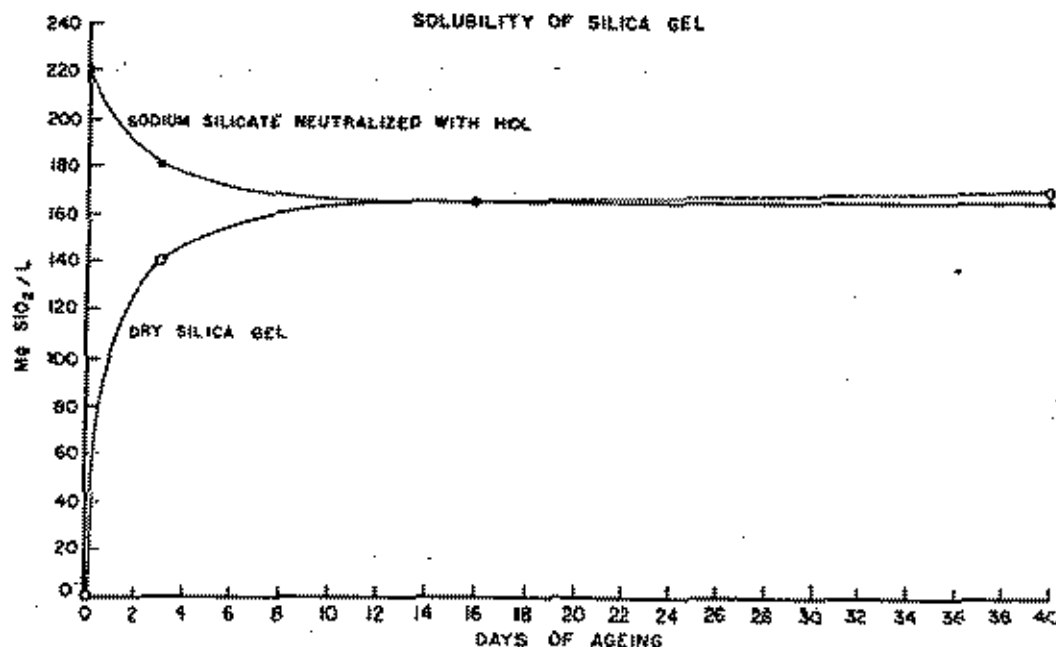


FIGURE 2

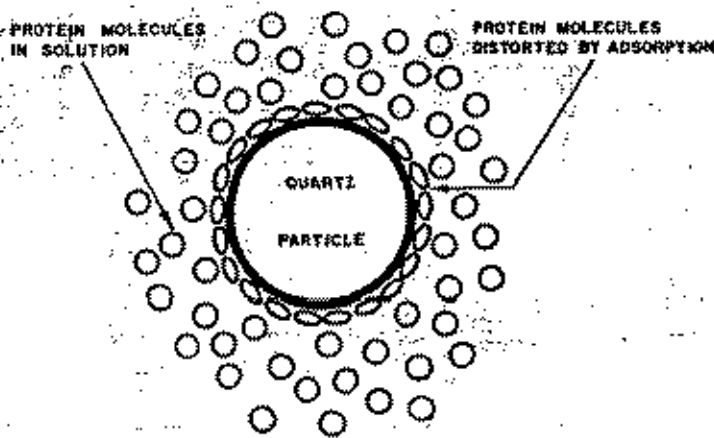
SURFACE PROPERTIES OF QUARTZ DUST

tension or surface free energy. The quartz surface has one component of this surface free energy which can be characterized. This component is the negative charge of the particle in water solutions. This surface charge is a colloidal characteristic which is a static expression of the nature of the distribution of forces in the surface of the particle. However, this static charge can exert a field effect on polarizable materials, just as an electrically charged condenser can orient a polarized metal object.

sorbed will be proportional to the concentration of the protein solution. In 0.01% crystalline egg albumen solution, about 1 mg. of protein is adsorbed per gram of 1μ to 3μ quartz particles. If the concentration is increased to 5% egg albumen, the amount of protein adsorbed increases to 120 mg. of protein per gram of particles.

By altering the hydrogen ion concentration of the protein solution, it is possible to give the protein molecule either a negative or a positive charge. Thus one can test the effect

DISTORTION OF PROTEIN MOLECULES BY ADSORPTION



Protein molecules are polarizable in an electric field and as such might be affected by the surface charge of the quartz particle. To test this idea, crystalline egg albumen was chosen, because it is a protein obtainable commercially in a reproducible state of purity. Further, egg albumen is a protein which produces in the rabbit specific antibodies to the native and to the denatured state. Thus it might be possible to determine the state of the protein on the surface of the particle if adsorption took place.

Our previously reported experiment⁴ showed that quartz particles 1μ to 3μ in diameter can tenaciously adsorb protein to their surface and that the amount of protein ad-

of the charged silica surface on the adsorption of protein molecules bearing various charged states. The alteration of hydrogen ion concentration in the suspending solution will not affect the nature of the silica surface forces. The amount of protein adsorbed may be expected to increase uniformly as the negative charge on the protein decreases. When the protein molecule becomes positively charged, the amount of protein adsorbed increases sharply. Thus the charge on the surface of the silica particle plays some part in the adsorption of protein molecules to the surface.

In an attempt to characterize the nature of the protein adsorbed by the quartz particle,

rabbits were immunized to native and to denatured egg albumen. Quartz particles were then coated by exposure to native albumen solutions, washed thoroughly, and tested for agglutination by exposing them to the antibodies of immune rabbit serum. It was found by this test that the particles reacted with both native and denatured albumen antibodies.

To determine whether the alteration in the protein characteristics during adsorption on the surface causes a permanent change in the protein structure, some of the adsorbed egg albumen was eluted and tested with the immune rabbit serum. The eluted egg albumen was found to react only with native antibodies.

Thus the structure of egg albumen adsorbed to the particle surface has been shown to be altered only during the adsorbed state. This effect may be schematically presented as shown in Figure 3.

Thus in the adsorbed state the protein molecule is distorted to such an extent that the surface presented to the immune antibodies has lost its structural specificity.

This description of protein adsorption and alteration is evidence for the formation of a new surface on the inhaled quartz particle which is presented to the body as a result of the protein content of the interstitial tissue fluid. In an effort to determine the effect of the protein coat on the tissue reaction, the following experiment was carried out.

Quartz particles 1 μ to 3 μ in diameter were suspended in a saline solution at a concentration of 1 mg. per milliliter by boiling under a reflux condenser for four hours. The particles were then coated with rabbit serum by adding 2 ml. of serum to 10 ml. of the suspension of quartz particles and agitating the mixture gently for eight hours. The suspension was centrifuged and the supernatant solution decanted and discarded. The protein-coated particles were washed six times by resuspending them in 10 ml. of saline solution and separating them from the wash by centrifugation. The washed particles were next suspended in saline at a concentration of 10 mg. per milliliter, and this suspension was injected subcutaneously into the rabbit ear so that 1 mg. of

particles was placed at each injection site. A similar quantity of uncoated quartz particles from the same batch originally suspended in saline was injected subcutaneously into the other rabbit ear at the same time. The site of injection was removed at intervals from the rabbit ear by means of a sharp cork borer, fixed, sectioned, and examined microscopically.

The result of this experiment confirmed cytobiologically the presence of the adsorbed protein layer.⁴

SUMMARY

Evidence for the solubility and surface-action theories of the action of quartz is reviewed.

The rate of solubility of glass is greater than that of quartz.

There is no demonstrable interaction between protein molecules and monomolecular silicic acid.

Silicic acid is rapidly eliminated via the kidney, thus preventing its concentration to form colloidal silica.

Quartz particles have, because of their surface characteristics, the faculty of adsorbing and denaturing protein.

The effect of this adsorbed layer of protein on animal tissues was experimentally investigated.

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Fig. 1.—Reaction to quartz introduced subcutaneously into rabbit ears (low power). *A*, uncoated quartz: seven hours; initial focus of reaction. *B*, protein-coated quartz: seven hours; initial reaction resembles Field *A*. *C*, uncoated quartz: nine days; limited, circumscribed, semi-necrotic residuum. *D*, protein-coated quartz: nine days; expanded, proliferative, fibrocellular granuloma.

While these major lesions are interesting to contemplate, the essential changes are more readily observed under high-power and oil-immersion microscopy. Typical features at the quartz mass center, at the edges, and in the surrounding tissues have been assembled in Figures 2 to 4.

SERIAL TISSUE REACTIONS

Quartz—Seven Hours.—The basic reaction is well defined within seven hours. At this stage the essential process consists of marked aggregation around the mass of particles of eosinophilic polymorphonuclear leucocytes and histiocytes with a small proportion of plasma cells and lymphocytes (Fig. 2*A*). Interstitial edema may be seen for a distance of about 2 mm. all around the quartz deposit, and in and beyond this circumferen-

tial zone the eosinophiles and histiocytes and occasional plasma cells, lymphocytes, and fibrocytes are migrating toward the primary lesion. There is a little hyperemia subjacent to the dust focus, but this is not a significant feature, and there is no extravasation of erythrocytes.

Where the dust is well contained as a circumscribed focus, a decisive wall of demarcation separates it from the circumjacent edematous tissue (Fig. 3*A*). This containing wall is composed of amorphous matter (altered tissue protein) in which some fibrocytes and collagen may be seen. The cells appear to be relatively healthy in this zone. More centrally, necrosis has commenced and manifests itself essentially as disintegration of some of the eosinophiles, whole granules and nuclei being scattered among the quartz par-

CYTOBIOLOGICAL MANIFESTATIONS OF QUARTZ

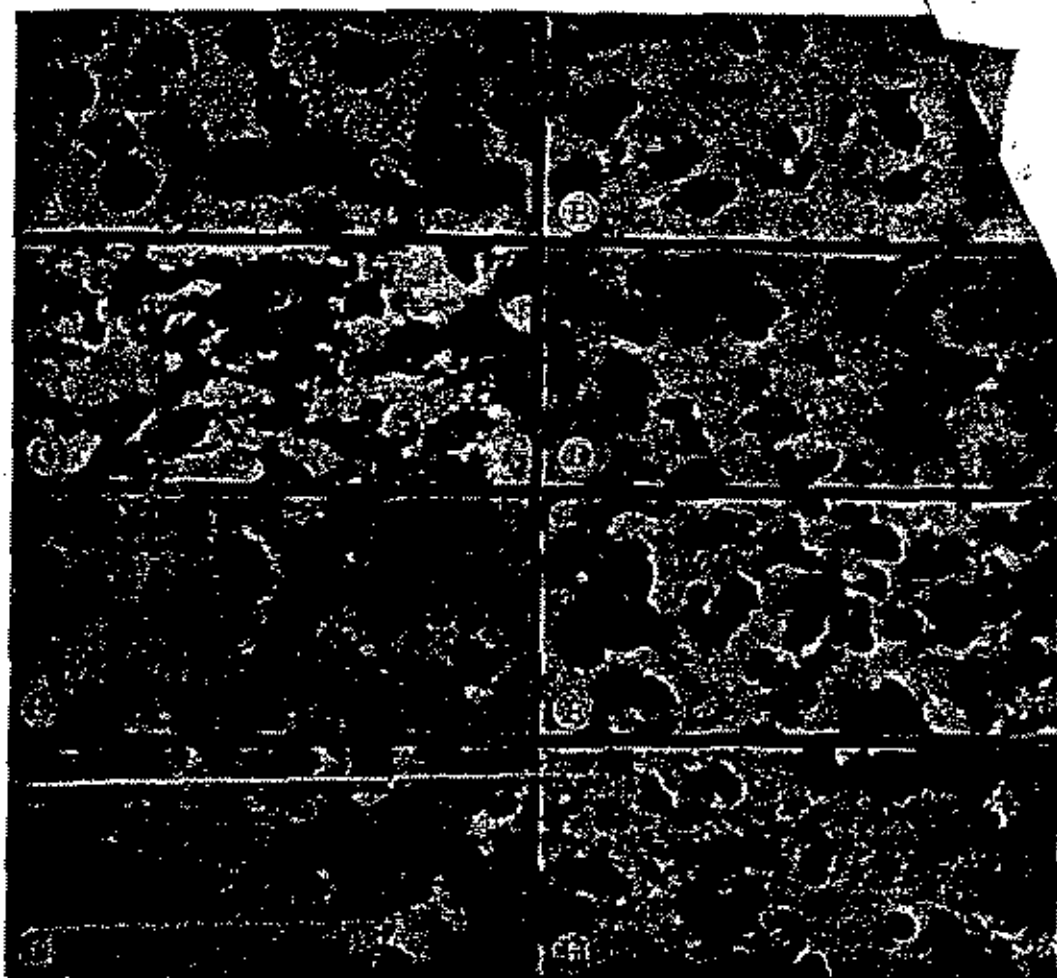


Fig. 2.—Cytoclastic processes at the center of the quartz mass (oil immersion). *A*, uncoated quartz: seven hours; commencing cell damage; dominant cells are eosinophiles with a few lymphocytes. *B*, protein-coated quartz: seven hours; no lymphocytes present. *C*, uncoated quartz: 12 hours; extensive protein precipitation demonstrated. *D*, protein-coated quartz: 12 hours; cells are better preserved and tissue protein denaturing less advanced. *E*, uncoated quartz lesion: 24 hours; cell approximation and damage. *F*, protein-coated quartz: 24 hours; greater survival of cells and nuclei. *G*, uncoated quartz: 72 hours; marked necrosis. *H*, protein-coated quartz: 72 hours; some karyorrhexis present.

ticles. The lymphocytes, plasma cells, and histiocytes are more resistant to injury by the quartz (Fig. 2*A*).

Protein-Coated Quartz—Seven Hours.—

At the corresponding seven-hour stage, the tissue reaction provoked by the introduction of 1 mg. of rabbit serum-coated particles of quartz shows many similarities to the reaction to uncoated quartz but also differs from it in several significant respects. In both instances there is a marked aggregation of

cells in relation to the mass of foreign particles, and a surrounding halo of edema is present in which cytotropic effects are to be seen.

Though the protein-coated dust deposit remains limited to the site of injection, no decisive line of demarcation in respect of cytological response is noted. The new cells overflow the edge of the particle mass and shade off gradually into the surrounding tissue. No degenerated formed elements are to be observed (Fig. 3*B*).

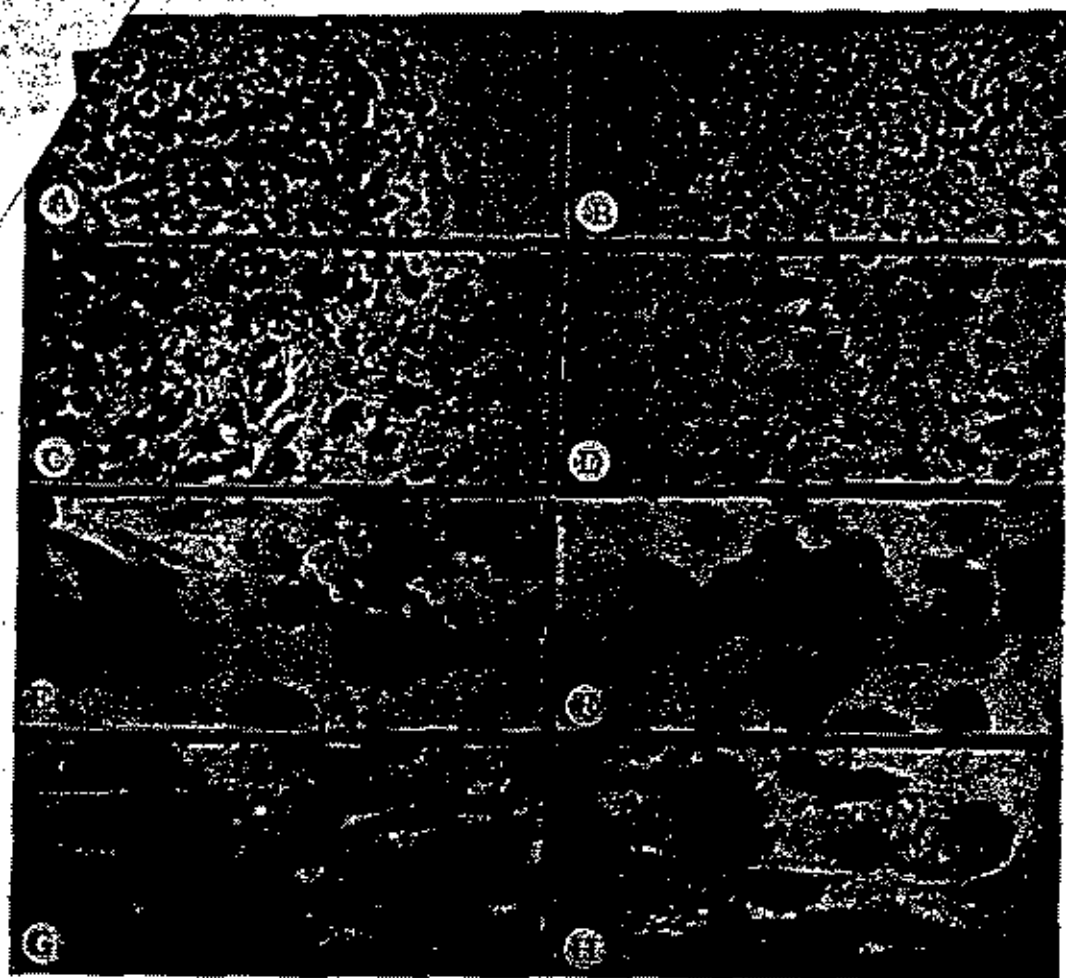


Fig. 3.—Cellular phenomena at the edge of the site of quartz deposition (Fields A—D, high power; Fields E—H, oil immersion). *A*, uncoated quartz: seven hours; sharp demarcation of reactive zone. *B*, protein-coated quartz: seven hours; absence of sharp edge delimiting the reaction to the quartz mass. *C*, uncoated quartz: 12 hours; commencing histiocytic invasion of borders; *D*, protein-coated quartz: 12 hours; zone of transition obscured by migrating quartz-filled cells. *E*, uncoated quartz: 24 hours; fibrocytes and histiocytes advancing on quartz mass. *F*, protein-coated quartz: 24 hours; eosinophiles, lymphocytes, and histiocytes. *G*, uncoated quartz: 72 hours; fibrocytes aggregating together to form a continuous capsule. *H*, protein-coated quartz: 72 hours; particle-filled histiocytes with intervening fibrocytes.

Once more there is an accumulation of eosinophilic polymorphonuclear leucocytes and histiocytes among the protein-coated quartz particles (Fig. 2*B*). This time there are, however, no plasma cells or lymphocytes; nor are the latter cell types to be seen in the surrounding tissues. Though eosinophiles also predominate at the center of the lesion, there is now a higher proportion of histiocytes migrating toward the mass of

coated quartz particles. Occasional fibrocytes may also be seen.

Though there is some suggestion of necrosis within the denser areas of cells, this change has by no means attained the stage seen in the sites of uncoated quartz. Once more this necrosis is limited to the eosinophile polymorphonuclears. The histiocytes, on the contrary, show ingestion of the protein-coated particles to a marked degree without any apparent injury.

CYTOBIOLOGICAL MANIFESTATIONS OF QUARTZ

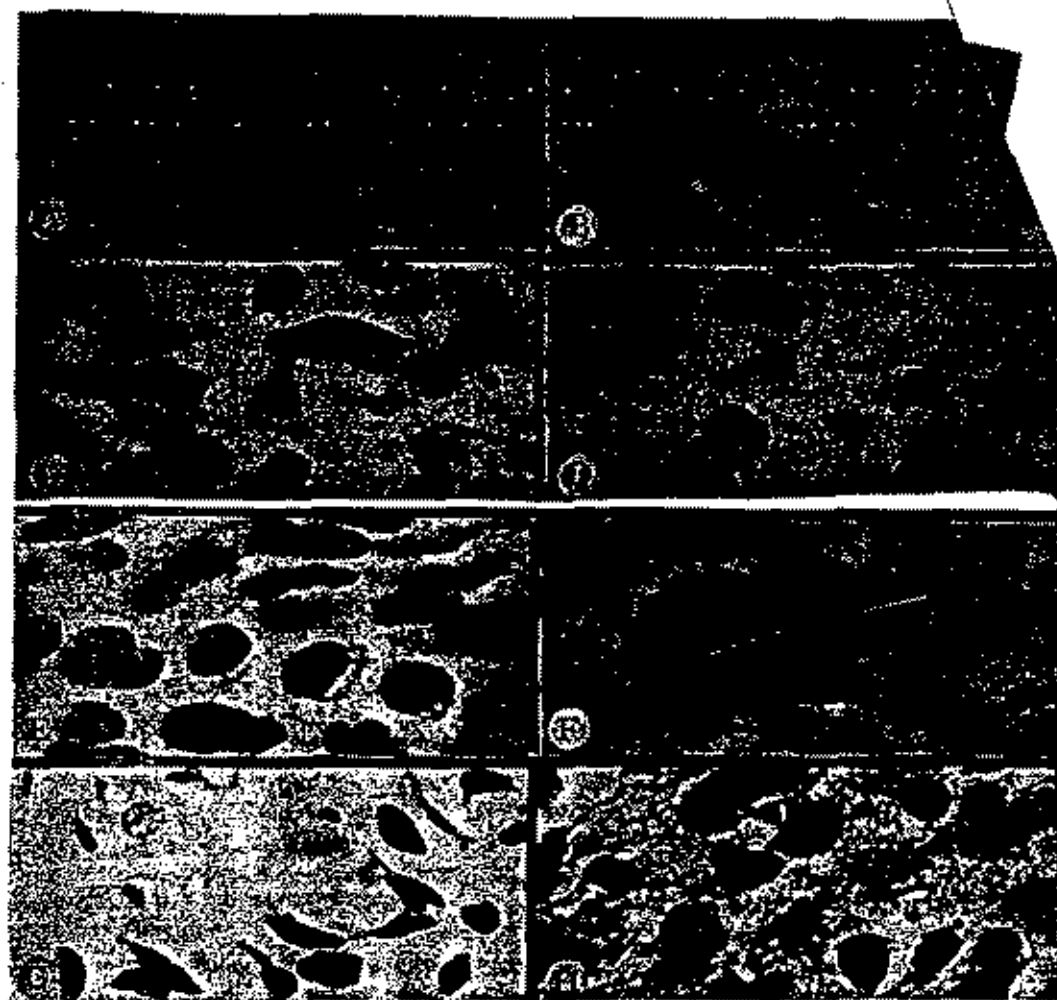


Fig. 4.—Sequence of cytological changes in the peripheral zone around the quartz site (oil immersion). *A*, uncoated quartz: 12 hours; phalanxes of eosinophiles advancing on the lesion. *B*, protein-coated quartz: 12 hours; sparse presence of histiocytes. *C*, uncoated quartz: 24 hours; fibrocytes abundantly present. *D*, protein-coated quartz: 24 hours; histiocytes, lymphocytes, and eosinophiles. *E*, uncoated quartz: 48 hours; admixture of fibrocytes and histiocytes. *F*, protein-coated quartz: 48 hours; particle-filled histiocytes, departing from the quartz site, passing fibrocytes and histiocytes advancing toward it. *G*, uncoated quartz: 144 hours; subsiding cytological response. *H*, protein-coated quartz: 144 hours; fibrocytes interposed among emigrating particle-filled histiocytes and immigrant histiocytes.

Quartz—Twelve Hours.—After 12 hours, the reaction to the uncoated quartz has advanced. The particle mass still retains its circumscribed character, but the whole is now cut up into multiple units by interposed cellular elements, the lesion giving a reticulated sectional effect. There remains a sharp line of demarcation between the focus of reaction and the surrounding edematous zone (Fig. 3C). However, this edge is no longer formed

by a peripheral condensation of cells or formed elements, as the whole of the center now has opaque amorphous protein fragments evenly disposed throughout it (Fig. 2C).

At the periphery of the lesion and farther afield the cytological response now is an almost pure eosinophile outpouring. Solid phalanxes of these cells may be found advancing on the quartz mass, and more such

to be seen within distended capillaries (Fig. 4A). Among the eosinophiles are found sparse numbers of histiocytes. Fibrocytes have now made their appearance in greater numbers.

Protein-Coated Quartz—Twelve Hours.—In the 12-hour protein-coated quartz lesion, the same essential differences noted at the 7-hour stage once more prevail or are even somewhat exaggerated. Again the edge of the lesion shades off into the surrounding area without the establishment of a demarcating line (Fig. 3D). At the center of the lesion necrosis has not advanced perceptibly, and the majority of eosinophiles are as yet normal in appearance (Fig. 2D). Phagocytosis of protein-coated quartz particles by histiocytes has proceeded apace, and in some sites these cells are markedly filled by such particles.

In the surrounding tissues there are but few cells, and these are predominantly histiocytes, though some eosinophiles are yet being attracted. No plasma cells or lymphocytes are in evidence and but few fibrocytes (Fig. 4B).

Quartz—Twenty-four Hours.—At the end of the first day (24 hours), the edema surrounding the quartz reaction has receded to some extent. This emphasizes the sharp line of transition between the necrotic cellular zone which is coextensive with the mass of quartz particles.

The majority of cells within the lesion are now necrotic (Fig. 2E). The injury they sustain is limited, however, to the cellular cytoplasm, and nuclei show pyknosis and karyorrhexis to a limited extent only. Much of the fluid within the lesion has been withdrawn, so that the cells are densely crowded together. At the edge of the lesion fibrocytes are accumulating (Fig. 3E).

At the periphery of the lesion great numbers of large fibrocytes and even fibroblasts may be found among the eosinophiles and histiocytes. Such fibrocytes are present even at a considerable distance from the dust mass (Fig. 4C).

Protein-Coated Quartz — Twenty-four Hours.—The lack of definition of the edges

of the protein-coated quartz lesion is further emphasized at the 24-hour stage (Fig. 3F). It is quite evident that this dust is being dispersed beyond the confines of the initial site of deposition. At considerable distances from the lesion, therefore, histiocytes may be found which have phagocytosed the particles and are transporting them away from the original site. More histiocytes are to be seen advancing on the dust site (Fig. 4D). The accumulation of these cells may account in some measure perhaps for the preponderance of histiocytes over eosinophiles, but it seems certain also that the number of the latter type of cells has fallen off somewhat. In the center of the primary site there is some additional evidence of necrosis (Fig. 2F), but it is apparent that the cells and formed elements remain well protected against the noxious effects of the quartz as a result of the interposed protein layer.

Quartz—Forty-eight Hours.—By the end of the second day there are few cells surviving intact in the center of the injected area. At the edge of the lesion rather more are seen which have not undergone too great a change.

At the periphery of the lesion fibrocytes are now clearly the dominant cell type (Fig. 4E). They may be seen advancing on the quartz zone in large numbers. Occasional histiocytes and eosinophiles lie among them. Many of the fibrocytes have taken position around the quartz area, and others have penetrated into it. The edge of the lesion has become somewhat irregular through the emergence of dust-filled histiocytes from the central area.

Protein-Coated Quartz — Forty-eight Hours.—In the case of the protein-coated quartz, on the contrary, the periphery of the lesion shows but few fibrocytes, and the dominant cell still remains the histiocyte. A larger proportion of these cells are now filled with particles and, judging by the constant position of the nucleus in relation to the particle-filled cytoplasm, may be presumed to be departing from the quartz area while the distended cells advance on it (Fig. 4F). The

edge of the lesion is now a little better defined, owing to the accumulation of a zone of nuclear debris around the necrotic center. Cell destruction has advanced further during the past 24 hours and has reached the stage the uncoated quartz had already brought about a whole day earlier.

Quartz—Seventy-two Hours.—The most distinctive feature marking this stage of evolution of the quartz lesion is the incipient emergence of a capsule (Fig. 3G). This component tends to consist of two elements, namely, a circumferential multilayered zone and an internal layer, intermediate between the fibrous capsule and the central necrotic area consisting mainly of greatly swollen, dust-filled histiocytes.

A larger number of fibrocytes have also penetrated into the edge of the necrotic mass, and it is plain to see that the essential process is now that histiocytes carry the dust to the outer edge, while fibrocytes insinuate themselves into the necrotic area. A small locus of cellular debris remains in the center (Fig. 2G).

Protein-Coated Quartz—Seventy-two Hours.—While there is now a comparable tendency toward peripheral fibrocytic aggregation, a decisive capsule is not yet being formed, probably owing to the greater dispersal of the dust-laden histiocytes into the surrounding tissues. Indeed, it would seem that at this stage almost more protein-coated quartz particles are confined within greatly distended histiocytes outside the original focus of infection (Fig. 3H). The central portion of the lesion appears consequently denser because of closer approximation of the cellular components to one another through withdrawal of the particles (Fig. 2H).

Quartz—Fourth to Tenth Day.—The final process of coping with this mass of foreign particles appears to consist of a progressive increase in the number of dust-filled histiocytes in the zone between the peripheral capsule and the central necrotic area. These cells appear unusually well preserved despite the presence of particles within them. Fibro-

cytes progressively come to lie between these macrophages so that ultimately the intermediate capsular zone consists of a mixture of distended histiocytes and fibrocytes. This zone increases progressively, and by the 10th day it equals in width the residual central necrotic core. Capillaries have now also penetrated into it, and along extensive stretches this zone is sharply demarcated from the center by layers of fibrocytes. The necrotic area now consists largely of an acidophilic granular cell debris within which nuclei may persist. Quite a considerable amount of quartz is still retained within it. The superficial fibrous capsule has not developed any further. The whole terminal lesion is now relatively well circumscribed and about equal in size to the original area of reaction. At the periphery the cellular reaction has become relatively quiescent (Fig. 4G).

Protein-Coated Quartz—Fourth to Tenth Day.—Owing to the initial greater range of peripheral dispersion of the quartz particles through the centrifugal migratory propensities of the histiocytes and the diminished cytotoxic effect and the delay in fibrous reaction at the edges, the cross sectional area of the ultimate lesion provoked by the protein-coated quartz particles is almost four times as extensive as that due to the uncoated quartz, and the residual necrotic center is all but resorbed, its edges merging with the surrounding cellular zone with no tendency toward the deposition of intervening fibrous layers. Nor is the outer zone too clearly defined from the surrounding tissues, a decisive fibrous capsule never having been laid down. The edge of the whole lesion is now rather better demonstrable, however, by virtue of the marked contrast between its intrinsic highly cellular character and the relative acellularity of the surrounding tissue from which the intense eosinophilic and histiocytic reaction, previously so much in evidence, has been conspicuously withdrawn.

The main mass of the granuloma now consists largely of particle-filled histiocytes and fibrocytes (Fig. 4H). Owing perhaps to the

fact that the histiocytes had traveled farther and become better spaced apart, relatively greater numbers of fibrocytes and other cells intervene among the individual histiocytes. Capillaries are also more numerous. Occasionally eosinophiles are yet present. A fairly considerable amount of fine collagen has been deposited between the histiocytes, especially at the edges.

The residual central debris is now much more of an amorphous basophilic mass than is the case with the pure quartz lesion, in

Both forms of quartz immediately attract to them a large and equal number of histiocytes and eosinophilic polymorphonuclear leucocytes; the latter initially being destroyed almost as rapidly as they reach the quartz masses. Very soon, however, it becomes evident that the pure quartz particles are the more destructive, and the initial necrosis, therefore, proceeds the more rapidly in relation to them. The protein coating of the quartz in the relevant lesions, on the con-

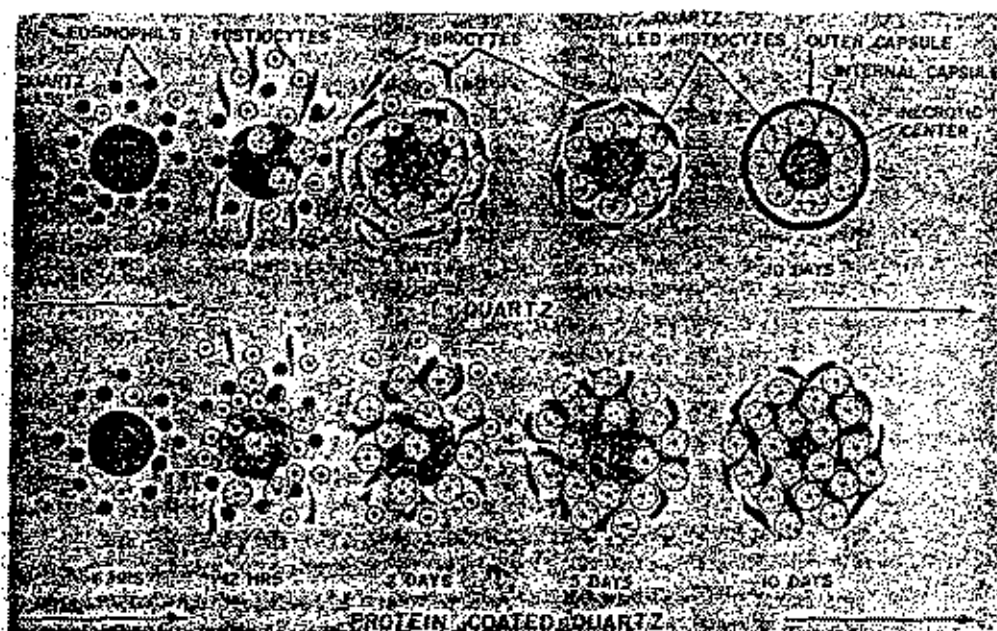


Fig. 5.—Differential connective tissue cellular reaction to uncoated and protein-coated quartz particles, showing manner of evolution of encapsulated and proliferative lesions.

which nuclear structures are still distinguishable, the cytoplasmic remnants of the corresponding destroyed cells imparting an acidophilic character to the area. Virtually no quartz particles survive here.

COMMENT

The differential effects of uncoated and serum-coated quartz in the rabbit ear subcutaneous tissue are apparently explicable in terms of the relative rates at which cytological events follow one another and have been schematically summarized in Figures 5 and 6.

trary, affords an initial protection to the leucocytes.

As a result of the marked local toxicity of the pure quartz, a peripheral protein barrier is set up which defines the lesion from surrounding tissue. The protein-coated quartz does not provoke this interstitial reaction. Instead, the line of demarcation is soon lost.

The latter change is accelerated by the behavior of the histiocytes. In the case of the protein-coated quartz, these histiocytes are not immediately as seriously injured as are those which phagocytose the pure quartz

CYTOBIOLOGICAL MANIFESTATIONS OF QUARTZ

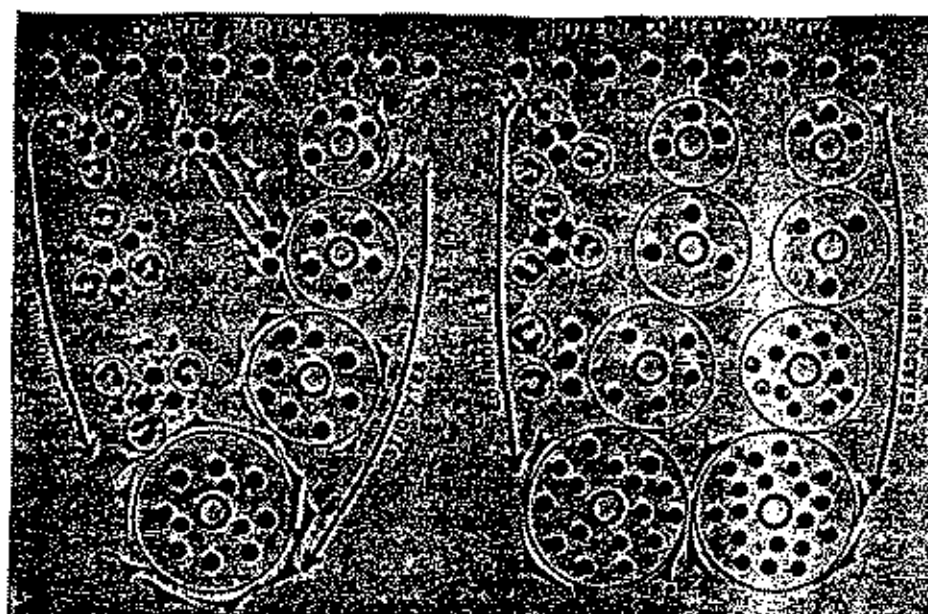


Fig. 6.—Differential chemotropic, cytotoxic, and fibrogenic action of uncoated and protein-coated quartz particles.

particles. Consequently the histiocytes migrate beyond the confines of the protein-coated quartz deposit, whereas this change is not seen to any great extent in the case of the quartz deposit. In this manner the protein-coated quartz is immediately more widely dispersed. At the same time greater numbers of histiocytes advance out of the zone of the protein-coated quartz deposit and take the place of those which have escaped outward fully charged with their particle loads.

The uncoated quartz attracts fibrocytes more readily to their vicinity, and thus a fibrous capsule is more readily thrown up which further limits the spread of the lesion. The whole subsequent process must now proceed within the confines of this capsule, which tends to limit or retard the entry of histiocytes and to determine the strong zonal differentiation which ultimately ensues.

In the case of the protein-coated quartz lesion, virtually all the quartz is rapidly withdrawn from the original site by the phagocytic histiocytes. This feature determines the final absence of a line of demarcation between the cortical fibrocellular zone

and the residual central amorphous center. The generous subsequent deposition of fibrous tissue between the histiocytes may perhaps be explicable on the supposition that a fibrogenic stimulus is gradually released from the quartz particles contained within the histiocytes.

The final conclusion which may be arrived at is that these different effects are entirely explicable in terms of some barrier action which the protein coating, which is adsorbed onto the particle surface, exerts. This barrier for connective tissue cells which the quartz may thus modify the selective chemotropism particles exert. The uncoated quartz immediately attracts eosinophiles, histiocytes, and fibrocytes. The coated quartz has a stronger tropism for histiocytes.

The delayed attraction of fibrocytes by the protein-coated quartz after ingestion by histiocytes may perhaps be explicable on the supposition that the protein layer is slowly digested off the quartz and metabolized, whereafter a histiocyte filled with such particles would not differ materially from one initially filled with uncoated quartz. At this stage the quartz would commence to exert

its full deleterious influence on the living cell components.

The greater migratory propensity of the protein-coated-quartz-filled histiocytes may perhaps also be explained on the assumption that such cells are protected for a short while from injury by the quartz, which manifests itself only after the protein layer has been digested off.

The whole phenomenon affords good confirmation that protein is indeed adsorbed onto the quartz particles and sound evidence that such particles exert their harmful influence on tissue cells by virtue of the physico-chemical phenomena which operate at the quartz particle surface.

SUMMARY

Serial cytological responses to the subcutaneous introduction of protein-coated and uncoated 1μ to 3μ quartz particles are described.

The adsorbed protein acts as a barrier which selectively retards and modifies chemotropic and cytotoxic responses to the presence of quartz.

The quartz is consequently more widely dispersed by histiocytes, with a resultant exuberant fibrocellular lesion.

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An Experimental Study of the Effects of Glass Wool on Animal Lungs

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and

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The increasing modern industrial application of glass fibers in the production of reinforced polyester resin plastics has revived interest in a series of experiments on glass wool and glass cotton in which one of us (A. B. D.) participated during the period 1939-1947. These studies were conducted in The Saranac Laboratory under the direction of the late L. U. Gardner, M.D., whose unexpected and lamented demise prevented the publication of reports on the results obtained.

Three samples of glass wool were studied by the intratracheal injection technique. The experimental animals were guinea pigs. In addition, a long-term inhalation experiment was conducted, using glass wool during the first phase and glass cotton toward the end. This study involved the use of guinea pigs and rats.

INTRATRACHEAL STUDY

The diameters differed in the three glass-wool samples. The first batch (Batch A) ranged from 3μ to 8μ in diameter, with an average diameter of 6μ . The second batch (Batch B) was approximately 3μ in thickness, and the third batch (Batch C) measured 3μ and less in diameter, a large proportion being in the 1μ range. The desired length of the fibers for the intratracheal studies was



Photomicrographs of three batches of glass wool after reduction for purposes of intratracheal injection. A, reduced about $\frac{1}{4}$ from mag. $\times 100$; B, reduced about $\frac{1}{4}$ from mag. $\times 300$; C, reduced about $\frac{1}{4}$ from mag. $\times 300$.

20μ - 50μ . The fibers were prepared by preliminary grinding in a carding mill and were passed through a 200 mesh screen, ground lightly in an agate mortar, and separated by sedimentation in water. Two of the products were then prepared as 5% suspensions and the third as a 0.5% suspension by weight in isotonic saline. All three were thereafter autoclaved at 100°C for one hour. The Figure illustrates the physical appearance of the glass fibers from the three batches.

The glass fibers were introduced intratracheally in three doses of 0.5 cc. each at weekly intervals in each case. For Batch A, five guinea pigs were used, and all survived the process for a year. For Batches B and C, there were eight animals each. Two deaths occurred in each group, and there were, therefore, enough animals in each group to permit

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TABLE 1.—Pulmonary Effects of Glass-Wool Fibers
Intratracheal Experiment 905

Glass Wool Type	Guinea Pig No.	Survival, Wk.	Died or Killed	Gross Pulmonary Reaction
A	905-1	4	K	One focus of atelectasis
	2	8	K	Paravertebral adhesion
	3	17	K	Large hyperemic foci
	4	22	K	NI
	5	22	K	Isolated conglomerate areas of pigmentation
	904-4	2	D	Left caudal lobe atelectatic
	3	4	K	Focus of atelectasis
	2	17	K	NI
	3	22	K	NI
	5	22	K	NI
B	7	76	D	Pneumonia with necrotic areas
	6	78	K	General atelectasis and congestion
				Large necrotic apical lesions
	8	78	K	Focal atelectasis and necrosis
C	1058-1	4	K	Linear focus of atelectasis
	2	4	D	Pneumonia
	3	17	K	Small focus of atelectasis
	5	22	D	Pneumonia and multifocal atelectasis
	8	22	K	One focus of atelectasis
	7	22	K	Area of atelectasis in each set of lungs

samplings at 4-, 8-, 17-, 13-, and 52-week intervals. In the case of Batch B, animals were examined 76 and 78 weeks after the initial injection.

The results of these intratracheal studies have been summarized in Table 1. It would appear that glass wool of the first type, A, was relatively inert. No animals died, and the pulmonary lesions were minimal. This result may have been anticipated in view of the relative thickness of component glass fibers.

In the case of glass wool type B there were no early reactions except for foci of atelectasis. However, in the animals killed after the 75th week, major pulmonary damage was revealed.

Glass wool of the third type, C, whose component fibers were relatively slender, appeared to provoke mainly focal atelectasis.

The prevalence of focal atelectasis is exceptional in this series and may represent a specific type of reaction to the introduced glass wool fibers of the caliber and length used in these studies. It is to be noted that no fibrosis was macroscopically perceptible in relation to these areas.

INHALATION STUDY

The fibers of the glass wool used in the inhalation study approximated 6 μ in diameter. The material was dispersed from a modified dust hopper in a dust room measuring 8 by 8 by 8 ft. The dust concentrations inside the cages ranged from 0.143 to 0.146 mg. per cubic foot, as determined by the electrostatic precipitator method. Impinger counts gave readings ranging from 1,400,000 to 2,200,000 particles per cubic foot of air by light-field count. These were the maximum concentrations obtainable by this method of dissemination.

Chemical analysis of the parent material yielded the following percentage composition:

Component	%
SiO ₂	82.8
FeO ₂	0.4
Al ₂ O ₃	14.2
B ₂ O ₃	9.55
CaO	16.70
MgO	4.80
K ₂ O	0.22
Na ₂ O	0.20
H ₂ O	<110 C—0.25
H ₂ O	>110 C—0.42

One hundred guinea pigs were exposed to the glass wool for a period of 40 months. However, at about the 20th month, the nature of the dusting agent was changed from glass wool to glass cotton, with a maximum fiber diameter of 3 μ , and a concentration of 0.03 to 0.07 mg. per cubic foot of air was maintained. The experiment was thereafter continued until the end of the 40th month.

A series of 50 white rats were likewise exposed to glass wool in the same chamber for 20 months and subsequently to glass cotton dust until the end of the 24th month.

Animals were killed in batches of three to six at 2-, 4-, 9-, 12-, 18-, 24-, 36-, and 40-month intervals. The observations are recorded in Tables 2 to 5.

OBSERVATIONS

Attention may first be directed to the differential mortality rates for the guinea pigs and rats, respectively. Seventeen out of one hundred guinea pigs and twenty out of fifty rats died during these experiments. It should be recalled too that the guinea pig experiment was carried along for 40 months,

EFFECTS OF GLASS WOOL ON ANIMAL LUNGS

TABLE 2.—Effect of Inhaled Glass Wool and Glass Cotton on Guinea Pig Lungs
Spontaneous Deaths

Guinea Pig, No.	Survival, Wk.	Cause of Death	Gross Pulmonary Dust Reaction
67, 68, 70	4	Pneumonia	Nil
69	5		
66	20		
67	26		
57, 61	45	Bowel obstruction	Isolated foci of brown to black pigmentation measuring up to 1 mm.
20	102		
41	138		
36	138		
47	150	Pneumonia	Geometric pattern of pigmentation anteriorly, with isolated foci elsewhere
42	162		
58	180		
72	184		
37	176	Pneumonia	Dark green foci of pigmentation anteriorly
51	171		

while the rat exposures terminated after 24 months. Only nine guinea pigs had died by the end of the 24th month. The ratio between guinea pig and rat deaths under identical environmental stresses, therefore, comes to 9:40.

In all but a few instances deaths were attributed to pneumonia in the case of the guinea pigs, while the rats likewise died of pulmonary inflammatory states in the majority of cases. In the case of the guinea pigs, the deaths are irregularly dispersed over the whole 40-month period, and there is no

TABLE 3.—Effect of Inhaled Glass Wool and Glass Cotton on Guinea Pig Lungs
Serially Killed Animals

Guinea Pig, No.	Killing Period, Wk.	Gross Pulmonary Dust Reaction
85, 87	8	Nil
1, 2	10	Marginal atelectatic areas
3 to 8	22	Isolated subpleural foci of black pigment, with pleural retraction
9 to 14	32	
15 to 24	78	
25 to 35	102	
40, 51, 71, 76, 82	136	Foci of atelectasis; scattered to confluent pigmentation, with incipient geometric pattern
51, 53	184	
37 to 40	156	Small discrete foci of dark green pigmentation anteriorly
45 to 48		
49 to 60, 60, 60		
52-55	173	Dark green pigmentation, with early geometric pattern anteriorly and widely scattered isolated foci elsewhere
62-65		
73-75		
76-80		
84, 85		

TABLE 4.—Effect of Inhaled Glass Wool and Glass Cotton on Rat Lungs
Spontaneous Deaths

Rat, No.	Survival, Wk.	Cause of Death	Gross Pulmonary Dust Reaction
21	16	Pneumonia	Nil
22	40	"	Minute foci of pigmentation
12	48	Pneumonia	Pleural pigmented plaques
22	50	Lung abscess	Nil
41, 42	51	Pneumonia	
43, 13	52	Lung abscess	
9	53	Pneumonia	
10	55	Abdominal tumor	Scattered nodules
45	55	Pneumonia	
14	52	Collapsed lung and contralateral emphysema	
15	54	Lung abscess	
95	63	Lung abscess	Nil
16	72	Pneumonia	
24	77	Salivary gland fibroma	
25	82	"	
46	85	Pneumonia	Pigmented foci and pleural plaques
27	100	"	Nil
28	104	"	Isolated foci of pigment
			Pleural pigmented plaques

mortality pattern which could not be accounted for readily by normal chance and the influence of age. The majority of the rats, on the contrary, appeared to die after the first year of exposure, and there is a maximal or peak death rate between the 50th and 70th weeks of survival.

It should also be observed (Tables 4 and 5) that lung abscesses were relatively common in the rats (10%). On macroscopic inspection, these abscesses resembled tumors. Comparable lung lesions were not found in the guinea pigs. In this group of animals there were signs of regional alimentary tract obstruction with distended stomach or large bowel in 7% of the pigs. This lesion, on

TABLE 5.—Effects of Inhaled Glass Wool and Glass Cotton on Rat Lungs
Serially Killed animals

Rat, No.	Killing Interval, Wk.	Gross Pulmonary Dust Reaction
1, 2	38	Isolated to moderate numbers of minute pigmented foci
3, 4, 5	40	
6, 7, 8	42	
22	74	Sparse black foci less than 1 mm., with atelectatic areas
17-20, 40	78	
28, 30	102	Pneumonic areas in Rat 18
47-49		
		Sparse focal pigmentation
		Rat 48—chronic upper lobe tumor. No abscess present

further analysis, appears, however, to have affected animals during the 30th month of their survival and probably has nothing to do with the glass wool, probably being due to a dietetic factor or intercurrent infection.

In the guinea pigs, dust reaction foci were not detectable by macroscopic examination until the 40th week of exposure. However, by the fourth month marginal atelectatic areas were already manifest, and these are presumed to be signs of glass-dust action because they appear definitely to be related to pigmented areas at a later stage.

It is of interest to note also that the earliest pigmented foci appeared subpleurally and were more frequent anteriorly, while a geometric pattern first made its appearance toward the 138th week of exposure. Ultimately dark green foci of pigmentation appeared.

In the case of the rats, on the contrary, the lungs were remarkable for the paucity of evidence of either dust pigmentation or reaction. Indeed, though foci of pigmentation appeared, these were less in evidence in the animals which had died spontaneously than in those serially killed.

COMMENT

These gross pathological phenomena will be further elucidated elsewhere.¹ It would appear from the foregoing, however, that the effect on the pulmonary tissues of animals of glass wool of the caliber and fiber length used in the experiment is not wholly inert. While the fibers are not fibrogenic, they do appear to be trapped in the lungs, and though they provoke no macroscopically detectable reaction, the prevalence of pulmonary infection in the rat particularly and the frequency with which focal atelectasis was seen in the guinea pig more especially suggest a possible

causal relation between these occurrences and the experimental dust exposure.

In this connection caution should be expressed against applying the information derived from this study too directly to the problem of the modern glass wool or glass fiber industry. Since these experiments were started, many technical changes have been introduced into the method of preparing glass wool or glass fibers, and the product currently available to commerce is considerably lighter in caliber than that used in the present study. The results of a current study on one such product will be communicated at a later date.

SUMMARY

The results of three intratracheal experiments with glass wool and one inhalation experiment with glass wool and glass cotton are described.

Focal atelectasis was the dominant lesion in the animals in which the glass wool was introduced intratracheally.

The severity of the reaction appeared to be inversely proportional to the caliber of the glass fibrils.

The inhalation experiment was attended by a relatively high mortality from pulmonary causes in the rat but with little gross evidence of dust reaction.

In the guinea pig, the glass wool was observed to be focally deposited and retained in animals that survived long enough in the dusty environment.

No macroscopic evidence of fibrosis was adduced.

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The Biological Action of Glass Wool

Studies on Experimental Pulmonary Histopathology

G. W. H. SCHEPERS, M.D., D.Sc., Saranac Lake, N.Y.

Glass wool is fabricated by ejecting molten glass by means of supercharged steam into a chamber where fragments varying from 25 to 30 cm. in length fall. During the process of manipulating this product in the manufacturing of textiles, fragments are released into the air and have been known to act as skin irritants,* but they have not been incriminated as a cause of pulmonary fibrosis,* though occasional cases have been cited in connection with which the inhalation of glass-wool dust has been implicated as a contributing cause of pulmonary disease of variable severity.* At the most, these reactions have been attributed to mechanical irritation, as glass does not contain any free silica. Powdered glass has been shown to be inert for subcutaneous or ocular tissues.

The increasing exploitation of glass wool and of glass fibers in industry and the similarity between glass spicules and asbestos fibers necessitate constant vigilance concerning the properties of these glass fibers. The description of the pulmonary lesions resulting from the introduction of glass wool into guinea pig lungs will serve to show that, though the silicon element in the glass is present as a silicate and thus does not provoke the characteristic nodular disease associated with quartz inhalation, glass fibers of the caliber and length used in this study, when effectively lodged within the lung tissue, are nevertheless capable of producing quite remarkable lesions.

The observations flowing, respectively, from the intratracheal and the inhalation experiments described by Schepers and Delahant* will be presented separately.

INTRATRACHEAL STUDY: 20-50 μ GLASS WOOL

One month after the intratracheal introduction of glass-wool fibers, areas of lung tissue are demonstrable in which the alveoli contain numerous multinucleated giant cells in which glass fibers may be found. Some alveoli may contain several such giant cells, and in others the giant cells are so large as to fill the greater part of the alveoli. The smaller the fibers introduced, the larger are the associated giant cells. No free-lying glass fibers could be observed. The alveolar walls are infiltrated by macrophage cells and occasional polymorphonuclear leucocytes at numerous points. There is, however, no appreciable hyperemia, and only isolated glass fibers have penetrated into the alveolar walls, either separately or in a phagocytosed state. Many of the longer fibers appear also to have either extremity embedded in an adjacent alveolar wall (Fig. 1A).

At several sites these islands of phagocytic reaction involve the lung lymph nodes, which are considerably hypertrophied, with lymphocytes overflowing into proximal alveolar walls (Fig. 1B). Glass fibers are not, however, found in the parenchymal lymph nodes. The hilar lymph nodes show some endothelial cell hyperplasia and prominent lymph follicles in which macrophages, with minute glass spicules, may be found.

The lung fields intervening between these affected areas appear relatively normal, except for a measure of incipient atrophic emphysema.

Around some of the smaller bronchioles the cellular infiltration may be quite abundant,

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Director, The Saranac Laboratory.

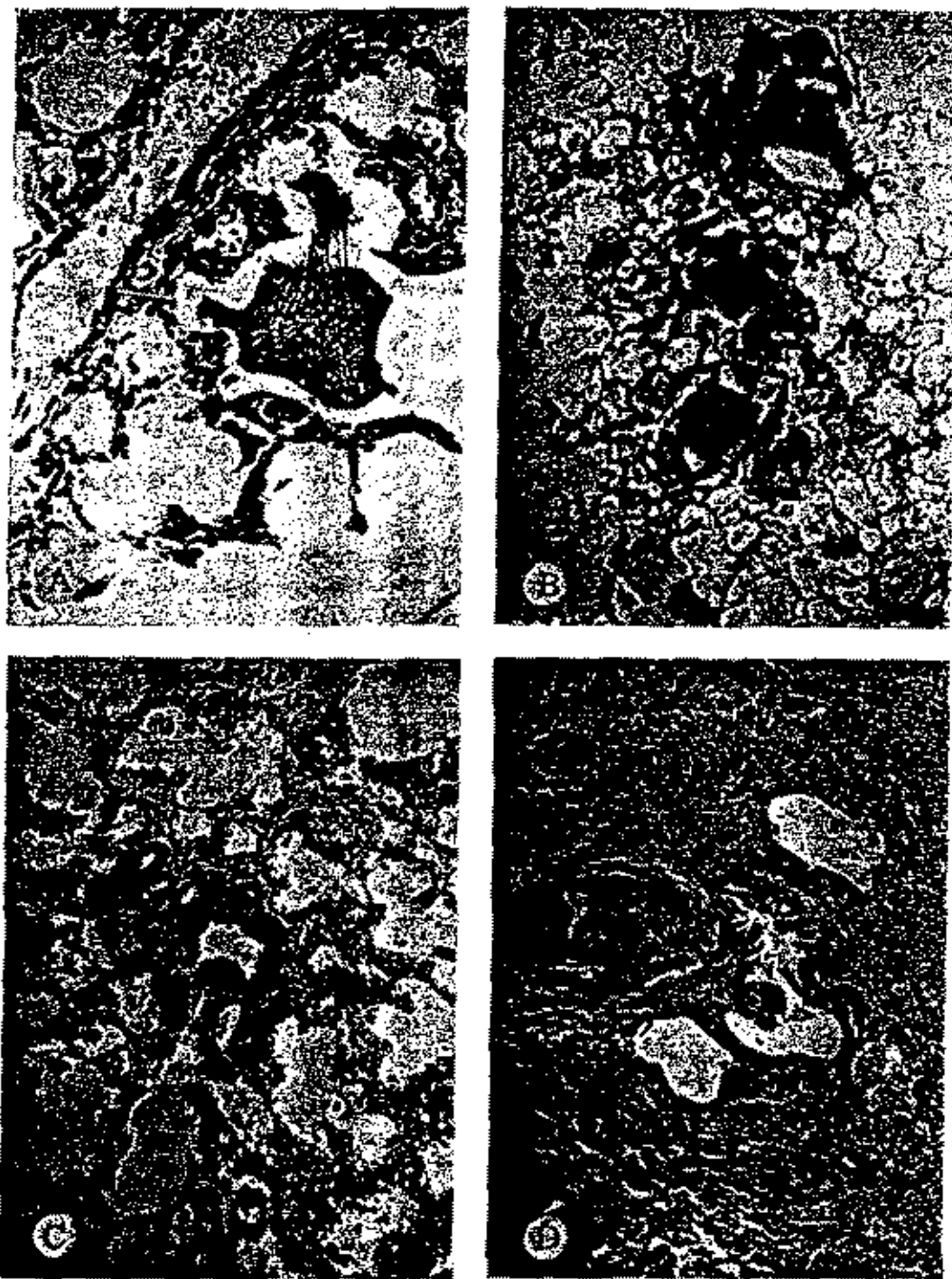


Fig. 1.—Acute pulmonary tissue reaction to long-fiber glass wool—guinea pigs: intratracheal injection of 204-50 μ fibers: result after one month. *A*, giant macrophage filled with glass spicules, some of which are seen to penetrate the alveolar walls and blood vessel walls. *B*, proliferation of lymph nodes and extension of the cellular reaction into adjacent alveolar walls. *C*, peribronchiolar cellular inflammatory reaction, with epithelialization of adjacent alveoli. *D*, wide zone of cellular infiltration around a bronchiole, which is distorted and linked to atrophic alveolar ducts; degenerative changes in adjacent vascular bundle.

BIOLOGICAL ACTION OF GLASS WOOL

and the lining epithelium shows considerable hyperplasia, with some superficial desquamation. Very occasionally, glass fibers may be seen adhering to the surfaces of the bronchial epithelium, but there is no mucosal reaction to their presence. These affected bronchi and bronchioles occur in proximity to the islands of parenchymal reaction (Fig. 1C).

At isolated sites there is a broad reactive cellular zone around the smaller bronchi, which completely obscures the pulmonary histioarchitecture. The trapped bronchus may be distorted and distended (Fig. 1D).

The tracheal epithelium tends to be somewhat hyperplastic and is covered by a thin layer of exudate which contains polymorphonuclear leucocytes.

Two months after the introduction of the glass-wool dust, much of the reaction seen within the first month has receded. There now are fewer parenchymal islets in which glass-filled macrophages occur within the alveoli. More frequently, these macrophages are to be seen diffusely scattered throughout the lung tissue. Isolated foci of intense, and even confluent, interstitial cellular infiltration also occur.

A new feature is the abundant presence of eosinophilic cells within the alveolar walls, the peribronchial or perivascular tissues, and also sometimes within alveoli or bronchiolar lumina. The bronchi and trachea show no material pathological deviations at this stage.

The lymphatic reaction has become modified, and the lymphocytes now occupy perivascular and pericapillary positions mainly. This change is fairly diffusely disseminated. The hilar lymph nodes show no further reaction.

At the end of 12 months, a considerable amount of glass still persists within the lung tissue, and there are isolated islets of confluent cellular pneumonitis. More of these fibers are now to be found within the interstitial pulmonary tissue in areas where such proliferation persists and such fibers tend to be relatively long. Generally the short fibers are within macrophages with relatively

atrophic alveoli, and the larger fibers are to be found in the alveolar walls. The bronchioles show some superficial epithelial desquamation (Fig. 2A).

Occasional bronchioles may be trapped within hyperplastic areas and appear stenosed. These areas differ from those demonstrated after the first month in that there are many more fibrocytes than inflammatory cells and the tissue has a poorer blood supply (Fig. 2B).

In the lymph nodes, the glass is now condensed into formless focal deposits, with no evidence of macrophages but with some cellular condensation around them (Fig. 2C). The lymph nodes of the lung parenchyma are normal once more.

At the end of 18 months, the interstitial parenchymal reaction may yet persist but is now minimal in degree. Glass fibers are now but scantily represented and occur mostly in the alveolar macrophages. Some glass rods may, however, be displayed within the interstitial tissues, and some are still seen to transfix alveolar walls. The main abnormality now concerns the bronchi and bronchioles which tend to be regionally distended and display many crypts and papillae covered by a thin lining of cuboidal or squamous cells. This bronchiectasia and bronchiolectasia had already commenced at 12 months, but the crypt and papillary formations are later trends. The condition is more marked with exposure to the shorter, narrower fibers (Fig. 2D).

INHALATION EXPERIMENT: 1/2 AND LESS FIBERS

The essential difference between the result of the introduction of glass wool by means of a single intratracheal injection and the slower inhalation of the fibrous particles under experimental conditions is quite striking.

There is no acute response of the bronchial mucosa to the inhaled glass-wool spicules which impinge upon its surface (Fig. 3A). Very little reaction occurs before the fourth month, whereas in the intratracheal experiment the maximal effect is achieved within the first month. By the fourth month there are many macrophages in the alveoli.

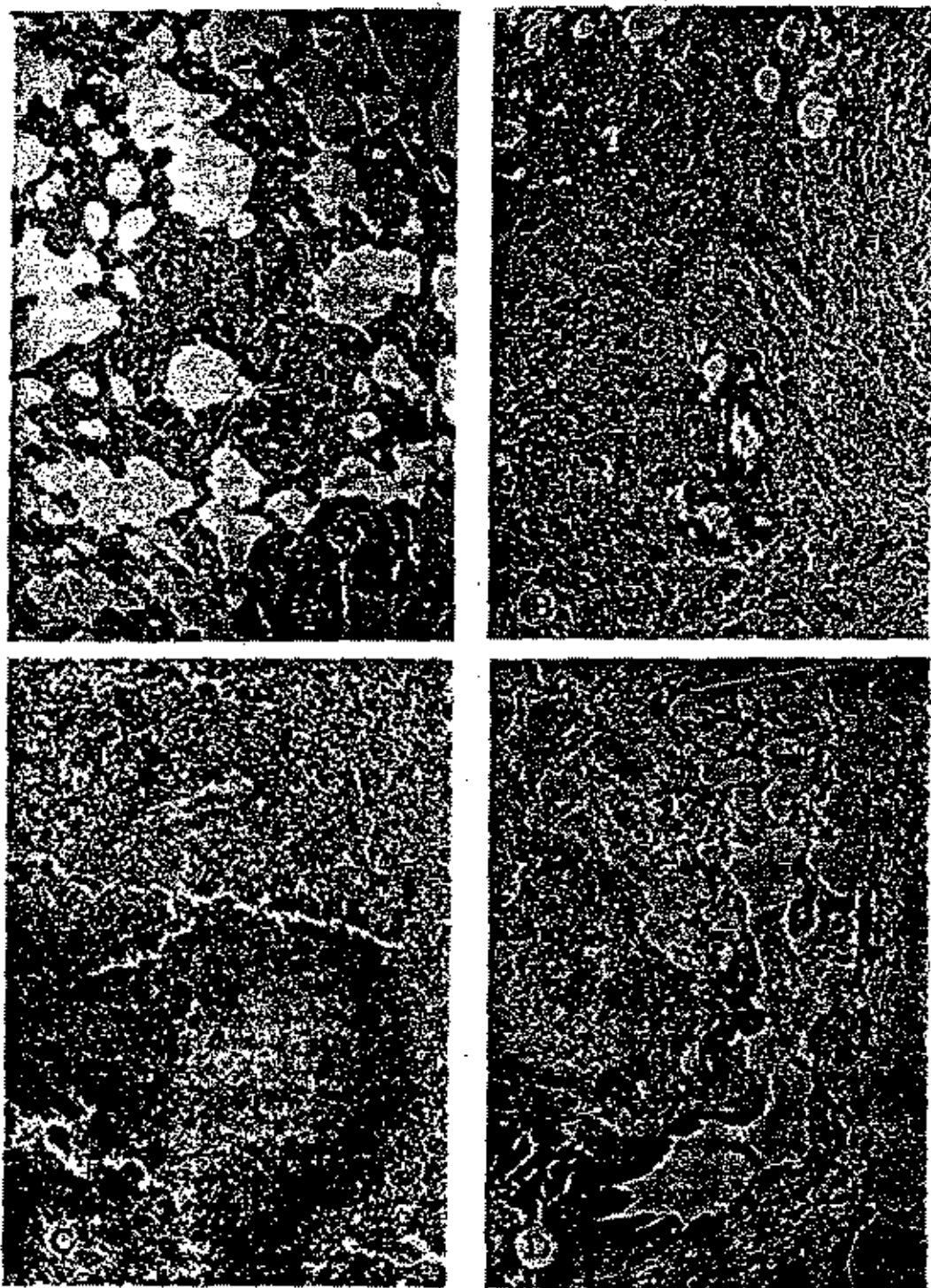


Fig. 2.—Chronic pulmonary reaction to long-fiber glass wool—guinea pigs: intratracheal injection of 20–50 μ fibers: result at 12 months. *A*, persistent dominantly cellular reaction around a distorted bronchiole; numerous glass fibers discernible. *B*, diffuse peribronchial cellular reaction now largely fibrocytic in character. *C*, amorphous accumulation within a lymph node, with a reactive surrounding zone. *D*, distortion and incipient crypt formation in a bronchiole which is surrounded by a fibrotic process.

BIOLOGICAL ACTION OF GLASS WOOL

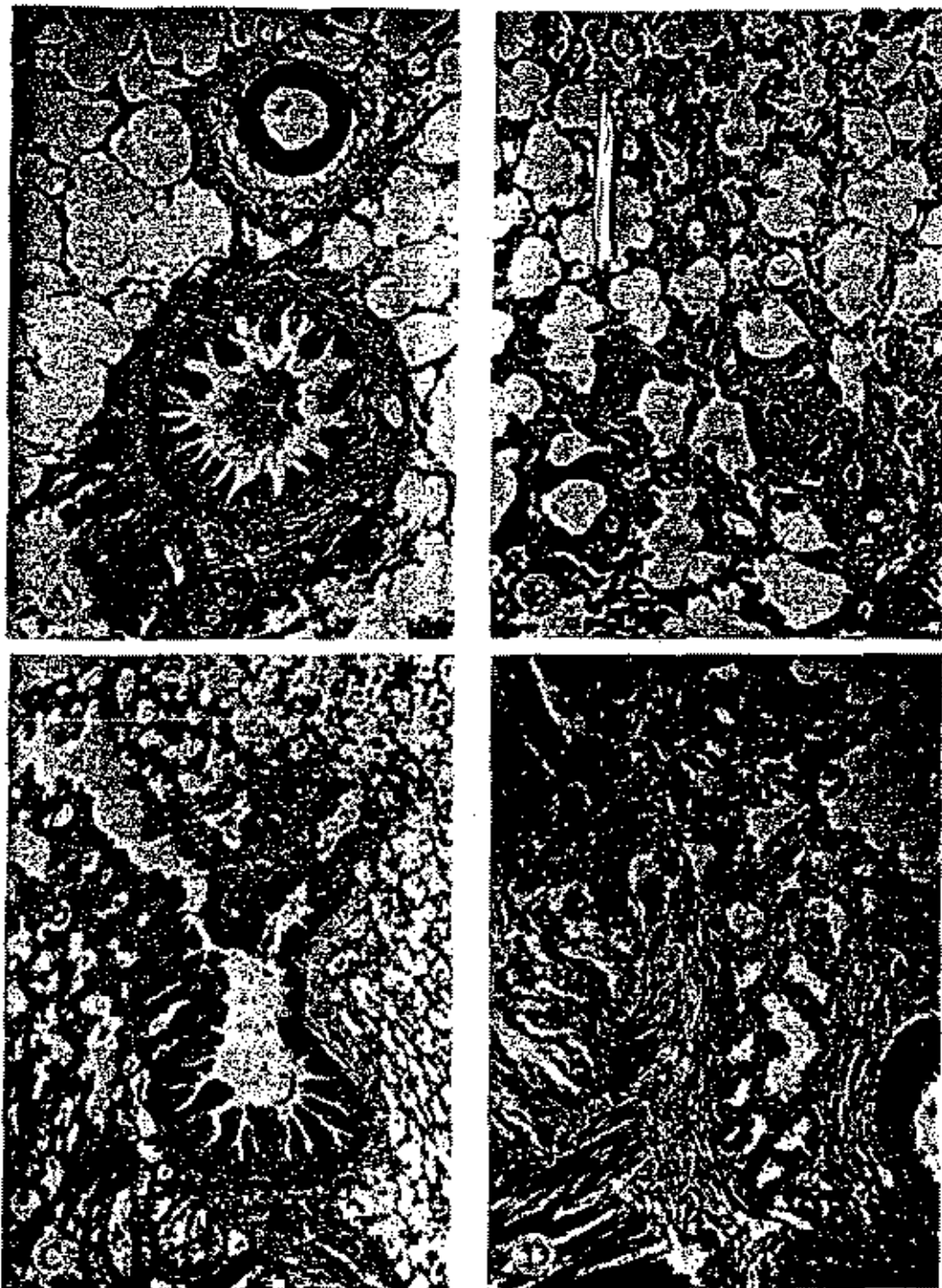


Fig. 3.—Early response to inhaled short-fiber glass wool—guinea pigs: inhalation study of less than 60 fibers. *A*, presence of glass-wool dust within a bronchus on the 18th day, showing absence of immediate reaction. *B*, cellular infiltration of alveolar walls, with hyperplasia of parenchymal pulmonary lymph nodes (reaction at four months). *C*, epithelial hyperplasia and peribronchiolar fibrocellular reaction, bringing about progressive narrowing of the lumen (reaction at four months). *D*, epithelialization of the alveoli adjacent to a bronchus (reaction after a year).

These are separate cells, and there is very little of a tendency to giant-cell formation. Eosinophiles are fairly numerous now, whereas they appeared later only in the intratracheal experiment. Glass fibers, on the contrary, are very scarce, and because the inhaled substance contains fibers less than 6μ only, they are limited to short spicules, all of which are intracellular.

In the lung parenchyma, there are patches of almost solid cellular reaction around the lymph nodes whose proliferating cells overflow into adjacent alveolar walls, while the presence of large numbers of macrophages within such alveoli contribute to the impression of a diffuse pneumonitis (Fig. 3B). There is no hyperemia. The hilar lymph nodes show no particular reaction.

In the bronchi, there is considerable epithelial hyperplasia and cellular desquamation, and a tendency to papilloma formation is present in the smaller bronchioles, with mucosal hypertrophy in the larger air passages. There tends to be marked peribronchial cellular infiltration at this stage, with the evolution of multiple bronchial glandular cysts and mucosal papillae. A tendency toward bronchiectasia and bronchiolectasia has commenced (Fig. 3C).

By the end of nine months, glass fibers commence to make their appearance in clusters within alveoli as well as in the koinophores. The bronchiolar crypts are more prevalent, and there is fairly considerable peribronchial and perivascular cellular infiltration, with some collagen deposition.

A year after the commencement of the glass-wool inhalation experiment, the guinea pig lungs show a bronchitis and bronchiectasia, with marked focal cellular pneumonitis.

The bronchial (bronchiolar) disease consists of epithelial proliferation and distention of the lumina, with extension of the bronchiolar epithelium over the walls of the proximal alveoli. This produces a very characteristic lesion, comprising a dilated bronchiole surrounded by a zone of epithelialized alveoli (Fig. 3D). A fibrocellular reaction about these bronchi may enclose such epithelialized alveoli, creating a spurious adenomatous

effect (Fig. 4A). A considerable degree of bronchial epithelial hyperplasia has supervened, and the lining shows marked rugosity and incipient metaplasia. There is no ulceration or submucosal infiltration (Fig. 4B).

The parenchymal islets of reaction are composed of thickened alveolar walls, with multinucleated giant cells and macrophages occupying the majority of such alveoli and containing many glass fibers. Occasional eosinophile cells are to be seen, but there is no hyperemia or collagenosis (Fig. 4C).

In the vicinity of lymph nodes, there is considerable dissemination of lymphocytes into adjacent alveolar walls. Many blood vessels also are ensheathed in fairly thick collections of lymphocytes. Some such arteries show medial myohypertrophy. The hilar lymph nodes are enlarged, owing mostly to medullary endothelial hyperplasia and infiltration by means of macrophages, many of which contain glass fibers.

By the 18th month of glass-wool dusting, the pulmonary tissue pathology ceases to reveal any significantly new features.

There still is intense alveolar wall thickening due to macrophage and plasma cell invasion, and there is also almost universal minor capillary hyperemia, with conspicuous perivascular macrophage infiltration. In numerous areas there is merely abundant intra-alveolar macrophage formation and no alveolar wall reaction of any consequence (Fig. 4D).

The parenchymal lymphatic tissue still escapes, even when lymph nodes may be almost completely surrounded by an extensive accumulation of macrophages. The bronchitis persists and comprises mainly epithelial hyperplasia, with increased goblet-cell activity and cellular catarrh, and there is also considerable peribronchial cellular infiltration.

Glass fibers are present everywhere. In stained sections they may be difficult to see, but scattered giant cells are to be found within alveoli. Dark-field examination of unstained sections shows up the universal distribution of the glass to good advantage.

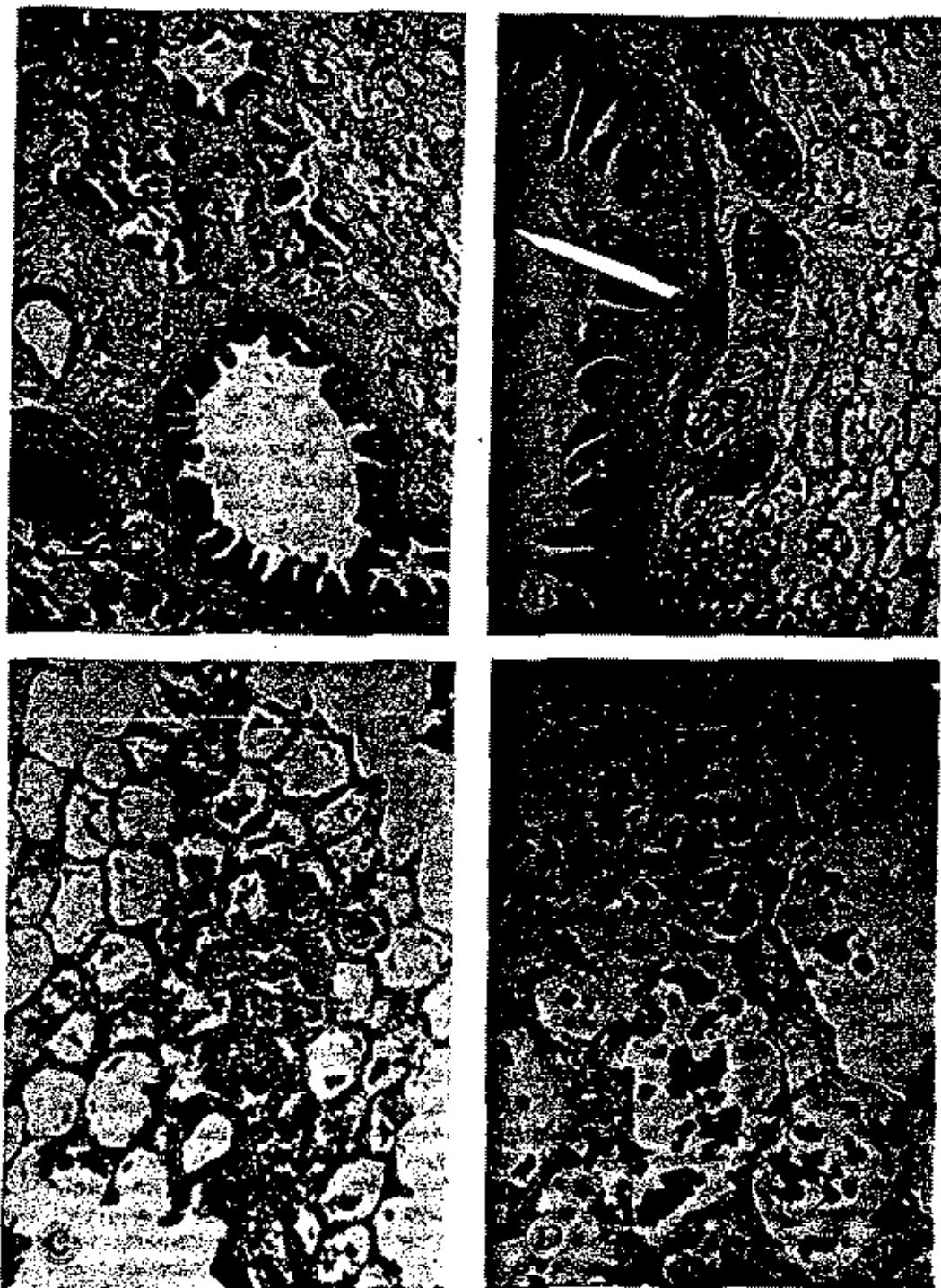


Fig. 4.—Chronic reaction to inhaled short-fiber glass wool—guinea pigs: Inhalation study of less than 64 fibers. *A*, peribronchial fibrocellular reaction which has surrounded epithelialized alveoli, thus producing a spurious adenomatous appearance (reaction at one year). *B*, hyperplasia of bronchial epithelium without inflammatory reaction in the mucosa (one-year result). *C*, focal parenchymal cellular reaction, with alveolar wall reaction and macrophage catarrh (one-year result). *D*, glass-fiber-filled macrophages, occupying alveoli whose walls show no significant reaction (result at 18 months).

COMMENT

These intratracheal and inhalation studies with glass wool have confirmed fairly conclusively that glass is not fibrogenic when retained in the lung tissue. At the same time the gravity of the type of bronchial lesion provoked necessitates caution in dismissing glass wool as innocuous. Indeed, it should be regarded as a potentially harmful substance in circumstances leading to the inhalation of large quantities of the type of product studied in these experiments. Other modern types of glass wool or fiber glass may not have any comparable effects.

In several respects, the pulmonary reaction to glass wool is similar to that produced by asbestos fibers, which the glass spicules resemble. However, despite the prominence of glass spicules in the lung tissue, no "glass-wool bodies" were observed which could be compared to "asbestos bodies." It is therefore not the shape alone of the asbestos fiber which leads to the formation of asbestos bodies.

It is to be noted also that asbestos fibers are intensely fibrogenic, whereas the lung tissue reacts to the glass fibers by means of a cellular response chiefly. This contrast again emphasizes the fact that the physical resemblances between glass wool fibers and asbestos do not determine their respective pathogenic propensities.

Obstructive damage to the bronchioles and the proliferative reaction of the bronchiolar and bronchial epithelium are obviously the more important lesions caused by the glass wool. There is but a limited range of substances which can provoke epithelial hyperplasia in experimental animals,⁶ and the specific effect of glass wool thus extends the list. The significance of this

observation in relation to oncogenesis needs further clarification.

SUMMARY AND CONCLUSIONS

When introduced intratracheally, long-fiber, medium-caliber glass-wool dust provokes early marked bronchiolar damage, which persists for more than a year without leading to well-defined fibrosis.

Some of the glass wool is transferred to the hilar lymph nodes where it accumulates without inducing local fibrosis.

Inhalation of short-fiber, medium-caliber glass wool produces a retarded pulmonary reaction, comprising partly an interstitial pneumonitis but dominantly an endobronchiolar and peribronchiolar lesion.

A tendency toward bronchial epithelial hyperplasia arises under the influence of prolonged short-fiber, medium-caliber glass-wool inhalation.

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Differential Susceptibility of Animals to Dust

A Critical Review

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The use of animals for the bioassay of dust hazards offers certain difficulties which are peculiar to the pneumoconioses. It is well established that the hazard to man of any particular dust depends on a number of factors. These include the chemical and physical nature of the material, its concentration, and the length of time over which the exposure is spread; in the atomic age radioactivity has also become recognized. In addition, the incidence of acute and chronic infection superimposed upon primary lesions may alter significantly the actual hazard. Since any one of these factors may be definitive, it is obvious that the bioassay of the total hazard to man becomes more complex than the controllable assay of such materials as drugs or hormones, for which well-defined methods have been worked out.* It is not surprising, therefore, that the accurate determination of the even more complex interaction of various modifying mechanisms, be they accentuating or antidotal, requires even more care.

Despite these difficulties, it is obvious to anyone reviewing the literature within recent years that laboratory experimentation has greatly enhanced our knowledge of the subject. Any danger from the possible misinterpretations of these findings from a practical standpoint arises from the fact that, as we have seen, we are usually dealing with a

number of often unrelated factors, any one of which may vitally influence the dimensions of the hazard. These may likewise emphasize independently species-difference in susceptibility.

In addition to these etiological complexities, the clinical nature of the resulting morbid state may vary considerably, even with the same material. Thus we may adopt as criteria of disease such widely diverse effects as the following: loss of physiological function of the lung resulting in limitation of ability to carry on work; intimate nature of the pathology produced, e. g., carnification, fibrosis, or necrosis; or susceptibility to intercurrent infection, with prejudiced outcome or, even more recently, the development of malignant new growth. All these clinical end-points have been used in the experimental assay of various dust hazards. It is, however, noteworthy that survival per se has seldom been adopted as a criterion.

Apart from clinical experience, a gamut of species of experimental animals has been used. These range from cockroaches to human criminals (their use has been suggested). To make interpretation even more difficult, a further gamut of methods of testing has been employed. In addition to dusting, materials have been introduced into veins, trachea, lungs, peritoneum, eyes, testes, buccal pouches of hamsters, and subcutaneous tissues and given per os. Studies have also been conducted in vitro on tissue cultures. All these methods have yielded useful information toward solving the practical problem. They can, however, provide conflicting information if due notice is not taken of the conditions governing the experiment.

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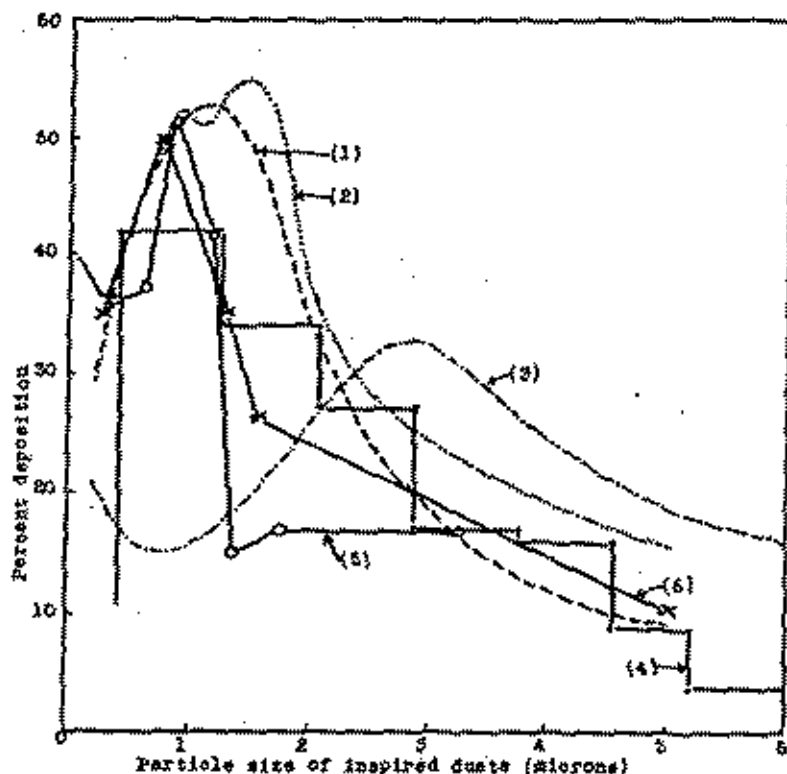
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It is obvious from a practical standpoint that the active moiety of any dust must be contained in that fraction which penetrates into and is retained in the lung of the worker. Considering first the physical attributes of the aerosol, such attributes as particle size, particle mass, and particle shape are involved. It is possible that electric charge, temperature, and color (photophoresis) may play some role in dust retention, but these have been generally assumed to be negligible. Radioactivity in certain instances is of importance.

The interrelation of size and specific gravity has been well considered recently by Watson.² The possible importance of particle shape is well illustrated by the extreme case of asbestosis. There can be little doubt that

the longest dimension of the asbestos fiber that is retained in the lung is several times greater than the similar dimension for more symmetrical dusts.

Returning to the problem of animal experimentation, we cannot help but be struck by the relatively good agreement that has been found in regard to the size distribution of dusts retained in the lungs of man as compared with the various experimental animals that have been studied, this despite the rather large difference in gross anatomical dimensions among species. This agreement may be an expression of anatomical consistency in microscopic tissue design, since the lung alveoli perform essentially the same function in the various species.



Alveolar deposition of dust of various sizes—human data compared with animal data.

Curve 1 (man) Brown, Cook, Ney, and Hatch, 1950² (china clay).

Curve 2 (man) Wilson and La Mer, 1948⁴ (Na^{22}Cl).

Curve 3 (man) Eisenbud after Landahl, 1952³ (triphenyl phosphate).

Curve 4 (mouse) Shoshkes, Banfield, and Rosenbaum, 1953¹⁰ (corn oil).

Curve 5 (guinea pig) Palm, 1954⁸ (various dusts to give range).

Curve 6 (monkey) Palm, 1954⁸ (various dusts to give range).

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To illustrate this comparison, the findings of a number of investigators who have examined the problem in man or in laboratory animals have been superimposed in the Figure. The curve of the per cent human lung retention of particles plotted against their size was determined by Wilson and La Mer⁴ by using Na^{22}Cl mists dispersed in glycerin and estimating their expulsion by measuring the radiation. Brown, Cook, Ney, and Hatch⁵ studied the retention of china clay in humans and measured particle retention by comparing the changes in dust concentration in the alveolar air as identified by the CO_2 concentration of various fractions of the expired air. The third human curve is based on that recalculated by Eisenbud⁶ from various data of Landahl and associates⁷ using triphenylphosphate clouds and estimated similarly by measuring the concentration changes in alveolar air fractions. It will be noted that the latter data show a considerable discrepancy below 2μ in size as compared with the other observations (consult Landahl and associates⁷ for discussion), although good agreement is found with the remainder of the curves. This discrepancy is considered to be an artifact by Palm⁸ on the grounds that the periods of observation in Landahl's experiments were too short to allow equilibrium to be established.

It will be noticed that these data agree essentially with the earlier findings of Drinker, Thomson, and Finn,⁹ who found a total retention of approximately 55% of dusts varying in size from 0.15μ to 6μ , i. e., within the size range that is chiefly concerned in penetrating into the lung alveoli.

The findings on human subjects are compared with those obtained in animals in the Figure. The latter include the data reported by Shoshkes, Banfield, and Rosenbaum¹⁰ using corn oil in mice, and by Palm⁸ in guinea pigs and monkeys using china clay, carbon black, antimony trioxide, and dark clay of various sizes equated for difference in densities by conversion according to Stokes' law. On the whole, the agreement between the alveolar deposition in the various species, including man, is striking.

Further corroborative data of this consistency of behavior are given by the findings of Barrett, Irwin, and Semmons¹¹ with the use of cadmium oxide fumes of estimated mean particle diameter of 0.4μ . Using as criterion the chemical assay for cadmium retained in the lungs, these authors found that "the average percentage for retention over a wide range of dosages is remarkably constant for all species tested and amounts to about 11 per cent" as measured 24 hours after dust exposures which varied from 15 to 30 minutes. The species studied included mice, rats, guinea pigs, rabbits, and monkeys.

As pointed out by Palm,⁸ this species consistency of retention is limited only to the fraction of the dust which is retained over a period of time. That deposited in nares and the upper respiratory tract does not show this degree of species agreement, but since the latter fractions are generally not retained, they are not therefore concerned with the development of the pneumoconiosis.

It is obvious, however, that only that fraction of the dust deposited in the alveoli which is retained in the lung over an appreciable period of time is capable of playing any significant role in the development of pneumoconiosis, with the possible exception of acutely toxic dust or of materials that are carcinogenic or radioactive. The information available on the score of eventual dust retention is less complete. Cember, Hatch, Watson, and Grucci¹² have reported on the fate of particulate radioactive barium sulfate injected as a hydrosol intratracheally into rats. Each animal received 0.15 cc. of the mixture containing a total of 25.7 γ of BaSO_4 . The curve of retention of the material with time showed an initial rapid disappearance which was complete within approximately six hours. This phenomenon was interpreted as being due to elimination by the ciliated epithelium. The rate of disappearance of the remainder which was considered to have penetrated to the lower respiratory tract equalled approximately one-fifth of the material per day corresponding to a half-life of 3.3 days. These authors remarked that the latter rate is more rapid than expected. Fur-

ther data have been supplied by Palm⁴ who studied the clearance rate from the lungs of guinea pigs of inhaled antimony trichloride dust, s. g. 5.6, 1μ in diameter. The animals were exposed for 12 minutes to a concentration of the order of 100 mg. per cubic meter. The guinea pigs were killed at various intervals up to 18 hours postdusting, and the dust retention was measured chemically. Palm's results agree with those of Cember and associates²² in that there is an initial rapid loss of material from actual "lung" samples which is more or less complete within six hours. This author likewise infers that this represents the removal of material which had not penetrated beyond the area of ciliary action and makes the point that, to estimate the true alveolar deposition, a six-hour holding period should be allowed after the dust exposure. The disappearance of the antimony after 6 hours is likewise at a slower rate, and the point on Palm's curve for 18 hours agrees very well with the 11% retention figure found by Barrett and associates²³ with the cadmium aerosols. The data of the latter authors also included rats and rabbits. We may conclude, therefore, that the relative agreement of eventual alveolar retention among various species may legitimately be extended to include these types as well. Rats, guinea pigs, and rabbits thus behave similarly on this score.

On the whole, therefore, we may conclude that, as compared with man, the alveolar dust retention of various experimental animals shows a reasonably good agreement, at least to the first approximation. This would indicate that, from the standpoint of dust retention, various animal dusting experiments might be expected to yield relatively reliable data in terms of the human equivalent. The variations among the various species studied and the human are not much greater than that reported, for example, by Landahl and associates⁷ for various humans under various breathing patterns.

It thus becomes evident that the human experience with natural dust with particles greater than 10μ in diameter, such as in the Sahara,²⁴ which fail to produce a well-

marked silicotic lesion, might have been foretold. These negative results confirm the validity of translating animal test assays into human terms in regard to a given dust when lung penetration may be the single limiting factor.

From the foregoing it is possible to make a rough calculation of the actual amount of dust retained by the lungs of an animal when exposed to a given dust. For example, using First and Drinker's figures²⁵ for dusty mine air of approximately 100 mg. per cubic meter (3 mg. per cubic foot), equivalent to something of the order of 5,000,000,000 particles less than 5μ in diameter per cubic meter, it can be calculated that a 250 gm. rat that breathes approximately 50 liters of such an atmosphere in an eight-hour day would inhale about 5 mg. of dust. Of this size range, as we have seen in the Figure, something of the order of 30% would be retained in the alveoli. A rat would thus be required to handle approximately 1.5 mg. of material within the space of a normal eight-hour day's exposure. This dose rate, although approximate, serves to orientate our thinking when it comes to the experimental study of the biological hazard of any particular dust.

In the bioassay of a human dust hazard by means of animal tests, the physical limits of the mechanical methods of lung clearance, be they by ciliary action, by exudate, by lymphatics, or by phagocytosis, must be considered. The available data leave much to be desired. All the above references include tests carried out for relatively short periods of time. Undoubtedly, if an occupational dust hazard exists, the duration of exposure is one of the dimensions of the trauma. Little real evidence of the relative behavior of man and various test animals is available.

There is, however, abundant information on the size distribution of particles found in the silicotic lung, which has been culled from human postmortem examinations. All this information agrees remarkably well with the findings on animals in the relatively acute experiments summarized in the Figure. Nevertheless, it must not be forgotten that

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the actual dust exposure is measured by the balance of dust deposition vs. dust removal in the lung over a period of time. When we realize that Cember and associates²² only followed a single injection of 28γ of material in the rat lungs and that Palm's exposure⁸ only lasted for approximately 12 minutes, involving the probable deposit of a similar amount of material (30γ), the need for caution in applying these results to the long-term problem becomes evident. These remarks likewise apply to experimental studies where amounts of material of a converse order of magnitude have been employed, e.g., 1000 times or more.²⁴

An important further parallelism between experimental animal and human behavior in respect to dust retention is to be seen in the fact that the lung in neither case ever comes into equilibrium with the dustiness of the environment during a normal life span. This is well shown in the case of humans by the findings of Belt and associates²⁵ who showed that the amount of residual ash recovered from human lungs increased continually with age. Experimentally in animals it has been a universal finding that the amount of dust retained in the lung increased progressively with duration of exposure, even in experiments where the dust concentration must be regarded as excessive by any standard. The eventual limit of lung capacity to retain dust has yet to be discovered.

When the chemical activities of various dusts are considered, the dose response of various animal species, as is well known, may differ widely from that for man. Tel-eky²⁶ has been prompted to conclude that the value of animal experiments has been overestimated in determining the human hazard and points out that indiscriminate deduction from animal experiments can be misleading, citing differences in lead susceptibility among species as an example. There can be no question but that this criticism is warranted, unless due caution is exercised. For example, Barrett and associates¹¹ found that cadmium dust retention by various species agreed remarkably well

with each other; yet when it came to measuring the actual toxicity of the material retained, the L. D.₅₀ varied from 500 minutes per milligram per cubic meter exposure for rats to 30 times that figure for monkeys, with other species ranged between these extremes. Only mice and rats showed evidence of an agreement within 100% of L. D.₅₀ dose.

The difference of the effect of inhaling various chemical dusts as among species usually depends on differences in systemic susceptibility to the poison rather than on differences in the local lesion. In order that any great confidence may be placed on results with animals, preferably at least two criteria should be met, namely, first, the pathological and physiological nature of the resulting experimental lesions should closely resemble that found in man and, second, there should be a demonstration that the lesion produced is predominantly local in character and not due to the systemic absorption of a poison.

It is obvious that uncomplicated silicosis is an example of a human disease that largely fulfills these criteria. The experimental lesion produced resembles closely that found clinically. The course of the disease in different experimental animals is comparable within close limits, and the disease is largely limited to the local lesion.

There remain, however, the possible differences in the influence of the time factor, as I have pointed out. We have generally assumed that the rate of production of a silicotic lesion in the smaller animals is more rapid than in man and is possibly somewhat akin to their relative metabolic rate. Well-paired quantitative data on this score are lacking. The relative metabolic rate of rats, guinea pigs, rabbits, and man is in the proportion 90 to 80 to 45 to 25 Cal. per kilogram per 24 hours, respectively. It thus will be seen that the rat metabolism is approximately twice that of a rabbit and three and one-half times that of man. If the rate of development of the silicotic lesion were directly proportional to the metabolic rate, there would be an obvious advantage in

using the smallest animal that will give a characteristic response, i. e., the rat or the mouse. However, it has begun to be recognized that this relation may not hold, in view of the accumulated reports of acute silicosis developing in man under conditions of extreme dust exposure and the realization that in most experimental situations the animal exposure has been of an order far beyond that occurring in industry, both in respect to time relative to life span and to atmospheric concentration. The intratracheal insufflation within the space of a few minutes of even 50 mg. of silica dust into a 250 gm. rat constitutes a trauma equivalent to approximately one month's exposure of eight hours daily to a dust equivalent to 5,000,000,000 particles per cubic meter. Yet this accentuated dose rate even in a rat requires approximately five months to produce a well-defined silicotic granuloma.¹⁸ When we consider the dimensions of this degree of insult both in concentration and in respect to amount and time, these rates of development of the silicotic lesion are not so far out of line with reports of acute silicosis that has developed in man under conditions that approach these in severity. There can be no doubt but that the acute experiments in animals have provided useful information, particularly when comparable materials are being compared, but such results must be regarded as qualitative when applied to the actual industrial problem. Actually little work has been done on animals with exposure to dust concentration which parallels the majority of human exposures today and which shows clinical signs of producing silicosis. In fact, King and associates¹⁹ have shown that with the insufflation technique little frank silicosis can be produced in the rat within the normal life span of this animal with doses of silica dust such as are liable to be inhaled by even the dustiest trades in the light of modern ventilation procedures. Are we to conclude, therefore, that these measures have removed entirely the hazard to man? The answer from the animal experiments, unfortunately, is not unequivocal, because the time factor

in the experimental assays differs widely, and their relative significance among species cannot be stated with certainty.

It would appear, however, that by the use of suitable animals a reasonably reliable measure of the dust fraction actually deposited in the lungs of workmen could be inferred from animal exposure to the actual dust conditions.

If it can be established that the role of development of the silicotic granuloma as among species is not proportionate to their respective metabolic rate, then indirect evidence will have been produced that the mechanism of the silicotic lesion is probably through an extracellular reaction or at least one in which some other factor than the reaction between the silica and the rate of production of any metabolite is concerned.

In the development of the simple silicotic lesion, the phagocyte and the fibroblast probably are the chief cellular structures concerned. In this respect it is noteworthy that the physical dimensions of these cells as among species show relatively little variation. The rat monocyte and the human analogue are essentially the same size. If these similar cellular elements remain dimensionally constant, it is not surprising that such factors as particle size appear to play a similar role in various animal experiments and in man. The size of dust particles which are found to be active in a rat[†] is similar to that found clinically at postmortem examination in man. An unfortunate circumstance, which undoubtedly plays a role in the development of many of the pneumoconioses, is that the particle size which penetrates to the vulnerable nonciliated alveolus is likewise of a size which is "biologically" active in relation to the phagocyte and other host cells.

Reverting again to silicosis, it can be said with considerable assurance that, if there are differences among species in respect to their tolerance of any chemical activity of silicotic dusts, then these differences are probably small.

[†] References 18 and 19.

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There is some qualitative evidence of species difference as shown by differences in production of asbestosis bodies experimentally. Thus in the classical experiments of Gardner,²⁰ it was found that the formation of asbestos bodies encountered in the lung of guinea pigs in every way resembles the golden-yellow beaded or haustrial rods pictured in human cases. In the rabbit, however, no typical bodies were found, and in the rat this occurrence was extremely rare. Since there is good evidence that the development of these bodies depends on a characteristic milieu, these differences may be taken as a qualitative measure of difference among species. This phenomenon is quite possibly related to the degree of hydration or reaction between the host tissues and the dust. Gardner considered that this lack of reaction in the rabbit was associated with at least a delay in the production of fibrosis from the dust, as compared with the guinea pig.

When the role of superimposed infection is considered, the difference among species susceptibility again becomes evident and makes difficult the accurate laboratory assessment of a clinical dust hazard. However, as the classical experiments of Gardner with the tubercle bacillus superimposed on silicosis have shown, the effect of the latter may in many respects reduce the species variation in regard to the former.

Similar remarks might be made concerning other pathological complications, such as the development of lung carcinoma. Species differences in the ease with which this disease can be induced experimentally are well known. It is now evident that real differences can exist even with different genetic strains within a given species.

In the bioassay of any response, it is axiomatic that more information is to be gained if the results can be measured quantitatively. The mere recording of the presence or absence of silicotic nodules following a given dust exposure does not yield as much information either in regard to the nature of the development of the process or of the eventual dimension of the hazard as can be gained from criteria in which an accurate

degree of response can be measured. Attempts to estimate the degree of change microscopically have been carried out in a number of laboratories, but all are subject to the judgment of the observer. The grading of the experimental silicotic lesion on a 1 to 5 basis of the Hammersmith school well illustrates this point.²¹ Undoubtedly this procedure is useful in judging results, but no one suggests that the development of the pathological process proceeds in a stepwise manner.

One cannot help but be impressed, therefore, with the usefulness of the recent development of a method by Aterman²² of estimating by quantitative chemical means the amount of collagen deposited in a given tissue. The application of this procedure to the study of the pneumoconiosis which is characterized by collagenous deposits, either within the lymph nodes, in the parenchyma, or even in the vascular tree, should provide a new dimension to the study of these diseases, as Stacy and King²³ have been quick to recognize. The method apparently is capable of providing useful information even in retrospect, since it may be applied to tissue samples after fixation. Similar methods to measure other parameters of the pathological response to dust exposure would be welcome.

As might have been expected, the influence of dust-exposure load rates on the development of pathological lesions in the lung becomes increasingly evident when the role of antagonistic substances is being studied. In such circumstances relative rates can become definitive. Thus in the experience of King²⁴ it was found that the influence of powdered aluminum in preventing the development of the silicotic lesions was not so apparent following a single intratracheal injection in rats as compared with the findings of Denny and associates²⁵ using dusting. The further finding that aluminum oxide is active under the former conditions of experimentation accentuates the point.²⁶ Animals which receive at one instance a dose of dust similar to what would normally be spread over a period of weeks, even in a very dusty atmosphere, are presented with

a challenge which may differ significantly when measured in relation to an antidotal process which may in turn have the limiting factors of relative solubility, molecular diffusion, adsorption, or even chemical interaction. The conclusion to be drawn from such experiments must of necessity be limited to the condition of the experiment and illustrates the fact that, when living processes are being studied, the one relative to the other, dose rates may be critical. In the last analysis, the process of dust inhalation and retention would appear to be one of the essential dimensions of a pneumoconiosis hazard.

CONCLUSIONS

1. Available data would indicate that there is a reasonable agreement among various animal and human species in regard to the dust retained in the lung. The use of experimental animals in the bioassay of dust hazards would therefore appear to be valid in this respect.

2. Due to large species variation, however, in regard both to the toxicity of various substances and to the relative susceptibility to concomitant infection, animal bioassay of industrial hazards has to be interpreted with caution.

3. Neither in man nor in experimental animals does the lung come into equilibrium with the dustiness of the environment. The continuous accumulation of foreign materials in the lung would appear to have increasing importance with the increasing life span. A given dust hazard must thus be judged in relation to the survival time relative to the exposure. Directly or indirectly it can be anticipated that the pneumoconioses will be of increasing interest to the gerontologists.

4. Newer chemical methods yielding a quantitative measure of tissue response offer effective measures to improve the bioassay of dust hazards, both clinically and experimentally.

5. Where relative rates of such factors as solubility, diffusion, or adsorption play a role in antidotal activity, the apparent bio-

logical efficacy of such substances depends on dose rate.

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An Experimental Study of the Effects of Rare Earths on Animal Lungs

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During the last few years of his life Dr. L. U. Gardner, then Director of The Saranac Laboratory, became tremendously interested in the problem of radiological changes which were discovered in workmen from Fostoria, Ohio, who were exposed to dusts containing rare earth oxides and fluorides. Dr. Gardner's observations led him to the conclusion that many of these shadows could be caused by the high atomic densities of the components of such rare earths.* To elucidate both this postulate and the possible biological action of the rare earths, Gardner conducted two series of experiments in which he sought to contrast the action of the following blends:

Blend 1	Per Cent
Carbon	51.5
Rare earth fluorides	39.5
Rare earth oxides	25.4
Potassium sulfate	5.5
Blend 2	Per Cent
Carbon	11.5
Graphite	1.0
Rare earth fluorides	55.5
Rare earth oxides	32.0
Potassium sulfate	5.0

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* The compounds commonly included under the grouping of "rare earths" include the elements lanthanum, cerium, praseodymium, neodymium, samarium, europium, gadolinium, terbium, dysprosium, holmium, erbium, germanium, thulium, ytterbium, and lutetium.

The studies with these substances included intratracheal and intraperitoneal injection experiments with both blends, which were commenced during 1943. An inhalation experiment and a study of the tuberculogenic propensities of the latter mixture were begun during 1945. Before these investigations could be brought to a conclusion, Dr. Gardner died. Two of us (A. B. D. and A. J. R.) who had assisted with the project had the responsibility of completing the study. In the present account the results of the intratracheal injections and the inhalation study are reported for the first time.

METHODS

For the intratracheal technique, the individual ingredients were prepared separately by grinding in a porcelain ball mill for as long as was necessary to obtain the desired sizes, 3 μ and under. They were then mixed in the foregoing proportions and adjusted to a 10% suspension in isotonic saline. The suspension was then autoclaved at 100 C for one hour. A dose of 100 mg. was administered intratracheally to two groups of nine guinea pigs in two equal amounts at seven-day intervals.

For the inhalation study, 75 guinea pigs were exposed to an aerosol of Blend 2 in a room measuring approximately 8 by 8 by 8 ft. The exposure period was for eight hours daily, five and one-half days per week for three years. Dust dispersion was accomplished by the hopper method. Dust concentrations were very high in the early weeks of the exposure but leveled off thereafter, to the order of 200,000,000 to 300,000,000 particles per cubic foot of air, as determined by light-field count. The calculated particle size was 1 μ to 2 μ .

RESULTS

For easy reference the results obtained have been assembled in Tables 1 to 4. Comments in this paper will be limited to the

EFFECTS OF RARE EARTHS ON ANIMAL LUNGS

TABLE 1.—Pulmonary Effects of Rare Earth Oxides
Intratracheal Method

Guinea Pigs, No.	Days After Injection	Died or Killed	Gross Pulmonary Reaction
8*	10	Dp	Congested with a single large conglomerate and smaller lesions
11*	10	Dp	Congested with a single large conglomerate lesion
12*	11	Dp	Congested with areas of consolidation and a single conglomerate lesion
7	25	K	One large black conglomerate lesion
9	125	K	Two conglomerate lesions with diffuse black pigmentation
24	255	Dt	Soft black conglomerate lesion
25	272	Dt	Soft black subpleural pigmentation
10	272	K	Large conglomerate lesion with mediastinal rupture
28	540	K	One large black soft conglomerate lesion with overlying pleural adhesion

* Died after second injection.
Dp—Died of pneumonia.
Dt—Died of typhoid.
K—Killed.

gross pulmonary features which were recorded at the time of autopsy. The analysis of microscopic features will be presented elsewhere.†

Reference to Tables 1 and 2 indicates that three of the guinea pigs died of pneumonia shortly after receiving the first mixture, in which there was a relatively high proportion of rare earth oxides, while four died similarly though after a slightly greater interval in the case of the mixture with the high rare earth fluoride content. It seems likely that these pneumonic casualties may have been at least partly ascribable to the chemical substances introduced.

The remaining animals survived the initial presumed trauma associated with the introduction of the foreign matter. Two of the animals from the first group and one from the second experiment died subsequently from rodent typhoid which decimated the animal population of The Saranac Laboratory

† References 1 and 2.

at the beginning of the winter of 1944-45. It is a significant fact, though, that animals survived to the end of the experiment, i. e., 540 days after the first injection.

Macroscopic inspection of the lungs revealed the presence of large, black, soft to slightly firm conglomerate lesions. These masses, which were commonest in the caudal lobe, were usually well circumscribed. In addition, an occasional animal exhibited small discrete foci of black dust pigmentation beneath the visceral pleura. Few differences in the character of the lesions were seen grossly in any of the animals in either group over the entire 540-day period. Nor were there any metastatic foci of reaction in any other organ, though some of the dust had become deposited in the mediastinal tissues and pleural space in isolated instances in a manner suggesting minor pleural ruptures at the time of the intratracheal injection.

In the case of the inhalation experiment, the casualty rate was comparatively high.

TABLE 2.—Pulmonary Effects of Rare Earth
Fluorides
Intratracheal Method

Guinea Pigs, No.	Days After Injection	Died or Killed	Gross Pulmonary Reaction
17*	11	Dp	Congestion and consolidation with one large conglomerate lesion
15*	15	Dp	Congestion with a single black conglomerate lesion
16*	25	Dp	Congestion with large conglomerate firm lesions
13*	30	Dp	Large black conglomerate lesions
14	125	K	One large conglomerate lesion and several small foci of pigmentation
26	275	Dt	Very firm tough conglomerate lesions
18	272	K	Atelectasis and pigmentation of left caudal lobe
27	540	K	Large black soft conglomerate lesions
28	540	K	Large black soft conglomerate lesions

* Died after second injection.
Dp—Died of pneumonia.
Dt—Died of typhoid.
K—Killed.

TABLE 3.—*Pulmonary Effects of Rare Earth Fluorides*
Inhalation Method: Animals Died Spontaneously

Guinea Pigs No.	Survival, Wk.	Cause of Death	Gross Pulmonary Reaction
7, 21, 39	3	Pneumonia	Early diffuse gray pigmentation
41	41	Pneumonia	Black diffuse pigmentation
69	72	Pneumonia	Heavy diffuse black pigmentation
8, 44, 51, 52, 64, 67, 69, 71	80	Scurvy (?)	Geometric pattern of heavy black pigmentation
73, 75	86	Pneumonia	Diffuse black pigmentation with focal consolidation
99	78	Pneumonia	Congestion and heavy black geometric pattern
2, 11, 47	92	Pneumonia	Voluminous lungs with marked pigmentation and scattered black foci
5, 9	110	Pneumonia	Marked pigmentation with geometric pattern
18, 14, 70	118	Pneumonia	Heavy diffuse black pigmentation with congestion
76	130	Pneumonia	Diffuse black pigmentation with discrete foci and congestion

Thus, during this lengthy exposure, 25 guinea pigs died of intercurrent causes. The remaining 50 animals were killed in groups of three, every two months, for the first two years and at more widely separated intervals during the last year, i. e., at three-month and, finally, six-month intervals.

In the majority of instances the deaths appeared to be due to pneumonia (Table 3), but an episode of apparent scorbutic fatalities appeared toward the end of the first year. Grouped in half-yearly casualty rates, a histogram with the following percentage peaks seems to emerge from this study.

Deaths	5	12	2	4	8
Months	6	12	18	24	30

This suggests a slight crescendo terminal mortality trend. There may be no pathological significance to this phenomenon, as it must be recalled that after three years in a dust chamber the effect of normal aging processes would begin to influence the rate of death in such a group. Indeed, this record would indicate perhaps the opposite phe-

nomenon, i. e., that for an inhalation study of such extreme duration the survival rate of the guinea pigs was relatively high.

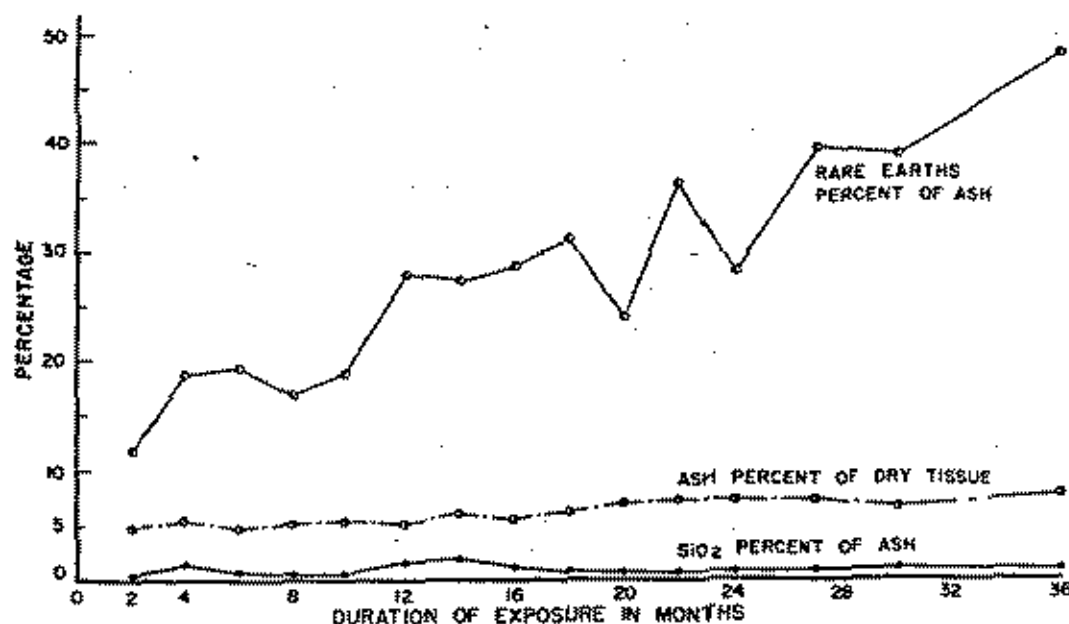
The gross observations (Table 4) revealed an ever-increasing pleural pigmentation. Pale gray diffuse pigmentation was already present in the anterior portions of the lungs at two months. During the succeeding two years the gray shade gradually deepened to black and slowly spread to the lateral and posterior pleural surfaces. Finally the anterior aspects exhibited a black geometric pattern or heavy diffuse black dust pigmentation, with a diffuse dark gray dust pigmentation of slightly lower intensity in other portions of the lungs. No lesions of comparable kind occurred in any other organ.

The chemical analysis of the lungs at the same killing periods is also of interest (Fig.). Determinations of the ash derived from the desiccated lung tissue and of the silica and rare earth content of the ash, expressed as percentages, are plotted against the duration of exposure. It may be noted that there was no increase of silica content of the lung ash over a period of three years, as could be expected, as there was no extraneous source of silica in the dust chamber to which the animals were confined. No significant increment in the lung ash could be observed

TABLE 4.—*Pulmonary Effects of Rare Earth Fluorides*
Inhalation Experiment: Animals Killed for Histological and Chemical Study

Guinea Pigs No.	Sampling Time, Wk.	Gross Pulmonary Reaction
8, 15, 16	8	Light gray diffuse pigmentation, heavier anteriorly
17, 18, 22, 23, 24, 25, 26	17	Dark gray diffuse pigmentation anteriorly, light gray elsewhere
27, 28, 29, 30, 31, 32	35	
33, 34, 35, 36, 37, 38, 39, 40	53	Heavy black diffuse pigmentation anteriorly, dark gray elsewhere; small focal accumulations of black pigment
41, 42, 43, 44, 45, 46, 47, 48, 49	61	
50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100	101	Universal heavy diffuse gray pigmentation with superimposed geometric pattern anteriorly; occasional discrete black focal accumulations
	117	
	130	
	150	

EFFECTS OF RARE EARTHS ON ANIMAL LUNGS



Graph showing the progressive retention of inhaled rare earth compounds in guinea pig lungs over a period of three years.

which could not be accounted for by age changes. There was, however, a progressive accumulation of rare earth compounds in the lung tissue, which matched the progressive pigmentation of these organs.

CONCLUSION

The precise nature of the pulmonary tissue response to the rare earth dusts, introduced into this series of 93 guinea pigs, becomes apparent only when the histological features are analyzed.† The gross observations indicate, however, that these two blends of rare earths with carbon and potassium sulfate act as relatively inert substances. The progressive accumulation of the earths could have been suggested from the steady increase in pigment in the lungs but was finally confirmed by chemical analysis. That the presence of this foreign matter, with its high atomic density, would cast radiographic shadows was adequately confirmed by other experiments to be reported on a subsequent occasion.

† References 1 and 2.

SUMMARY

Two blends of rare earths in which the oxide and fluoride ratios were reversed were introduced into guinea pigs by intratracheal injection.

An inhalation study with the mixture having a high rare earth fluoride content is also described.

The earths are progressively retained in the lung tissues.

Apart from evident deposition of the earths in the lung tissue, no gross pathological changes could be observed in the experimental animals indicating any form of pneumoconiotic fibrosis.

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The Biological Action of Rare Earths

I. The Experimental Pulmonary Histopathology Produced by a Blend Having a Relatively High Oxide Content

G. W. H. SCHEPERS, M.D., D.Sc., Saranac Lake, N. Y.

The rationale and method of this experiment have already been clarified.¹ Despite some initial losses of animals from presumably chemically induced pneumonia and later fatalities from intercurrent causes, a sufficiently representative series of guinea pigs survived to render possible a histological explanation for the pigmented areas found in the lungs. The effects of the rare earth blend which had the high oxide content can be more properly evaluated also by contrasting the microscopic appearances with those found in the experiment with the high fluoride blend.²

PULMONARY HISTOPATHOLOGY

Within a month from the time of the second injection of this dust, a distinctive histological pattern of lesions was found in those animals that survived the immediate toxic effects.

There occurred, first, a tendency to focal aggregation of the pigment particles within atrophic alveoli surrounding or adjacent to terminal bronchi and bronchioles. For the greater part such pigment was intracellular, being contained within large giant cells. Some of the particles also occurred within the alveolar walls (Fig. 1A).

The corresponding bronchi or bronchioles showed fairly extensive epithelial swelling, ulceration, and desquamation, the majority of the lumina being filled with cellular debris.

Around the air passages there were variable degrees of cellular infiltration (Fig. 1B).

The alveolar walls appeared prominently thickened, owing to remarkable distention and engorgement of the capillaries. There was, however, no tendency to intra-alveolar exudation or erythrocyte leakage.

Among these distended capillaries there were numerous swollen septal cells and a fair number of eosinophiles. These were of two types, viz., mononuclear and polymorphonuclear. None of the latter were present in the alveolar spaces. The macrophages showed instead a marked tendency to acidophilic staining of their cytoplasm, and they were inclined to be applied to the walls of the alveoli, and some could be seen to have penetrated into these walls. The mononuclear acidophiles, therefore, clearly represented these macrophages after they had found their way into the interstices between septal cells and capillaries of the alveolar walls.

A year after the introduction of the dust, some of the initial tissue responses had been completely reversed. The capillary engorgement, for instance, had given place to an ischemic state. Cells were now relatively inconspicuous within the alveolar walls except where the alveoli abut onto one another. Here macrophages, polymorphonuclear eosinophiles, and fibrocytes were congregated. Collagen was found to be sparsely laid down within the alveolar walls, and some of the latter tended to be ruptured.

Some of the peribronchial and subpleural macrophage accumulations persisted. For the most part they had disappeared, but when present the macrophages were still markedly

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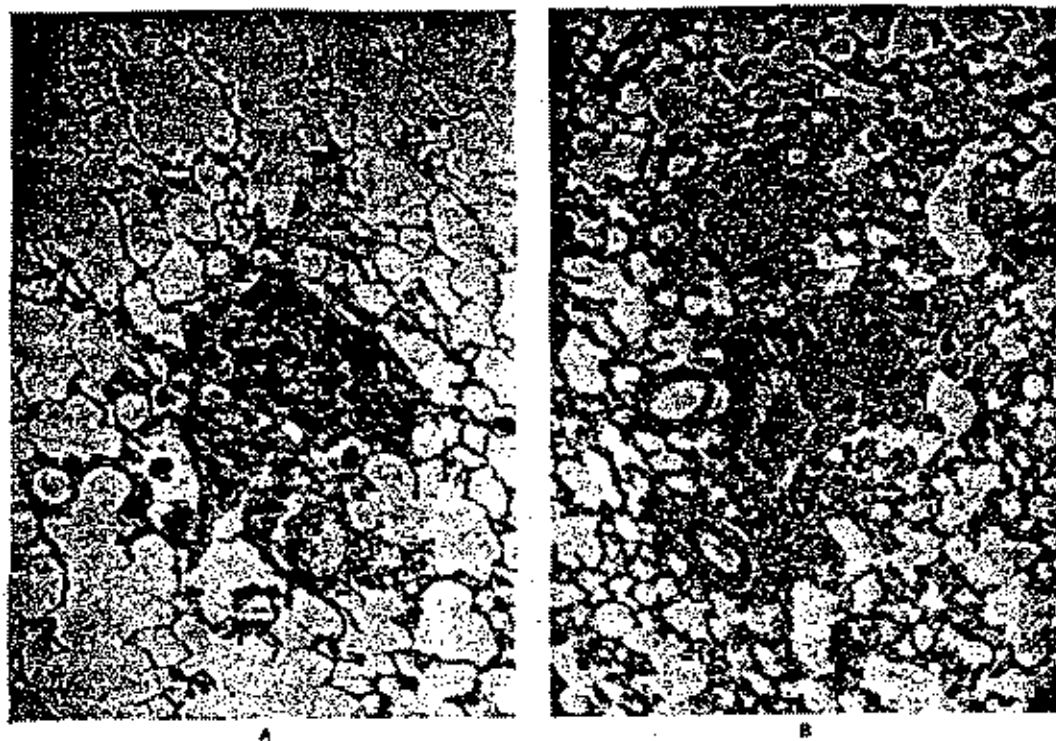


Fig. 1.—Action of rare earth oxides on the guinea pig lung—intratracheal injection; one month. *A*, focus of intra-alveolar accumulation of pigment; most of the dust has been engulfed by macrophages, and some is being transported to perivascular lymphatics. *B*, area of peribronchiolar pneumonitis, with foci of cellular proliferation; bronchiolar epithelial catarrh and swelling of alveolar walls are present.

Fig. 2.—Focal deposition of rare earths—result after one year. *A*, massive parabronchial pigmentation, with minimal cicatrization. *B*, minor parabronchiolar earth deposit, a fair amount of which is contained within macrophages.



eosinophilic and tended to form giant cells through confluence. In relation to the sites of dust deposition, no significant cellular reaction could be found. Most of these deposits were parabronchial, and in some instances the corresponding bronchus was surrounded by scar tissue (Fig. 2A and B).

The parenchymal lymph nodes showed some central endothelial cell proliferation, with perilymphatic fibrosis. The hilar lymph nodes displayed considerable medullary and follicular endothelial cell hyperplasia, pigment deposition, irregular fibrosis, and marked eosinophilia.

The main histopathological trend beyond the first year devolved on progressive hyperplasia or cellular infiltration of the parenchymal lymph nodes and hilar nodes. At the end of 540 days these structures had acquired an almost granulomatous character (Fig. 3A). The lymphocytes had been progressively displaced or even replaced by large

endothelioid cells, fibrocytes, and occasional pigmented cells. Collagen was found to have been laid down in sparse irregular bundles, but the nodes were fairly well vascularized and remained well demarcated from the surrounding lung tissue. Not only did the main lymph nodes of the parenchyma show this incipient granulomatosis, but comparable changes occurred at a multiplicity of pulmonary sites, generally parabronchial or paravascular in distribution. The hilar lymph nodes likewise showed marked medullary infiltration by means of solid phalanxes of partially pigmented, faintly acidophilic macrophages. The amount of pigment now present in the nodes was quite considerable, but there was no significant accumulation here of fibrocytes nor was there any deposition of collagen (Fig. 3B).

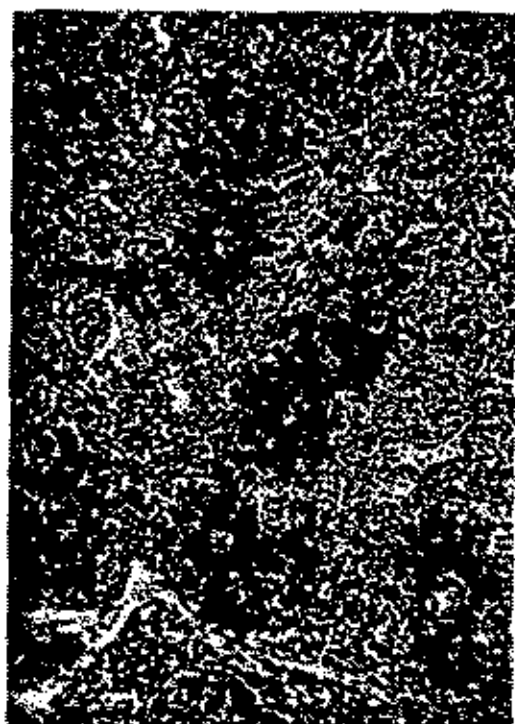
COMMENT

Several issues of significance are raised by the results derived from this analysis. Points

Fig. 3.—Delayed reaction to intratracheally introduced rare earths—result at 570 days. A, dominantly cellular paravascular pulmonary granuloma without conspicuous pigment content. B, hilar lymph node showing focal aggregation of the rare earth dust without associated reaction to its presence.



A



B

BIOLOGICAL ACTION OF RARE EARTH OXIDES

of possible industrial medical significance concern the conspicuous absence of fibrosis of any material degree and the focal aggregation of pigment in atelectatic alveoli.

The lack of fibrous reaction immediately directs attention once more to the fundamental contrast between the malignant effects of quartz dust at one end of the scale and the benignity of other dusts. There is a growing body of medical opinion which regards all dust as harmful, and few authorities will be found who would be prepared to deny this axiom provided that no limit is set for the range of dust levels to which it applies. But, dose for dose, it is clear that dusts vary markedly in respect of their fibrogenicity, and the rare earth blend under review must be classified as inert except for its capacity to provoke some chemical pneumonitis. There was too little potassium sulfate in this blend (3%) to have played a significant role as an inhibitor of fibrosis but the carbon (31%) may have reduced any intrinsic pathogenicity which the earths may possess. It is in theory possible also that the ratio of rare earth fluorides to oxides would nullify any sclerosing influence of either component. Such leads naturally need to be followed up.

The injurious action of any dust may also express itself by way of its effects on the bronchi and alveolar membranes even when no fibrogenic stimulus goes forth from it. However, in this series of rare earth exposures neither bronchitis nor bronchiolitis persisted after the initial irritation caused by the introduction of the dust suspension, and no terminal emphysema could be demonstrated.

The prolonged focal persistence of rare earth deposits may furnish a clue as to the reasons for radiographic mottled shadows which may be demonstrated in men who have been industrially exposed to these substances under conditions facilitating the inhalation of dust. Discovery of such shadows in plant personnel should clearly be interpreted with some caution; they would probably correctly signify a benign underlying condition comparable to *baritosis* or *argy-*

rosis rather than a disease associated with fibrosis or any other progressive process.

The foregoing deduction requires one specific exception. The delayed effects of the rare earth dust appear to include a propensity toward granulomatosis of a kind somewhat reminiscent of that already well popularized as a chronic lesion associated with the inhalation of certain beryllium compounds. Apart from the intrinsic significance of this lesion, the presence of such granulomata could possibly cast additional roentgenographic shadows.

It is of significance to note that the granulomata first appeared when the rare earth components were being progressively withdrawn from the pulmonary tissue. Incidentally, no study was made at the time as to whether beryllium compounds were or were not present in the rare earth blend. Attention should also be drawn to the fact that the granulomata developed within lymph nodes by a process of substitution for the lymphoid tissue. This process is somewhat contrary to the apparent sequence of events in beryllium disease where granuloma formation may oftener than not commence in alveolar walls or at the angles between separate alveoli while lymphoid tissue mostly escapes early involvement. A further point of contrast concerns the marked lack of the fibrogenic action in relation to these granulomata in the rare earth exposure.

The marked eosinophilic reaction is apparently a distinctive phenomenon in this case. Not only did eosinophiles occur early and persist to the end of the experiment, but they varied from polymorphonuclear cells to monocytes and could be found in the lung parenchyma as well as the hilar lymph nodes. The presence of eosinophilia has recently been reported in connection with the experimental exposure of guinea pigs to cobalt metal.⁸ It is also an early manifestation in the reaction to quartz dust,⁹ the difference being that quartz is acutely toxic to the eosinophiles whereas the rare earths do not appear to destroy them.

A final point of interest concerns the progressive transport of the earths to the hilar

lymph nodes and the delayed reaction at this site. By analogy this occurrence might signify that, given enough subsequent time in normal air, industrial personnel who had inhaled the dust and in whose lungs suggestive miliary radiopacities had become established may anticipate ultimate amelioration of this sign. It would be of interest to know whether such extrapolation is permissible.

SUMMARY AND CONCLUSIONS

When introduced into the lungs of guinea pigs, a blend of rare earths with a high oxide content produced fatal delayed chemical hyperemia in a third of the animals.

In those that survived the introduction of the dust, cellular eosinophilia was a prominent feature.

Most of the dust was trapped within focal atelectatic areas, and no material chronic cellular reaction or fibrosis occurred in relation to these deposits.

Isolated cellular vascular granulomata were found after a year.

Most of the pigment seemed gradually to be transported to the hilar lymph nodes but caused no significant reaction there.

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The Biological Action of Rare Earths

II. The Experimental Pulmonary Histopathology Produced by a Blend Having a Relatively High Fluoride Content

G. W. H. SCHEPERS, M.D., D.Sc., Saranac Lake, N. Y.

Although the blend of rare earths with a relatively high fluoride content was not significantly more toxic when introduced intratracheally than was the blend with the higher oxide ratio, to judge by the mortality trends,¹ the histological lesions provoked differed considerably.² In the present account the pulmonary lesions produced by the high fluoride rare earths, both on intratracheal injection and after a prolonged period of inhalation, will be described. These experiments have already been outlined.²

PULMONARY HISTOPATHOLOGY INDUCED BY INTRATRACHEAL EXPERIMENT

The immediate pulmonary tissue response to the intratracheal injection of 100 mg. of this dust manifested itself as a marked parenchymal hyperemia and as bronchitis and bronchiolitis.

This acute reaction was still present at the end of the first month after the second injection and was seen to consist of massive distention of capillaries, some being so engorged as to completely occlude the alveolar spaces. There was, however, no material tendency to leakage of serum or blood cells from these enlarged blood sacs.

The bronchitis and endobronchitis persisted in a subacute form at the end of the first month. There was considerable epithelial necrosis and desquamation, and plugs or debris filled the lumina of some of the air passages. More spectacular was the prominence of peribronchial cellular infiltrates,

comprised mainly of lymphocytes and macrophages. Eosinophiles were not prevalent. Dilated blood vessels were found lying among these cellular deposits. The bronchial muscular layer had become hypertrophied even at this early stage, and the alveolar ducts tended to be dilated. This suggests that a state of bronchial spasm and obstruction to air flow had prevailed in the preceding weeks. Regional peripheral emphysema also was in evidence (Fig. 1A).

Around the smaller blood vessels there were marked lymphoid concentrations, and the parenchymal lymph nodes themselves showed some marginal proliferation.

Scattered pigment deposits were present. The sites of election for these were in close proximity to bronchioles, more frequently in relation to those that had become partially plugged by mucus and cellular detritus. Most of this pigment was extracellular, though some was present in macrophages and some had entered the alveolar walls. Koniophores were, however, relatively scarce within the alveoli.

The enlarged hilar lymph nodes showed marked medullary endothelial-cell hyperplasia and infiltration by means of acidophilic pigment-bearing macrophages (Fig. 1B).

The tendency to capillary distention persisted regionally even after the expiration of a full year. This phenomenon was most marked where there were conspicuous dust deposits. At such regions some cellular proliferation in the walls of the containing alveoli also could be found.

More generally the alveolar walls had already become attenuated, relatively acellular and avascular, and contained very little pigment or koniophores. There was, however,

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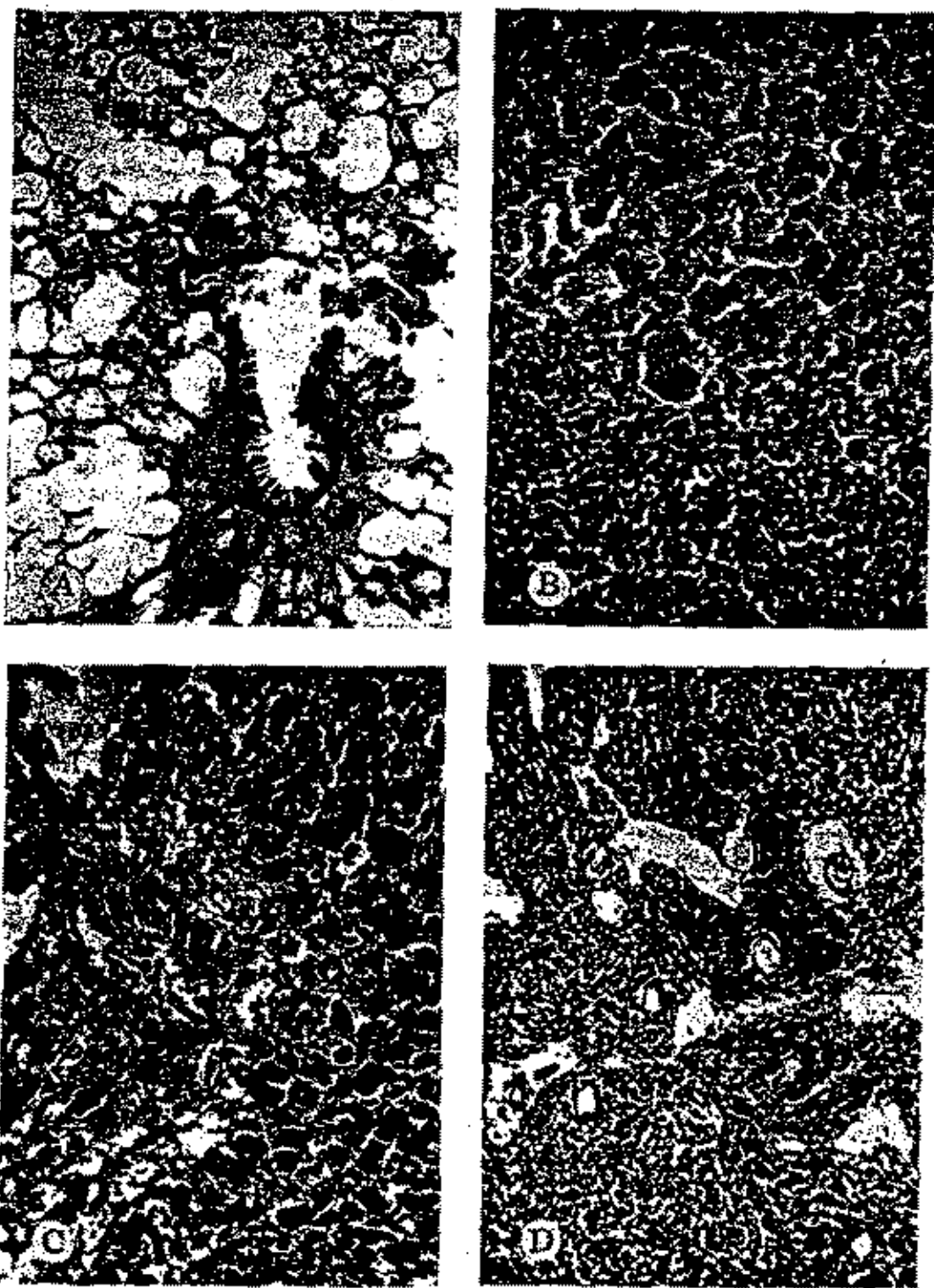


Fig. 1.—Early and delayed reactions to intratracheally introduced rare earths—100 mg. dose: guinea pigs. *A*, lung: marked hyperemia with bronchiolitis (one month). *B*, hilar lymph node: eosinophile infiltration in the medulla (one month). *C*, massive parabrachial deposits; dust trapped within atrophic alveoli around a partly regenerated bronchus (17 months). *D*, hilar lymph node: focal accumulation of pigment without regional fibrosis or vascular damage (17 months).

BIOLOGICAL ACTION OF RARE EARTH FLUORIDES

no atrophic vesicular emphysema through rupture of adjacent walls, but in some areas the alveoli remained relatively distended.

The cellular infiltration around blood vessels had receded, leaving an insignificant residuum of cellular collars encircling smaller vessels. The bronchioles and alveolar ducts were inclined to remain distended. There was some trend toward crypt formation and epithelialization of proximal alveolar walls. The lymph nodes showed marked medullary macrophage infiltration but no distinct fibrosis.

Healing proceeded very slowly, and by the end of 570 days regional hyperemia, cellular infiltration, bronchitis or bronchiolitis, and atrophic emphysema could still be found even though very few dust particles remained in the parenchymal pulmonary tissues. All such matter appeared to be within the occasional koniophores which were present. At isolated sites where the dust had been heavily deposited around bronchioles, the lack of fibrous reaction could be well seen (Fig. 1C). The affected bronchioles showed some distortion but had become partially healed. The hilar lymph nodes also showed marked medullary infiltration by acidophilic macrophages and some fibrocytes, but there were no material collagen changes despite heavy focal deposits of rare earths (Fig. 1D).

HISTOLOGICAL CHANGES RESULTING FROM INHALATION EXPERIMENT

When the dust was introduced more slowly and caused to accumulate progressively within the pulmonary tissues by means of the inhalation experiment, certain essential differences in the tissue reaction could be observed.

The particles were readily phagocytosed by alveolar macrophages and evidently as rapidly transferred to the alveolar walls. Indeed, at the end of the second month as many dust-filled koniophores could be seen within the alveolar walls or at the interstices where different alveoli meet as could be demonstrated within the alveolar spaces or within free-lying koniophores (Fig. 2A). Pigment could be identified within the cytoplasm of the alveolar septal cells, and even the

epithelial cells of bronchi and bronchioles contained black granules. This observation constitutes a most unusual phenomenon in dust experiments and seems to signify an undue avidity of tissue cells for this dust.

A variable degree of cellular proliferation or accumulation occurred within the alveolar walls and consisted almost wholly of macrophages with occasional eosinophiles and plasma cells. Many of the alveolar walls appeared completely normal; yet many others showed marked capillary engorgement. Yet others seemed to have become devascularized. The latter appearance could be related to the fact that many of the smaller arterioles were closely ensheathed within dense collars of macrophages and plasma cells which encroached upon the vascular lumina.

No decisive trend toward regional aggregation of the pigment deposits or the cellular accumulations could be discerned at such an early stage. The parenchymal lymph nodes showed no proliferative response, but the hilar lymph nodes were found to be swollen through moderate medullary hyperemia and macrophage infiltration. This reaction was out of proportion to the limited amount of pigment concentrated here.

The bronchi and bronchioles tended to be a little distended, but the epithelial surfaces were normal except for a tendency to absorb pigment.

At four months from the onset of the inhalation experiment, the tissues revealed a decisive change. Now numerous areas of intense cellular accumulation could be found in subpleural, perivascular, and peribronchiolar or parabronchiolar locations. At some sites the swollen alveolar walls had become virtually confluent (Fig. 2B). The main components of these areas appeared to be macrophages and plasma cells, but some lymphocytes and polymorphonuclear leucocytes were also to be seen, and vascular capillaries survived within these consolidated areas. No eosinophiles were present.

For the most part the capillaries were engorged, and at isolated points the distended capillaries had ruptured, with extravasation of erythrocytes into the alveoli.

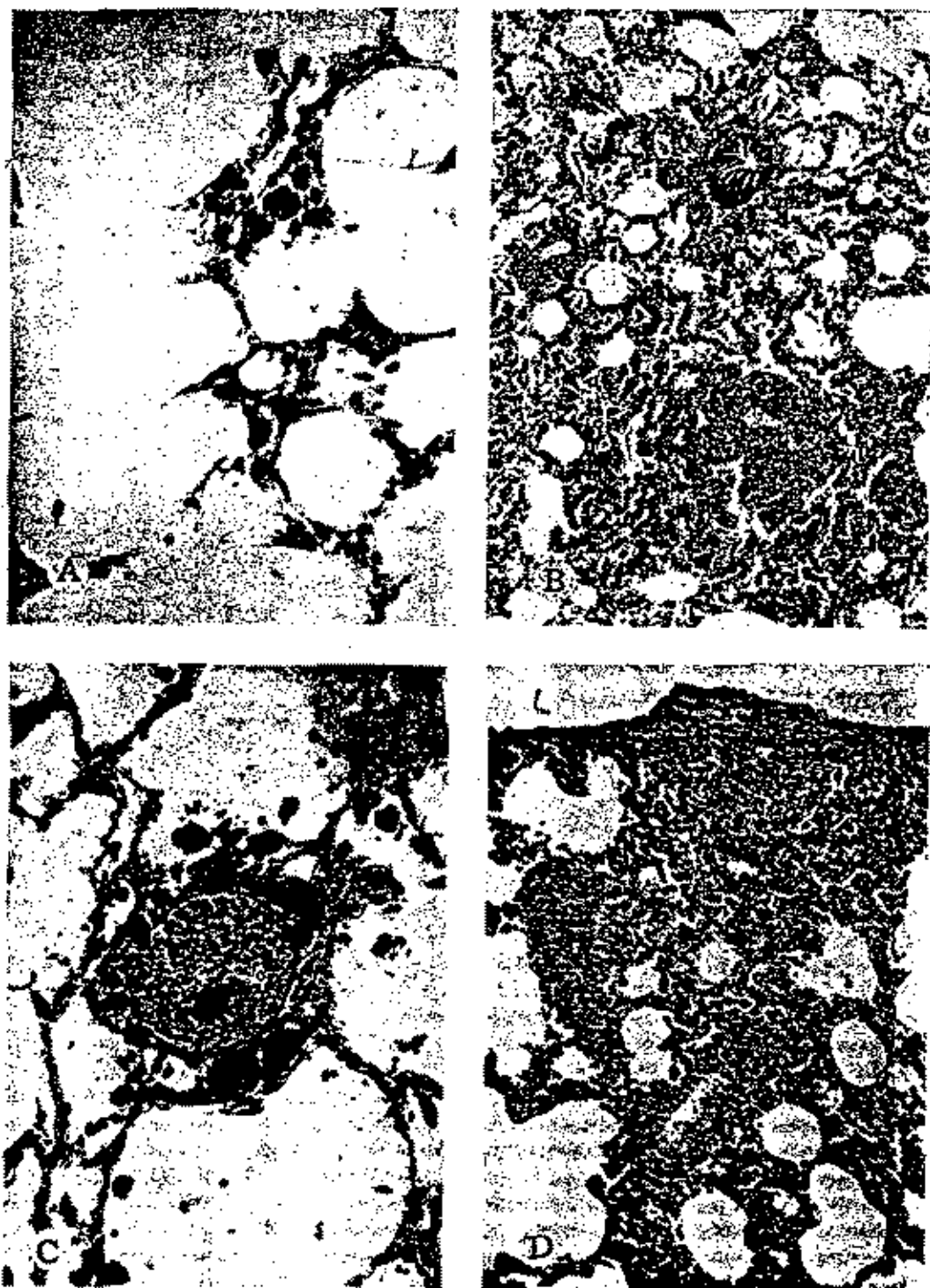


Fig. 2.—Early pulmonary response to inhaled rare earths—guinea pigs. A, alveolar walls showing pigment-filled macrophages applied to and penetrating the alveolar walls (two months). B, diffuse and focal cellular proliferation in the pulmonary parenchyma (four months). C, perivascular accumulation of intracellular pigment (12 months). D, subpleural focus of cellular infiltration (12 months).

BIOLOGICAL ACTION OF RARE EARTH FLUORIDES

An interesting feature regarding the dust pigment concerned its marked predilection for incorporation within enormous koniophores, which showed distinct pseudopodia by means of which they adhered to adjacent alveolar walls. Distended though these koniophores were, nevertheless they managed to insinuate themselves into the interstices of the alveolar walls, and many could be observed partly imbedded within the alveolar septa and partly protruding from them.

The lymphoid tissue in the lung also showed some marginal proliferation, with cells infiltrating into the adjacent alveolar septa. At this early stage the hilar lymph nodes did not show any marked change beyond that already noted.

By the end of the first year the foregoing pattern of reaction to the inhaled dust had become well established, and certain additional features had been added.

The progressive accumulation of particles within the alveolar spaces and around smaller blood vessels was now much more apparent. This pigment occurred as large masses in relation to which macrophages were not always detectable, though it may be presumed that some cytoplasmic elements were cementing the particles together (Fig. 2C).

Cellular masses were now more prevalent in the subpleural zones, and within the centers of some of these areas some necrotic changes were noted. Frequently these cellular zones were also markedly hyperemic, and hemorrhages occurred into and around these regions (Fig. 2D).

Quite an advanced degree of atrophic vesicular and hypertrophic focal to bullous emphysema had supervened at a multiplicity of sites toward the end of the first year. Some of the former types of emphysema could have been due to degenerative changes in the alveolar membranes, but the latter variety was almost certainly related to associated changes in the bronchi.

Chronic bronchitis and bronchiolitis had become well established. The essential lesions comprised epithelial necrosis and desquamation with attempted papillary regeneration,

but a mucosal reaction was not a prominent feature. The air passage distention seen at earlier stages now constituted a distinct bronchiolectasia, and a certain measure of crypt formation was present. Desquamated detritus occupied some bronchi.

Toward the end of the first year the inflammatory type of reaction had almost completely subsided. The lessened alveolar wall hyperemia even gave way to apparent ischemia. At isolated foci there still was some evidence of cellular infiltration, and areas of almost complete lobular consolidation by macrophages could be found. No fibrosis was observed in these areas. This type of reaction did not increase as the experiment proceeded, and the presence of these reactive zones could have represented residua of earlier more extensive inflammatory reactions.

Throughout the subsequent two years of this inhalation experiment, the rare earth dust slowly accumulated in the lung tissue. The maximal deposition occurred subpleurally and as paravascular and parabronchial condensations. The pigment was found not only in macrophages applied to the alveolar walls in these regions but more particularly accumulated in lymph spaces and nodes in the lung. The hilar lymph nodes, however, showed no significant progressive infiltration during the second and third years, beyond the stage already reached by the end of the first year; nor was there any focal cellular or fibrous reaction to the presence of these pigment deposits.

The emphysema which had become evident at a quite early stage of the experiment evolved into a characteristic and progressive disorder during the second and the third year. The atrophic vesicular phase receded in significance once the inflammatory stage had subsided. In its place the hypertrophic focal variety evolved into a multifocal bullous disease. This change was most marked at the lung periphery and in the apices and bases. Many of the bullae became so large that they compressed adjacent alveoli. Though their walls became extremely attenuated, they did not readily rupture. In some instances epithe-

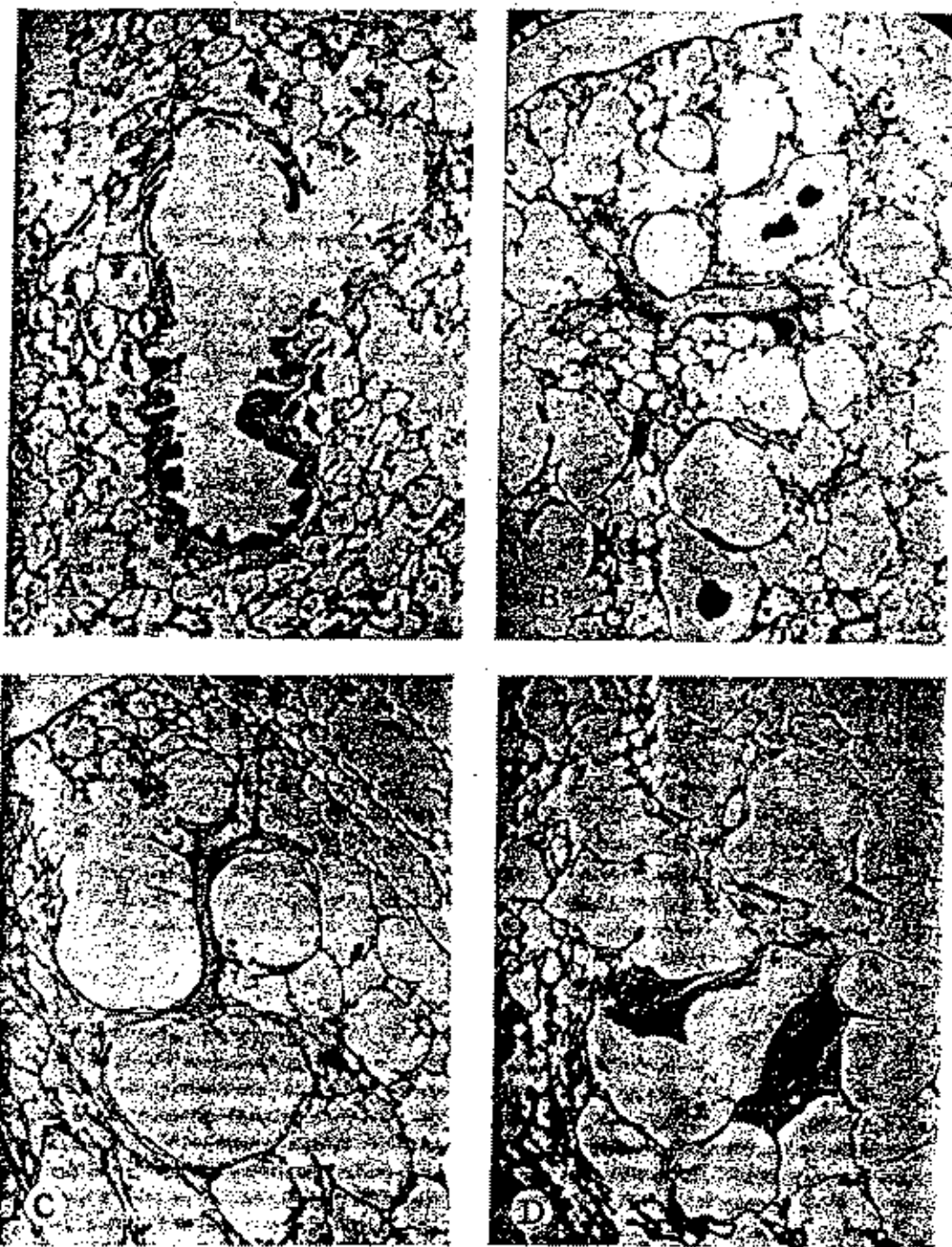


Fig. 3.—Genesis of focal hypertrophic emphysema—inhaleation of rare earths: guinea pigs. *A*, bronchiole with distended alveolar ducts (12 months). *B*, cluster of distended alveolar ducts around a blood vessel (16 months). *C*, alveolar ducts dilated at the expense of adjacent alveoli which they compress (24 months). *D*, perifocal emphysema through deposition of pigment in relation to blood vessel (30 months).

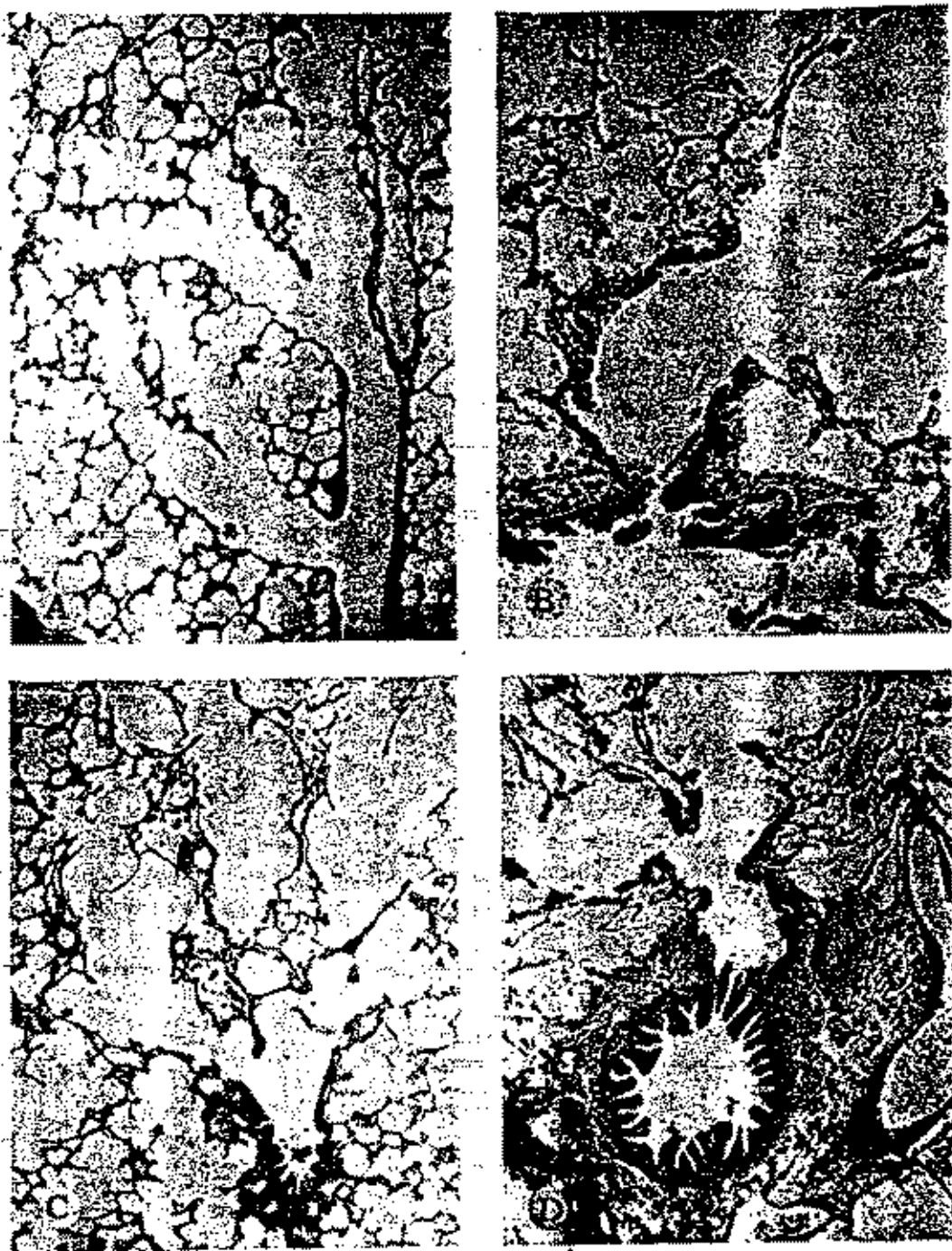


Fig. 4.—Genesis of focal hypertrophic emphysema—inhalation of rare earths: guinea pigs. *A*, incipient distention of alveolar ducts with normal alveoli and bronchioles (two months). *B*, sphincteric narrowing at point of juncture between alveolar ducts and bronchioles (16 months). *C*, distention of alveolar ducts and bronchioles with some mural rupturing (36 months). *D*, distention of peribronchial blood vessels and sphincteric narrowings at points of bifurcation of bronchioles (36 months).

lialization of these bullae proceeded outward from the proximal alveolar ducts and bronchioles, many of these alveolar ducts themselves having become markedly distended and resembling bullae. Where the bullous spaces invaded areas of cellular proliferation, a very characteristic honeycomb effect was produced.

The evolution of a characteristic cluster of bullae has been traced in Figure 3. As is evident, the distention of alveolar ducts commenced at an early stage and preceded enlargement of the alveoli, which became plowed open from the proximal to the distal portions. The distending alveoli then became clustered about the parenchymal vascular system and by compressing and displacing intervening alveoli eventually abutted directly on the vessels. At this stage, reached toward the end of the second year, the emphysema cannot yet be classified as of the pericardial variety. However, during the final year of the experiment, the intrapulmonary pigment increased markedly, and by infiltration around and in relation to the blood vessels, the characteristic grouping of bullae round a focus of pigment (Fig. 3D) is seen.

The walls of these distended spaces appeared to be very thin but apparently did not rupture readily, though some interrupted septa could be seen toward the end of the third year (Fig. 4C). Cuboidal epithelium lined these spaces partially, and it is clear that these cells were remnants of normal constituents of the lung, having been derived from the alveolar ducts which had changed into these bullae.

Considerable pulmonary vascular medial myohypertrophy, apparently associated with this emphysema, had supervened toward the end of the third year of exposure. Capillary circulation through the walls of the alveoli appeared unimpaired for a prolonged period after the initial phase of engorgement. Toward the latter months of the third year of the inhalation experiment, alveolar wall ischemia became partially evident, and it is, of course, possible that these regional changes may be related to the muscular hypertrophy in the blood vessels. Unfortunately no record was

kept of any possible associated *cor pulmonale*. Distention of the bronchial vessels was demonstrable at the end of the three years of exposure (Fig. 4D) and may possibly have some relation to the evolution of the restricted pulmonary circulation and the possible establishment of a collateral circulation.

The respiratory passages revealed a series of interesting changes. Fusiform distention of the bronchioles and alveolar ducts was demonstrable within two months from the start of the experiment, shortly after the acute bronchitis had commenced to change to a more chronic phase (Fig. 4A). By the end of the first year chronic inflammation had become associated with the development of prominent epithelial rugae and sphincteric contractions of the lumen at points of bifurcation of the bronchial tree. Isolated sacculations of the walls of bronchioles and of the alveolar ducts were also present (Fig. 4B). The scars of earlier periods of more acute inflammation could frequently be seen to distort bronchial walls at points where the muscularis was interrupted (Fig. 5A). That even at this delayed stage (18 months) the bronchial mucosa was still actively participating in the retention of the rare earth dust is evident from Figure 5B. The masses of pigment demonstrated are all contained within koniophores. It is not clear, of course, whether the pigment was being extruded by this route, after having been trapped within the alveoli and transported by the lymphatics to the bronchi, or whether the pigment represented new dust recently absorbed directly by the bronchial epithelium.

While some of the alveolar ducts had become grossly dilated, others of these ducts persisted among the bullae as relatively atrophic structures surrounded by pigment-laden cells (Fig. 5C). Toward the end of the third year of exposure, the focal deposition of the pigment in relation to the sphincteric narrowings, which lie proximal to the distended alveolar ducts, had become clearly demonstrable (Fig. 5D). These regional narrowings were not necessarily associated only with bronchi which were the seat of active chronic inflammatory reaction.

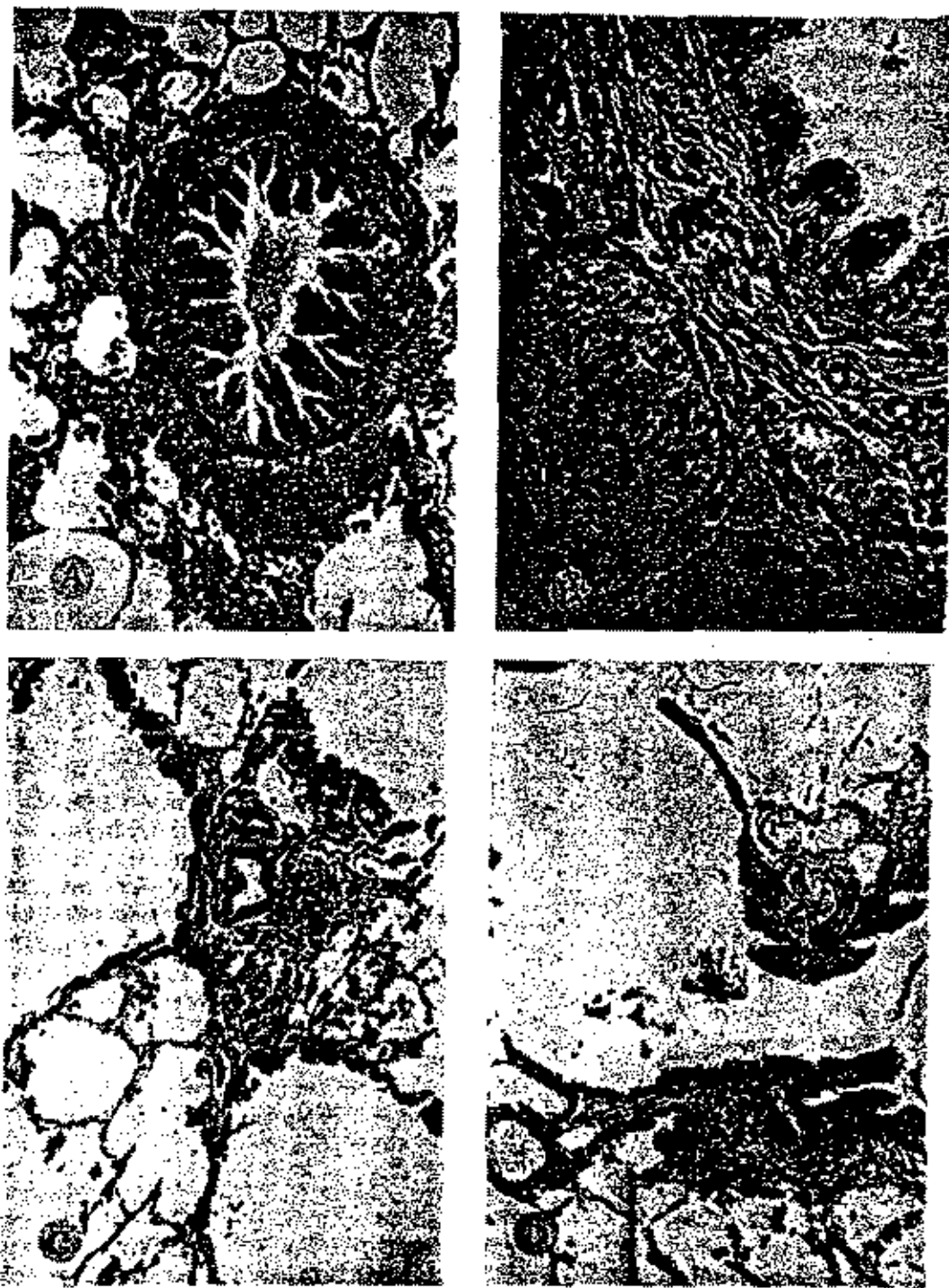


Fig. 5.—Bronchial changes induced by rare earths—inhaleation method; guinea pigs. *A*, peribronchial infiltration and minimal associated distortion of walls (18 months). *B*, pigment-laden cells infiltrating around distended blood vessel, into mucosa, and between bronchial epithelial cells (18 months). *C*, distended alveolar ducts resembling alveoli but partly lined by cuboidal epithelium; one atrophic duct surrounded by pigment-containing cells (18 months). *D*, deposition of rare earth particles in the adventitia of a bronchiole opposite constricted annular zone of transition to alveolar duct (30 months).

COMMENT

The results of this experiment with rare earths in which the fluoride salts predominated raise numerous issues beyond those specifically concerned with the toxicology of rare earths or of fluorides.

The dominant pathological effects provoked are the bronchial changes and the emphysema.

The explanation of this emphysema phenomenon appears to reside in the sequence of changes affecting the bronchioles. Indeed, as the bullae on final analysis really are distensions of the alveolar ducts, the disease process truly remains limited to the respiratory passages. Which came first? The widening of the alveolar ducts and terminal bronchioles commenced as early as the second month of the experiment, before there was any possibility of mechanical factors as a cause either in the form of obstruction or distortion through local pigment deposition or fibrosis. On the other hand, the regional valve-like or sphincteric appearances cannot be ignored as possible mechanisms in the final phases of the genesis of the emphysema. Morphologically speaking, these sphincters do not appear narrow enough effectively to block the air flow past them, and any obstruction rigid enough to achieve the latter result would more likely lead to regional atelectasis. It is possible that the prominent rugae near these narrowings may act as selective check valves, which are forced against the strictured segment of the lumen on expiration but move out of the way on inspiration. Some of the flaps demonstrated in this series could possibly act in such a manner, but others would have the diametrically opposite effect, to judge by their anatomical disposition in relation to the strictured zone. The more likely explanation seems entirely speculative and is based on the demonstrated deposition of the rare earth particles in juxtaposition to the sites of the autonomic ganglia and nerves via which the motor tonus, peristaltic waves, and other rhythmical contractions of the bronchi and bronchioles are regulated. It may be presumed that the same chemical components of

the rare earth blend which were capable of provoking the mild degree of chronic inflammatory reaction would possibly act chemically on the pulmonary system of innervation and particularly at the sensitive synaptic junctions. The latter are present in the lung as orthosympathetic relay stations; assuming for the moment that the parasympathetic fibers of the vagus are not as readily affected by the chemical agents, as they have no synaptic relays such as are known to exist for the orthosympathetic nerve fibers, the possibility of a focal inversion of autonomic balance would arise. This would then be an instance of a chemically induced neurogenic type of focal emphysema.

It is but one step from this experiment to Heppleston's⁴ concept of focal emphysema in coal workers. Coal has such a diversity of substances within its composition that it would not be surprising to learn that the essential components in the high fluoride rare earth blend which produced focal emphysema experimentally are present also in coal and thus would perhaps be the causative agents of coal miners' emphysema. It is perhaps not even necessary to have the identical chemical agents. I have recently shown⁵ that several unrelated heavy metals appear capable of producing comparable lesions.

Why then has focal emphysema not previously been experimentally induced by coal dust? Species specificity may partly account for the phenomenon. Thus, while coal may produce emphysema in man, it will not necessarily do so in animals. By the same token, one cannot extrapolate the results obtained by the present experiment directly to man. Not until emphysema does become an industrially significant disease in workers exposed to rare earth fluoride dusts, would the present findings on guinea pigs become applicable as an explanation for the human disease.

It is possible also that experiments on coal, carbon, or graphite have not always been carried through for a sufficiently long period. Emphysema became clearly established as a dominant disease in the present experiment

* References 4 and 5.

BIOLOGICAL ACTION OF RARE EARTH FLUORIDES

only after a period of prolonged exposure. Even in The Saranac Laboratory inhalation studies have not always been prolonged for three years. Perhaps repetition of the coal experiments over such a prolonged period would bring about the desired result.

A further significant discovery which has relevance to the problem of coal miners' emphysema concerns the observation that the focal distention of the alveolar ducts preceded the massive deposition of the dust in the lung. It has generally been assumed that in coal miners the anthracosis precedes the emphysema. A study of autopsies on coal miners who died from accidents in the early part of their career might reveal significant relevant data.

It should be pointed out too that in this blend of rare earths there was no silica. The opinion is widespread that quartz is the crucial factor in the genesis of disability of coal miners. Evidence seems to be at hand that the causative agent in coal need not necessarily be the quartz but may be some other ingredient.

The evident avidity of the koniophores for the rare earth blend in this experiment contrasts with the minimal degree of hilar node involvement in the inhalation experiment. The presence of dust-laden cells in the bronchial mucosa and epithelium furnishes a hint that the route of elimination of the dust was partly via the bronchial mucosa, so that the hilar lymph nodes were bypassed. The capacity of the koniophores to gorge themselves with the rare earth particles until they had attained up to 10 times their normal dimensions may have led to the implication that such juggernauts could not be transported all the way to the hilar nodes, dying on the way and ultimately accumulating focally in the lungs. It is also possible that such engorged cells may have blocked the finer lymphatic passages after they had ceased to be able to change their shape by amoeboid action.

It is possible too that no significant changes are produced in the hilar lymph nodes, because the particles are not necessarily permanently retained here, being redistributed to the rest of the reticuloendothelial system as fast as they reach the hilar nodes.

SUMMARY

1. When introduced by intratracheal injection, a blend of rare earth compounds dominantly composed of fluorides provokes an acute transient chemical pneumonitis, subacute bronchitis and bronchiolitis, and residual deposits in relation to which no reaction occurs.

2. The dominant histopathological changes which result progressively from the prolonged inhalation of the rare earth high fluoride dust comprise focal hypertrophic emphysema, regional bronchiolar stricturing, and subacute chemical bronchitis. Pigment is focally retained but provokes no fibrosis or granulomatosis.

3. The results furnish clues concerning the mechanism of coal miners' emphysema.

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An Experimental Study of the Effects of Talc Dust on Animal Tissue

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and

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The occurrence of a series of deaths from pulmonary disease following exposure to talc mining in upper New York State caused The Saranac Laboratory to inquire experimentally into the precise causative agent of this form of pneumoconiosis. This series of experiments, in which one of us (T. M. D.) participated, was conducted at The Saranac Laboratory under the supervision of the late Leroy U. Gardner, M.D., during the period 1937-1941, and the results are now reported for the first time. They have lost neither their relevance nor importance, as instances of talc pneumoconiosis recur sporadically, and a recently resected lung apical lobe from a paper-mill worker, suspected to be suffering from tuberculosis, revealed on study by one of us (G. W. H. S.) that talc dust may cause lung disease in the most unexpected of occupations.

A study of the dust to which eight fatal cases were exposed and of the minerals recovered from their lungs¹ showed that the mineral talc is but one of the components of commercial talc, to which they were exposed. Along with the talc there occur in variable proportions tremolite, anthophyllite, quartz, serpentine, and dolomite. The animal experiments were, therefore, designed to probe the specific effects of each of these compo-

nent substances. In these experiments the mineral, or mixture of minerals, in the form of a dust suspension was introduced into animals by the intravenous and by the intratracheal technique. Rabbits, guinea pigs, and rats were used, but not both techniques were employed for each species. Minerals selected for their purity were used, and in some instances contaminating substances were removed, or reduced in amount, by sedimentation in heavy liquids.

The progressive and essential steps followed in conducting these experiments are summarized in the accompanying Tables. A separate control study with quartz was not performed, as the effects of this substance had already been established by previous experiments at The Saranac Laboratory, and those experiments serve as a control standard.

The intravenous method of introducing dust into animals was used in an investigation in which the mineral dust, ground until the particles were 3μ and smaller in size, was injected into the vein of rabbits and of rats (Table 1). Both species were used in the studies with talc, soda tremolite, and serpentine, and rabbits only in experiments with soda-iron tremolite, anthophyllite, and dolomite.

The intratracheal technique was employed in three sets of experiments. In one set (Table 2), the four minerals studied were injected in the form of particles 3μ and less in size, and, in addition, two of the minerals (tremolite and anthophyllite) were used as a dust composed of particles 20μ and smaller in diameter. In the second set (Table 3), which was conducted with fibrous minerals, the material was crushed and then separated

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EFFECTS OF TALC DUST ON ANIMAL TISSUE

TABLE 1.—Intravenous Injection Experiments with Talc and Associated Minerals

Dusts Composed of Small Particles or Short Fibers				
Dosage: The total amount of dust injected was 150 mg. divided into 15 equal doses (each dose was 10 mg. of a 1% suspension) injected twice a week for 15 weeks into the ear vein. For rats the total amount of dust injected was 150 mg. divided into 15 doses (beginning at 0.5 ml. of a 0.25% suspension and increasing to 0.5 ml. of a 1% suspension) injected twice a week for nine weeks into the tail vein. Periods at Which Animals Were Killed: Usually at intervals of 4 to 6 months up to one year after injection and at intervals of 6 to 12 months thereafter.				
Mineral	Time After Injection, Mo.	Animals	Maximal Survival After Last Injection, Mo.	Results
Talc (Georgia)	1,000	4 rabbits	24	Bronchitis, bronchiectasis, endarteritis proliferans, macrophage catarrh, pleural thickening
Talc (Georgia)	72	6 rats	26	Inert
Tremolite (Alps)	100	4 rabbits	19	Inert
Tremolite (Alps)	43	4 rabbits	24	Inert
Tremolite (Alps)	210	4 rats	10½	Minute cellular infiltrates
Anthophyllite	1,400	4 rabbits	24	Minute cellular infiltrates
Serpentine	50	4 rabbits	22	Persistent perivascular granulomata
Serpentine	50	4 rats	22	Persistent perivascular granulomata
Pyrophanite	100	4 rabbits	24	Transient hypercoagulability and toxemia

TABLE 2.—Intratracheal Injection Experiments with Talc and Associated Minerals
Dusts Composed of Small Particles or Short Fibers

Dose: The total amount of dust injected was 150 mg. divided into 15 equal doses (each dose was 0.5 ml. of a 10% suspension) injected a week apart.					
Animals Used: Guinea pigs.					
Periods at Which Animals Were Killed: Usually at intervals of 4 to 6 months up to one year after injection and at intervals of 6 to 12 months thereafter.					
Mineral	Time After Injection, Mo.	Particle Size, μ	Animals	Maximal Survival After Last Injection, Mo.	Results
Talc (Georgia)	650	5 and less	12	26	Bronchiectasis and bronchitis; perivascular and peribronchial cellular proliferation and fibrosis; interlobular pleural sclerosis
Tremolite (Alps)	50	5 and less	6	68	Transient macrophage reaction and persistent eosinophilia; perivascular and peribronchial lymphocytic infiltration
Tremolite (Alps)	...	20 and less	6	12	Incipient bronchiectasis and peribronchial fibrosis; incipient perivascular cellular infiltrates
Anthophyllite	1,700	5 and less	6	12	Outstanding bronchitis; peribronchial, perivascular and cellular masses; peribronchial fibrosis
Anthophyllite	...	20 and less	6	12	Bronchiectasis and catarrhal bronchiolitis; peribronchial fibrosis
Serpentine	1,800	5 and less	6	12	Chronic bronchitis and bronchiectasis

TABLE 3.—Intratracheal Injection Experiments with Talc and Associated Minerals
Dusts Composed of Long Fibers

Dosage: The total amount of dust injected was 75 mg. of tremolite and 75 mg. of anthophyllite, divided into equal doses (each dose was 0.5 ml. of a 1% suspension) injected a week apart. There were three injections of tremolite and two of anthophyllite. Animals Used: Guinea pigs. Periods at Which Animals Were Killed: For tremolite 1, 4, 8, 12, 17, and 20 months and for anthophyllite 1, 8, 12, and 20 months after last injection.				
Mineral	Fiber Length, μ	Animals	Maximal Survival After Last Injection, Mo.	Results
Tremolite (Alps)	20-50	4	18	Bronchiectasis and bronchitis with peribronchial proliferative fibrosis and catarrhal; interstitial fibrosis and perivascular proliferations; tremolite bodies; cellular metaplasia
Anthophyllite	20-50	4	12	Bronchiectasis and bronchitis; local peribronchial cellular reaction; irregular fibrosis

An experiment with long fiber talc was not conducted because attempts to locate mineral specimens containing long fibers of talc were unsuccessful.

TABLE 4.—Intratracheal Injection Experiments
Mixtures of Talc Minerals and Quartz

Dosage: The total amount of dust injected was 75 mg. divided into three equal doses (each dose was 0.5 ml. of a 5% suspension) injected a week apart.
Animals Used: Guinea pigs.
Periods at Which Animals Were Killed: Usually 1, 4, 8, and 12 months after last injection.

Mineral Mixture	Per Cent	Particle Size, μ	Ani- dial	Maximal Survival After Last Injection, MO.	Reaction
Talc..... Quartz.....	75 25	2 and less	0	12	Multiple fibrocellular granulomata; bronchiolitis and bronchiectasia; perivascular fibrocellular reaction; peridontitis and lymphoid hyperplasia
Tremolite..... Quartz.....	55 45	2 and less	0	12	Massed macrophages and some central necrosis and peripheral minor fibrosis; transient bronchitis
Anthophyllite..... Quartz.....	55 45	20-50 2 and less	0	12	Massed confluent subpleural, alveolar mural and perivascular cellular proliferation; minimal fibrosis; bronchiolitis and bronchitis
Tremolite..... Anthophyllite..... Talc.....	20 30 50	2 and less 20-50 2 and less	0	12	Subpleural, peribronchiolar, and perivascular macrophage and fibrocytic proliferation
Tremolite..... Anthophyllite..... Talc..... Quartz.....	20 37 43 14	2 and less 20-50 2 and less 2 and less	0	12	Massive exuberant macrophage and fibrocytic cellular proliferation; bronchiolitis and bronchitis; minimal fibrosis

by sedimentation in alcohol to isolate fibers approximately 20 μ to 50 μ long. It is reported that the mineral talc may exist in fibrous form,¹ but attempts to obtain talc samples suitable for preparing fibers 20 μ to 50 μ in length were unsuccessful. The occurrence of talc as a long-fiber mineral would appear to be uncommon.

The third set of intratracheal experiments (Table 4) was specifically designed to mimic the dust exposures of the upper New York State industries and particularly to probe the influence of quartz on the combined or separate pathogenicity of the other components of commercial talc. The effects of these substances may now be scrutinized.

EFFECTS OF TALC AND OF ASSOCIATED MINERALS ON TISSUE

Dolomite.—The intravenous introduction of dolomite proved toxic to the rabbits, some dying while the injections were being made and others within a few days. Such animals showed a macrophage reaction in the alveoli by the third day, with perivascular and peribronchiolar cellular accumulations. Occasional eosinophilic infiltrates were to be seen. The lungs of animals surviving to 24 months showed no abnormality, a condition suggesting either a complete recovery or a lack of chronic response in the first instance.

Serpentine.—When introduced into rabbits by the intravenous route, serpentine dust produced within three months a moderate degree of alveolar macrophage catarrh, with septal cellular proliferation. Dust particles could be seen particularly within perivascular macrocytic accumulations. In the case of the rat there is no comparable alveolar catarrh at 12 days, but there are some macrophage and multinucleated giant-cell accumulations at the angles between alveolar septa. In both the rabbit and the rat small isolated granulomata, composed of multinucleated giant cells, well-charged konoiphores, unpigmented macrophages, plasma cells, lymphocytes, and fibrocytes with intermingled capillaries, may be found at 12 months. These foci have a perivascular and peribronchiolar distribution.

The intratracheal introduction of serpentine in guinea pigs provokes within the first month bronchial epithelial hyperplasia, with submucosal and adventitial cellular infiltration and scattered intra-alveolar konoiphores. By the end of a year this condition has stabilized as a chronic bronchitis, with bronchiolitis and distortion. There is considerable epithelial desquamation, with some papilloma formation.

Talc.—When introduced into the rabbit by the intravenous route, talc produces within

EFFECTS OF TALC DUST ON ANIMAL TISSUE

one month numerous focal areas of alveolar macrophage catarrh and pleural thickening through superficial fibrocytic and macrocytic hyperplasia. The talc spicules are universally distributed throughout the pulmonary parenchyma but avoid the lymphoid tissue, and the alveolar macrophages do not yet show much talc. At the end of two years this talc is still present in the alveolar bronchial and vascular walls, and the intra-alveolar macrophages now also contain some talc. Isolated foci of marked vascular muscular proliferation may be seen. More usually there is a perivascular alveolar reaction. Endangitis proliferans is commonly seen in the smaller blood vessels. Alveolar walls are thickened through cellular proliferation. A moderate degree of chronic bronchitis and bronchiolar dilatation is seen, together with bronchopneumonic foci displaying a high proportion of macrophages. The pleural cellular proliferation shows no advance on that seen at the end of the first month.

The rat lung is apparently immune to the effects of talc introduced by the intravenous route. No reaction is demonstrable at the end of the 1st month, and at end of the 15th month a few talc-laden macrophages may occasionally be seen in the alveoli. Practically all the talc introduced is still readily demonstrable in the lumina of blood vessels by means of polarized light.

When introduced into guinea pigs by the intratracheal route, particulate talc calls forth within one month perivascular and peribronchiolar focal intramural cellular accumulations comprising histiocytes, fibrocytes, plasma cells, and rare eosinophiles. Dust-containing macrophages form irregularly distributed confluent pneumonic patches (Fig. 1). Within eight months multiple foci of dust-filled koniophores in alveoli surrounding bronchioles and arterioles may be seen, but dust cells may also effectively occupy pulmonary alveoli over extensive areas, producing a solid effect. Some eosinophile and fibrocyte infiltration into peribronchial tissue is seen, and there is some fibrosis, with bronchiolar distortion and epithelial proliferation. Where dust-laden macrophages reach



Fig. 1.—Pulmonary effects of talc injected intratracheally (Experiment 902—guinea pig lung; reaction one month after injection). Focal accumulation of talc-filled koniophores within pulmonary alveoli.

the pleural surface, a fibrocellular sclerosis with subpleural deposits may supervene.

At the end of the first year the pleural reaction is well established, consisting of an outer fibrocellular layer, a cellular inner zone, and interposed foci of pigment-filled macrophages. The dense perivascular sheaths of cells are now seen to be spilling over into the proximal alveolar walls. Immediately adjacent to the blood vessels is a zone of lymphocytes, and somewhat further afield are some fibrocytes. The hypertrophy of the bronchiolar mucosa has advanced further, and there is now some epithelial desquamation and muscular hypertrophy.

At the end of the second year the dominant residual change caused by the talc is the bronchiolectasia and bronchiolitis with epithelial catarrh. Marked focal cellular deposits and peribronchial fibrosis occur. Fibrocytes may now be seen to be intersecting the massed koniophores, and a delicate web of

collagen is being laid down. Capillaries invade these areas.

When particulate talc and quartz of the same particle-size range are combined in the ratio of 3:1, the essential additional effects in the guinea pig on intratracheal injection of the mixture are perceptible within the first month. The effects consist essentially of a greater prevalence of masses of dust-filled koniophores, with numerous eosinophiles at the edges of the alveoli (Fig. 2A). There is a distinct tendency to alveolar septal cell proliferation, and in the cellular masses alveoli may survive as cuboidal-cell-lined spaces.

At the end of the first year the combined talc-and-quartz lesion may be defined as a fibrocellular granuloma (Fig. 2B), and now numerous multinucleated giant cells occupy alveoli at the periphery of the koniophore masses. There is a distinct increase in lymphoid tissue not only in the parenchymal nodes and hilar nodes but also around the small blood vessels. At the fringes of the

lymph nodes there is considerable macrocytic infiltration.

The bronchiolar distention and distortion produced by exposure to pure talc, though present, are less marked when the quartz is added. There is, however, more marked epithelial desquamation, and there is more peribronchial and perivascular fibrosis.

Tremolite.—The reaction of the rabbit and the rat to the intravenous introduction of particulate tremolite (3μ and less in size), either of the soda-iron or soda varieties, is essentially negative. Most of the tremolite remains in circulation even at the end of the 19th month, though some particles may be demonstrable in alveolar walls and lymph nodes. However, even in the latter locations the dust may be within the capillaries. Very few macrophages are to be seen, and they are limited to minute perivascular infiltrates of macrophages and fibrocytes.

When tremolite of similar particle-size range is introduced into the lungs of guinea

Fig. 2.—Pulmonary effects of the intratracheal injection of talc combined with quartz (Experiment 902—guinea pig lung). A, reaction one month after injection; massed accumulation of talc-filled koniophores obscuring the alveolar pattern. B, reaction 12 months after injection; persisting macrophages; granuloma with slight fibrotic changes and some capillary infiltrations.

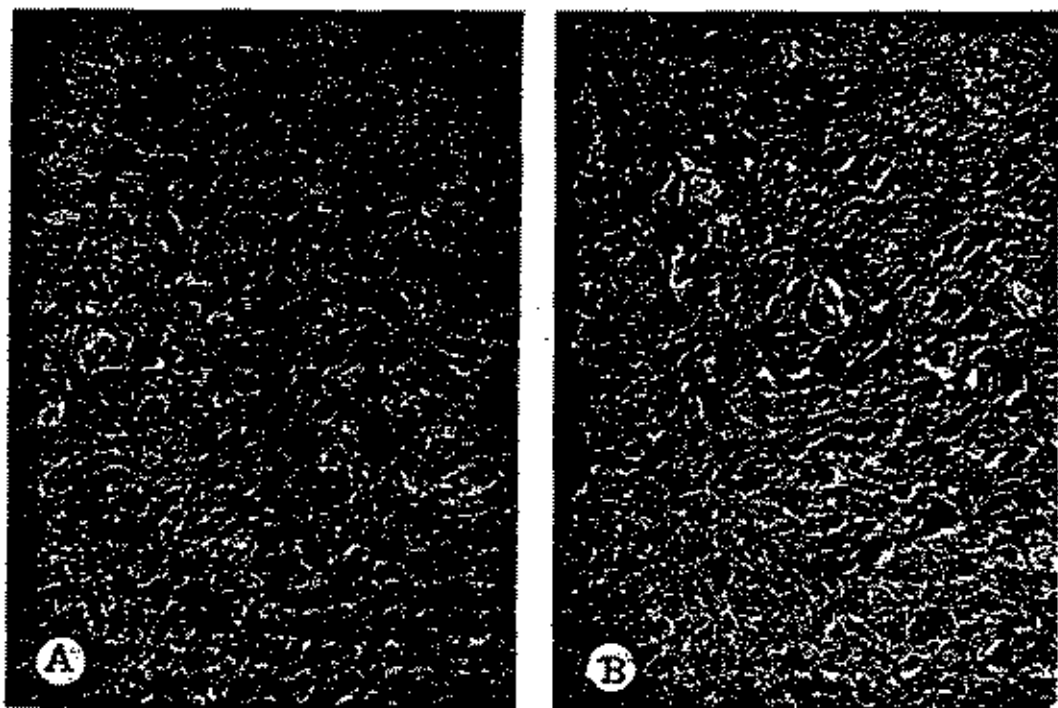




Fig. 3.—Pulmonary effects of tremolite injected intratracheally (Experiment 900—guinea pig lung: reaction one month after injection). Commencing crypt formation in a bronchiolar wall at the end of the first month under the influence of tremolite fibers 3 μ in length.

pigs, many of the bronchioles are observed to have undergone erosion at the end of the first month, with peribronchiolar fibrocytic and macrocytic accumulation. The epithelium tends to be proliferated and to be desquamated. Giant macrophages filled with tremolite particles occupy the alveoli immediately adjacent to the alveolar ducts, and some scattered eosinophiles are to be seen among these cells. The reaction may, however, be limited to slight bronchiolar evagination (Fig. 3).

At the end of the first year there may be residual periarteriole and peribronchiolar lymphocytic infiltration and isolated islets of particle-filled macrophages. Eosinophiles lie scattered among them. The bronchiolar mucosa also shows considerable eosinophilia.

When the tremolite is introduced in the form of particles up to 20 μ in length, the spicules may be seen to be well dispersed and closely applied to the alveolar walls of the guinea pigs at the end of the first month. Numerous macrophages may also be seen containing such particles, but these dust cells are by no means comparable in size to the giants seen in the preceding instances. There is a great abundance of eosinophiles and commencing fibrocytic infiltration of alveolar walls. The bronchioles are a little distended and distorted and show incipient crypt formation.

The latter change is seen to have advanced appreciably at the end of the first year, and

goblet cells are now present in greater profusion. There is also now more cellular infiltration and fibrosis of the bronchial walls, with macrophage discharge into the bronchial lumina.

The intratracheal introduction of tremolite fibers 20 μ to 50 μ long produces marked disease rapidly and extensively. Within one month the guinea pigs show complex masses of tremolite fibers trapped within the bronchi and bronchioles. There is considerable bronchiectasia and distortion, with peribronchial fibrosis and cicatrization. Many of the long fibers may be observed to have penetrated into the walls of the respiratory passages (Fig. 4). At the end of 18 months the resultant lesion is a marked fibrocellular diffuse pneumonitis, with marked bronchiectasia and epithelial destruction (Fig. 5) and vascular and perivascular damage (Fig. 6). This extensive lesion is directly comparable to the mature human lesion and is even replete with tremolite bodies, i. e., tremolite fibers surrounded by a brown iron-containing protein sheath, showing typical terminal clubbing and some measure of segmentation where it covers the shaft of the tremolite fiber. Many metaplastic cells are also found among the macrophages (Fig. 7). There is also a characteristic pleural and subpleural fibrocellular reaction (Fig. 8).

When particulate tremolite (3 μ and less in size) is mixed with quartz dust of the same size range in a ratio of 13:7 and introduced into guinea pigs by the intratracheal route, the immediate effect is much greater than that observed with either the tremolite or the quartz alone. A permanent lesion comparable to that which may be expected with quartz alone is, however, not established. Apparently the healing process, seen when tremolite alone is introduced, also mitigates the quartz effect. Within the first month there is an exuberant koniophore and multinucleated giant-cell reaction which obliterates all semblance of preexisting pulmonary cytoarchitectonics around the bronchioles. Many of the trapped bronchioles are distended and distorted, with epithelial desquamation and pro-

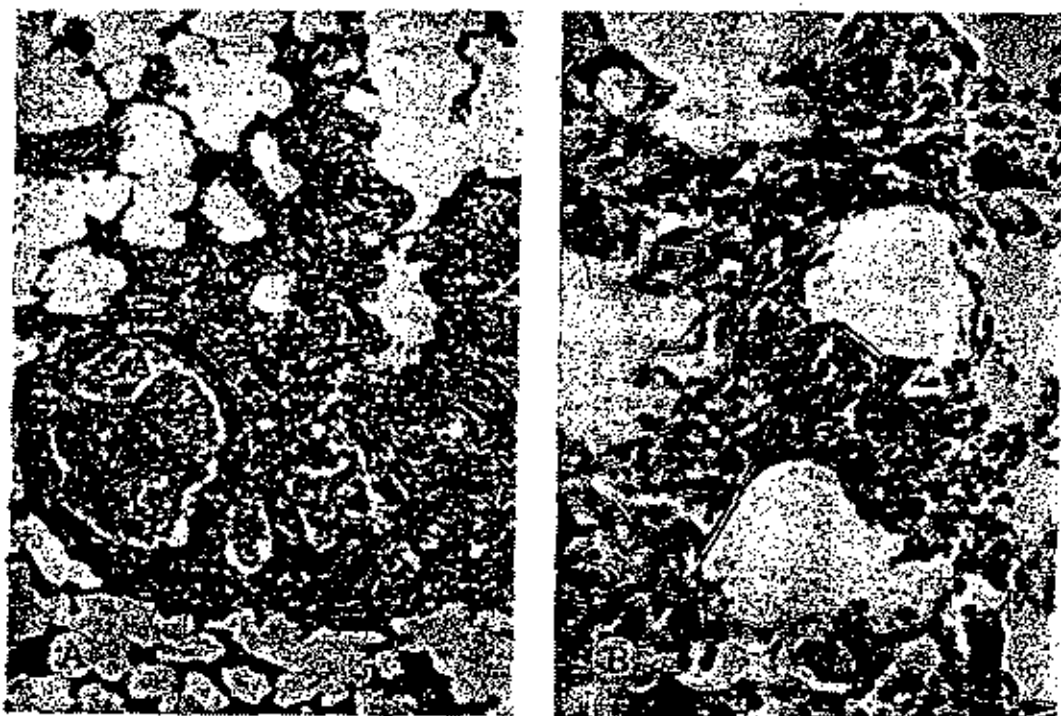
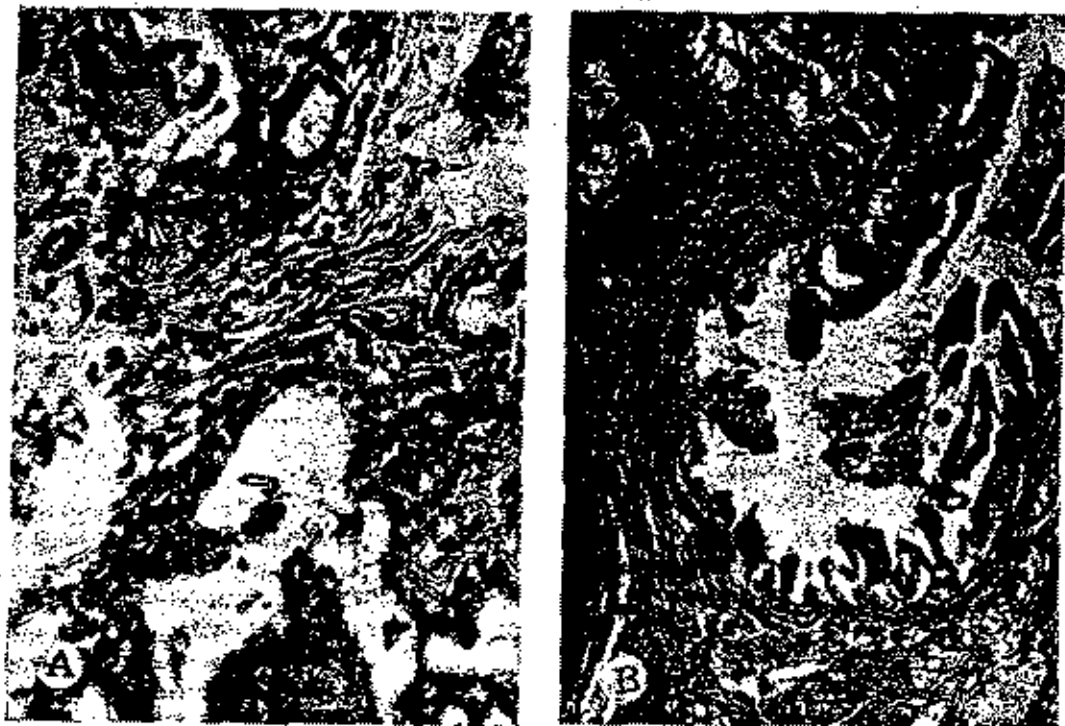


Fig. 4.—Pulmonary effects of tremolite fibers 20 μ to 50 μ long injected intratracheally (Experiment 995—guinea pig lung: reaction one month after injection). *A*, bronchiole choked with fibers and debris, showing breakdown of its wall and peribronchiolar cellular reaction in relation to trapped tremolite fibers. *B*, high-power view of parenchymal pulmonary reaction, showing tremolite fibers, macrophages, fibrocytes, plasma cells, and occasional lymphocytes.

Fig. 5.—Pulmonary effects of tremolite fibers 20 μ to 50 μ long injected intratracheally (Experiment 995—guinea pig lung: reaction 18 months after injection). *A*, interstitial pulmonary fibrosis, with prevalent cellular elements and trapped tremolite fibers. *B*, distortion, distention, partial mucosal hypertrophy, partial epithelial desquamation, and peribronchiolar fibrosis.



EFFECTS OF TALC DUST ON ANIMAL TISSUE

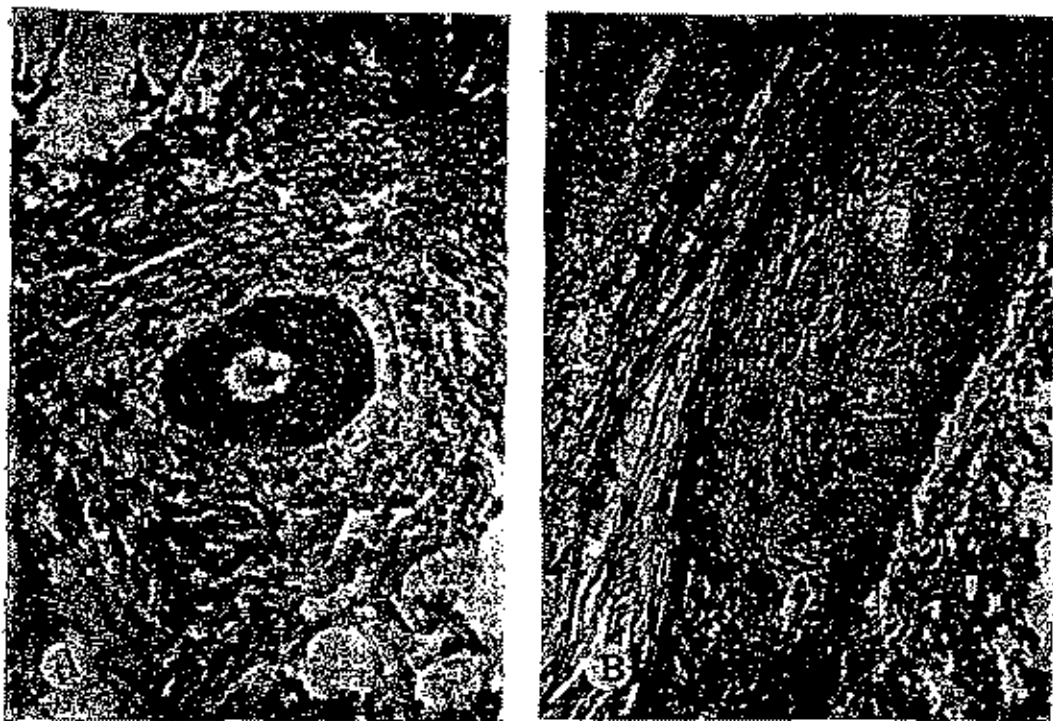
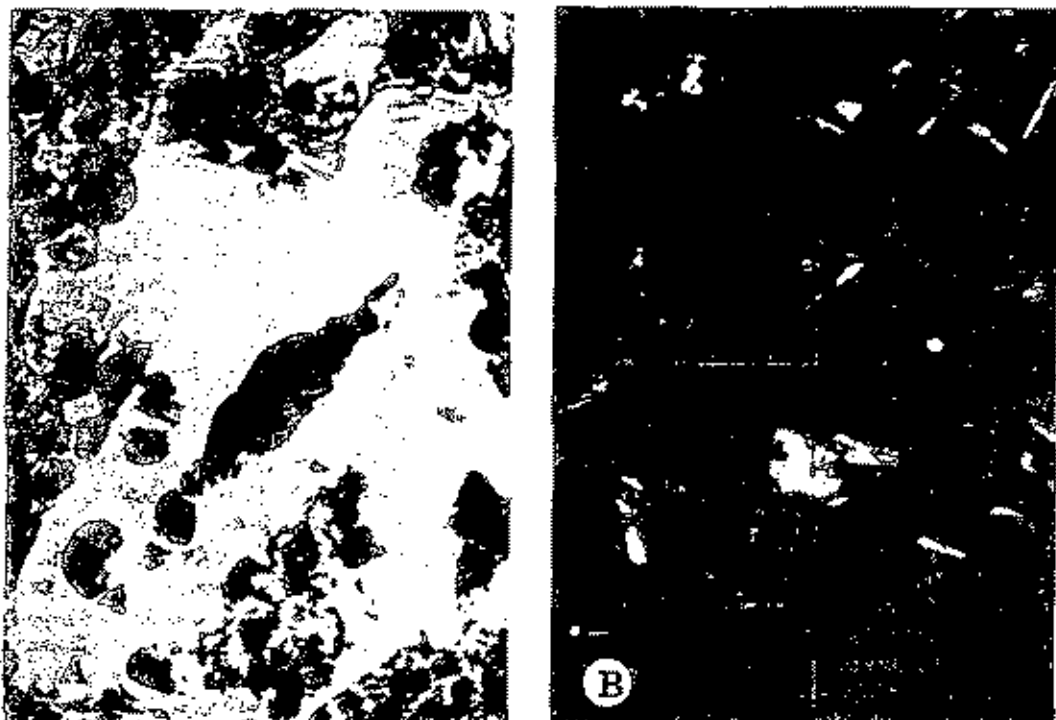


Fig. 6.—Vascular damage caused by tremolite fibers 20 μ to 50 μ long (Experiment 995—guinea pig lung; reaction 18 months after injection). *A*, periarteriolar fibrosis; fibers sparsely present. *B*, vessel almost completely obliterated by fibrotic reaction around trapped fibers.

Fig. 7.—Fate of tremolite fibers 20 μ to 50 μ long in lung tissue (Experiment 995—guinea pig lung; result 18 months after injection). *A*, tremolite fiber engulfed by macrophages with commencing clubbing of the fiber ends. *B*, birefringence of trapped fibers, some intracellular and some extracellular.



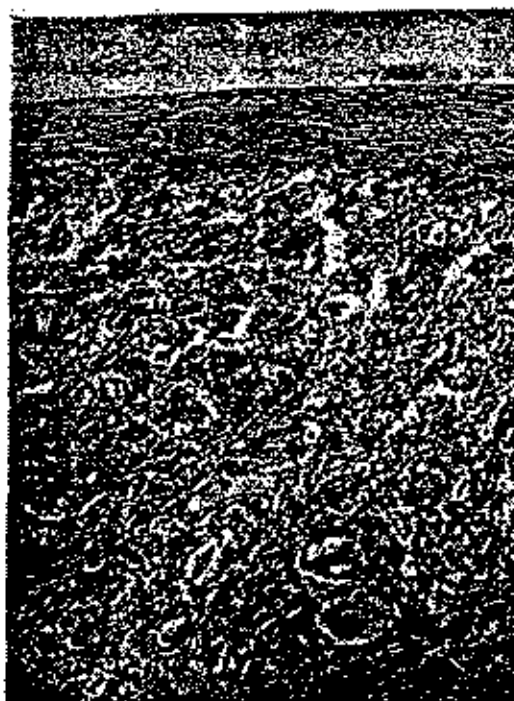


Fig. 8.—Pulmonary effects of tremolite fibers 20 μ to 50 μ long (Experiment 995—guinea pig lung; result 18 months after injection). Pleural sclerosis and subpleural dominantly cellular reaction around tremolite fibers.

literation. Foci of necrosis are present, and fibrosis is commencing at the periphery. The majority of alveolar walls are infiltrated with macrophages, and there is some perilymphatic konoiphore accumulation as well.

At the end of the first year there has been a measure of recovery from the initial exaggerated reaction. Foci of massed konoiphores may still be found, but there is very little reaction around these cells. Necrosis is still seen at some areas. Small lymphocytic sheaths accompany some of the bronchioles and arterioles, and the bronchiolar epithelium has recovered in large measure.

Anthophyllite.—The intravenous introduction of particulate anthophyllite (less than 3 μ in size) produces minimal pulmonary lesions only in rabbits. The lesions are limited to macrophage proliferation and plasma cell accumulation at pericapillary and intra-alveolar sites, and the reaction should be classified as inert.

An intratracheal introduction of anthophyllite in this particle-size range was performed in spite of the essentially negative intravenous result. At the end of the first month areas of intramural and intra-alveolar cellular accumulation occur. Most of these are dust-filled macrophages, but there are several eosinophiles among them. After one year areas of irregular fibrosis may be seen to surround distorted and distended bronchioles. Numerous areas of bronchiolar epithelial desquamation with necrotic cellular plugs in the lumina may be found. There are also massed peribronchiolar accumulations of konoiphores with commencing interstitial fibrosis.

The effects of the introduction of anthophyllite fibers in the less than 20 μ length range are comparable to the effects produced by the 3 μ particles, with the exception that fewer macrophage masses are formed at points distant from the bronchioles. There is a greater tendency also for diffuse alveolar wall thickening through cellular infiltration and a higher proportion of fibrocytes to macrophages where cellular reactions are provoked, especially in the peribronchial tissues. The birefringent particles all seem to lie in relation to the fibrocytes. Bronchiolectasia and catarrhal bronchiolitis reach a somewhat more advanced degree (Fig. 9).

The long-fiber anthophyllite (20 μ to 50 μ) has an enhanced and even more rapidly injurious effect on the guinea pig lung. Within one month it produces a marked and extensive focal peribronchial fibrotic and cellular reaction, consisting mainly of macrophages, fibrocytes, and eosinophiles with areas of lymphocytosis (Fig. 10). Anthophyllite fibers and spicules are embedded within these cells, and some may be partly engulfed by giant cells. Areas of necrosis occur. Bronchitis and bronchiolitis with distortion and distention are present, and the lumina of such passages contain necrotic cellular debris. At the end of 12 months a more advanced stage of essentially the same lesion may be seen, with, however, more central and irregular fibrosis within the nodules of reaction. There is now some bronchiolar stenosis as well as ectasia.

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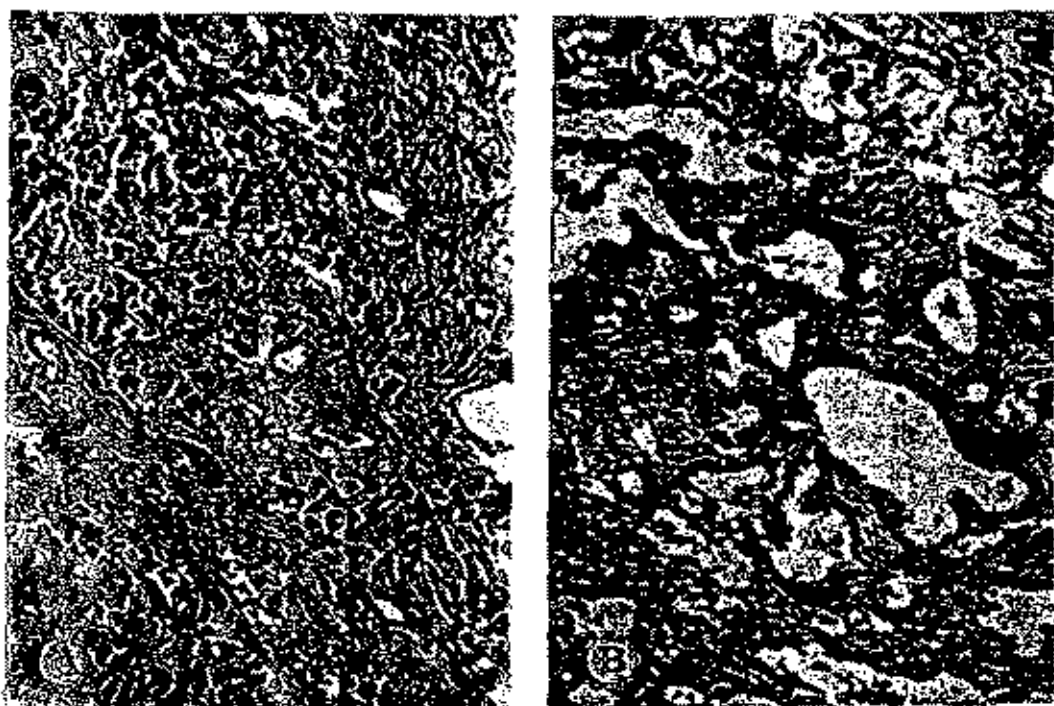
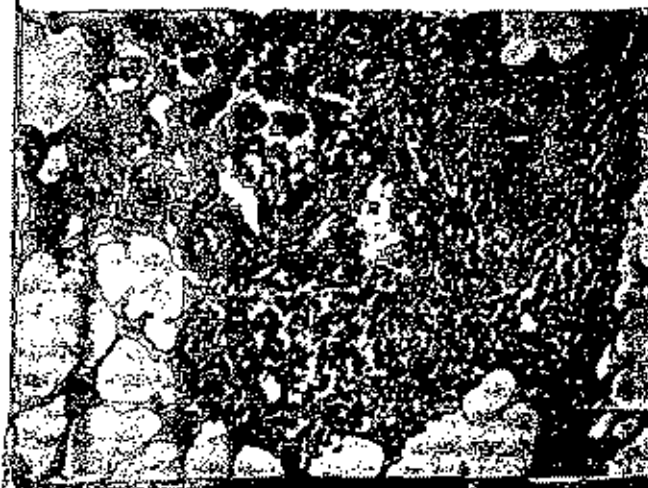


Fig. 9.—Pulmonary lesions caused by anthophyllite fibers less than 20 μ long (Experiment 285—guinea pig lung: result 12 months after injection). A, mixture of dust-filled macrophages, fibrocytes, occasional plasma cells, and collagen strands. B, bronchiolectasia within an area of fibrocellular reaction; multiple evaginations create a cystic effect.

When anthophyllite fibers and quartz are mixed with each other in a ratio of 11:9 and introduced into guinea pigs, a marked subpleural cellular reaction, confluent mural proliferations, and perivascular cellular accumulations may be found within one month. Solid foci of macrophages occur, and there is commencing distention and distortion of

Fig. 10.—Pulmonary effect of anthophyllite fibers 20 μ to 50 μ long injected intratracheally (Experiment 993—guinea pig lung: reaction one month after injection). Section shows rapid degeneration of bronchiole, peribronchiolar dominantly cellular deposit in relation to trapped fibers, but failure to involve the lymph node.



bronchioles. By the end of a year the lungs are occupied by multiple masses of cellular reaction consisting mainly of fibrocytes, though some macrophages are still present. Advanced multilocular bronchiectasia may be found within these cellular zones. An interesting feature of the reaction, which shows forcibly the modifying influence of the anthophyllite on the quartz, is the fact that, though such cell masses may encroach on and surround the lymphoid nodules, they do not involve them. Small foci of acellular necrosis occur in some of the larger cell masses, but there is no distinctive tendency to fibrosis, such as may be seen in a pure quartz lesion at a comparable stage.

COMBINED EFFECT OF TREMOLITE, ANTHOPHYLLITE, AND TALC

The purpose of this experiment was to attempt to define the relative influence of quartz on a mixture of components which simulates the natural talc product mined in upper New York State. The study was there-

fore conducted in two stages, viz., with and without the quartz.

When no quartz is included, the initial reaction to talc, tremolite, and anthophyllite is very mild. At the end of one month there is slight bronchiolar epithelial catarrh and some plasma cell infiltration into the bronchiolar mucosa. Isolated small foci of dust-filled macrophages may be found. At the end of a year the area of reaction around the pigmented macrophages is somewhat more extensive and includes some capillary hyperemia. Such areas may occur in relation to the bronchioles and subpleurally. A little bronchiolar distention and distortion may be seen.

The addition of 14% quartz to the talc, tremolite, and anthophyllite mixture rapidly provokes massive focal lesions consisting of macrophages and fibrocytes with scattered giant cells. Multiple foci of diffuse alveolar wall thickening due to macrophage invasion and septal cell proliferation also occur. In the air passages there are incipient epithelial hyperplasia and submucosal plasma cell or lymphocytic infiltration. At the end of a year this exuberant cellular response still persists, but fibrocyte accumulation is limited almost to being a fringe phenomenon. The distortion and distention of the bronchioles and epithelial catarrh have also progressed somewhat, but the degree to which this has occurred is by no means comparable to the lesions which may be provoked by either long-fiber tremolite or anthophyllite alone.

COMMENT

Though one must acknowledge at the outset the limitations of the techniques employed in this series of experiments, the diversified results obtained, not only by exploiting different minerals but also through modifying their particle sizes or varying the route of introduction or the species of experimental animal, justify the inference that at least some progress has been made in elucidating the role played by components of commercial talc in producing disease and the mechanisms by which the terminal results are achieved.

Thus it seems that the basic reaction to the presence of any of these dusts is a macrophage catarrh into the alveoli, the cells becoming engorged with large particles so rapidly that they remain immobilized and fail, except in rare instances, either to return to the tissues or to be extruded from the lung via the respiratory passages. It is possible that this is merely a mechanical result due to their large size. On the other hand, it is possible that the koinophores are actually paralyzed. They certainly do not tend to undergo necrosis; nor are collagen or other types of fibrous elements stimulated to invade the cell masses in the majority of instances, except when the component fibers are long.

The degree to which fibrosis supervenes depends on the length of fibers rather than on their chemical composition. Thus when the minerals have been reduced to 3μ and less in maximal dimension, they have practically no fibrogenic effect. On the other hand, the 20μ to 50μ length tremolite and anthophyllite fibers produce extensive regional fibrosis. Unfortunately talc could not be obtained in this fibrous form, so that it is not certain whether this rule applies to talc also. It was observed, however, that talc evokes fibrocytes, but the presence of these cells does not tend readily to lead to collagen deposition.

Attention must be drawn to the triple localization of the lesions produced by talc, tremolite, or anthophyllite, namely, at perivascular, peribronchiolar, and subpleural or pleural sites. In addition, cellular accumulations having no such apparent topographical relation to the blood vessels, air passages, or pleura may occur. It is possible, however, that these macules are merely examples of the standard lesion cut at a tangent. The lymphatic tissue escapes almost entirely, and alveolar walls are not affected except near the focal deposits or when quartz is present too.

The marked tendency to bronchiolar distention and distortion is readily explained when large masses of sharp elongated fibers are trapped within the bronchioles or when there are extensive peribronchiolar cellular

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masses of fibrotic cicatrization. The mechanism is less readily apparent when such obvious causes are in abeyance. The mineral particles could not be readily demonstrated in the bronchial wall except when advanced disease was present. On the other hand, it must be granted that we do not yet know the lower size range of particles of those minerals which may be active.

The lack of secondary infection in spite of the marked pulmonary changes observed is remarkable. Unfortunately the study was not elaborated to include observations on the influence of the talc minerals on the course of tuberculosis. Such a project would be worth pursuing in view of the conflicting reports concerning the prevalence of tuberculosis among human talc victims. It would, however, involve a costly inhalation study.

Contrary to expectation, the addition of quartz did not materially enhance the pathogenicity of the talc minerals. Indeed, there seems to be some indication that the fibrogenic effect of the quartz is reduced by the presence of talc in particular. This may be explicable on the supposition that if all the konochores are effectively occupied and immobilized by the talc the quartz cannot influence them to the contrary and thus does not truly enter the body, remaining trapped in the konochores lying in alveoli and thus truly still outside the body. The lack of a lymphoid tissue response favors such a simple and mechanistic explanation. On the other hand, the difference in reaction may be more subtle and dependent on chemical or physical interaction between the quartz and the other minerals.

While there are these evidences of opposing or inhibiting actions, and, as has been shown, they are not limited to quartz, there is also some suggestion that in certain combinations separate components may augment one another. This applies particularly to the combination of quartz with tremolite or anthophyllite.

The successful experimental production of a tremolite body provides strong evidence that the bodies found in human "talcosis"

are truly provoked by the tremolite component of the talc dust. Comparable bodies were not demonstrable in the anthophyllite series. There is, therefore, more than length of fiber required to cause them to develop.

This feature firmly links the animal pathology to the human disease. Indeed, this series of experiments elucidates most satisfactorily the nature of the human talcotic reaction and the factors responsible for its production. At the same time it sheds further light on the asbestos problem while confirming certain observations previously recorded concerning silicosis. Furthermore, the relative immunity shown by certain animal types serves to confirm the general concept of variable susceptibility of man and animals to disease.

SUMMARY

The pulmonary response of rabbit, rat, and guinea pig lungs to dolomite, serpentine, talc, tremolite, anthophyllite, and quartz, either separately or in combination, was explored by the intravenous and intratracheal techniques.

Dolomite and serpentine are relatively inert.

While talc is dominantly cytogenic, tremolite and anthophyllite have both cytogenic and fibrogenic propensities.

Quartz modifies the effects of these substances.

The effects of these substances are different from the effects of the substances in combination acting singly.

Talc, tremolite, and anthophyllite all tend to damage the smaller respiratory passages and blood vessels to a variable degree.

The long tremolite and anthophyllite fibers produce rapid and grave peribronchiolar lesions.

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The Biological Effects of Calcined Gypsum Dust

An Experimental Study on Animal Lungs

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Studies dealing with the biological effects of calcined gypsum dust on experimental animals were initiated at The Saranac Laboratory during 1933 by the late Leroy U. Gardner, M.D., Director. Although the investigations were pursued over many subsequent years, only partial accounts of the results have been published thus far.* Carried along by the momentum of a succession of studies of increasing importance, Dr. Gardner had to divide his time among many investigations, and his ambitiously planned monograph on The Saranac Laboratory experiments with calcined gypsum dust remained unwritten.

In the present paper the results of a comprehensive series of long-term inhalation experiments, with the conduct of which two of us (T. M. D. and A. B. D.) were intimately concerned, will be recorded. Owing to the broad range of the experimental program, the paper must necessarily be limited to the presentation of an over-all survey of the investigations. More detailed treatment of individual histological aspects will be given

in subsequent papers. Effort has been made to avoid repetition of what has already been placed on record by Gardner, and though for the sake of completeness and logic reference has to be made to such matter, most of the material now presented will appear for the first time, and the interpretation of experimental records and slides are our own.

MATERIALS

The calcined gypsum used in the experiments was the standard product of plaster mills and, being a commercial material, varied somewhat in composition from time to time. The following approximate estimate of composition and particle-size range refers to the product received during the early part of the experimental studies; for material forwarded later the per cent of hemihydrate was higher and of calcite, lower:

Component	Per Cent	Approximate Particle Size	
		Range, μ	Average, μ
Hemihydrate $\text{CaSO}_4 \cdot \frac{1}{2} \text{H}_2\text{O}$	20	1-75	5
Anhydrite CaSO_4	10	1-40	5
Calcite CaCO_3	15	1-30	5
"Dead-burned gypsum"	8	1-30	5
Quartz SiO_2	<1		..
MgCO_3	2		..
Fe_2O_3			
Al_2O_3			
"Calcined gypsum"	100	1-40	5

The quartz was a commercial product supplied as a finely ground powder with an SiO_2 content which exceeded 99%. The tubercle bacilli used for the infection phase of the study were of the R₁ low-virulence human strain whose tuberculo-genic properties and cultural characteristics have been well documented.[†]

SCOPE OF EXPERIMENTS

The present report will deal with the results obtained in inhalation experiments in

Recorded for publication July 15, 1955.

Director (Dr. Schepers), Associate Director (Mr. Durkan), and Research Associate (Mr. Delahant), The Saranac Laboratory.

* References 1 to 4.

† References 5 and 6.

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which guinea pigs were exposed to dust under various environmental conditions, as follows:

- Calcined gypsum dust for 24 months.
- Calcined gypsum dust for 24 months and then normal air for 22 months.
- Calcined gypsum dust for 24 months and then quartz dust for 18 months.
- Quartz dust (comparison) for 18 months.
- Calcined gypsum dust for three weeks and then, alternately, quartz dust for one week and calcined gypsum dust for the next week, with a continuation of this program of alternating weekly exposures for 24 months.
- Mixed dust composed of equal parts of calcined gypsum dust and quartz dust for 25 months.
- Mixed dust composed of equal parts of calcined gypsum dust and quartz dust for 25 months and then normal air for 12 months.
- Mixed dust composed of two parts of calcined gypsum dust and one part of quartz dust for 29 months.
- Calcined gypsum dust for 6 months, then infection with *R. tubercle bacilli*, and then calcined gypsum dust for 18 months more.
- Calcined gypsum dust for 25 months, then infection with *R. tubercle bacilli*, and then normal air for 12 months.
- Mixed dust composed of equal parts of calcined gypsum dust and quartz dust for 3 months, then infection with *R. tubercle bacilli*, and then the mixed dust for 27 months more.
- Infection control *R. tubercle bacilli* for 22 months.

EXPERIMENTAL TECHNIQUES

The inhalation experiments were conducted in 8 ft. cubical rooms. The animals, kept in cages along the sides of the room, were exposed to the aerosol for eight hours a day, five and one-half days a week. During such periods a rotating paddle device created and maintained in the room an atmospheric suspension of the dust under study. For the rest of the time the air in the room was free of any substantial amount of dust. Periodically, in most cases at intervals of a few months, animals were killed for study, so that the progression of any tissue reaction to the dust or to any infection given to the animals could be closely followed. Chemical analyses to estimate the amount of dust retained in the lungs were carried out on some animals.

During each experiment the dust concentration was checked frequently by the impinger method.

Infection by the *R.* strain of tubercle bacilli was achieved by means of the intratracheal insufflation

technique perfected in The Saranac Laboratory.¹ Each animal received 6 puffs of the atomizer from a suspension of *R. tubercle bacilli* containing 15 to 20 single organisms per oil-immersion field.

1. EXPOSURE TO CALCINED GYPSUM DUST ALONE

The results of this experiment on 21 normal uninfected guinea pigs have been summarized in Table 1. The guinea pigs were exposed to only calcined gypsum dust. For the entire exposure period the average dust concentration was 448,000,000 particles per cubic foot of air. The guinea pigs were exposed to the dust for periods up to 24 months, animals being sampled at various intervals. At the end of 24 months the surviving animals were removed from dust and transferred to a normal atmosphere to constitute the second part of this experiment. Some of this group lived as long as 22 months after the termination of the dust exposure, and samples were taken at 3-month intervals during this period.

Twelve of the twenty-one guinea pigs died of pneumonia or other pulmonary lesions. This mortality trend was widely dispersed over the whole experimental period. Deaths were slightly commoner in the earlier months but perhaps not significantly so. It would seem that the death rate of 28.5% per annum was slightly high. The mortality trend in guinea pigs in one of The Saranac Laboratory experiments with a comparatively inert amorphous silicate dust was about 22% per annum. The fact, however, that all deaths in the experiment with calcined gypsum were from respiratory causes may be meaningful.

In spite of these observations no significant gross signs of pulmonary disease manifested themselves, and no nodular or diffuse pneumoconiosis ensued. In isolated animals pigmentation commenced to appear toward the end of 10 months, and minute foci of atelectasis could be seen. After a year of dust exposure a minimal amount of pigmentation became an almost constant sign, and atelectasis was more frequently observed. The microscopic counterparts of these features will be described in further

TABLE 1.—*Biological Action of Calcined Gypsum Dust*
Guinea Pigs Were Continuously Exposed by Inhalation to the Dust Until Death

Guinea Pig No.	Exposure to Dust, Days	Fate	Cause of Death	Tissue Reaction in			
				Lungs		Pulmonary Lymph Nodes	
				Focal Pigmentation	Atelectasis	Focal Pigmentation	Enlarged Nodes
555-20	54	Died	Pneumonia	..	..	..	..
56	55	Died	Pneumonia	..	..	..	..
57	512	Killed		..	..	..	..
58	763	Died	Pneumonia	..	..	..	..
59	784	Died	Pneumonia	..	..	..	..
64	285	Died	Pneumonia	..	..	..	..
65	290	Killed		+	+	..	..
66	300	Died	Pneumonia	..	..	..	++
67	312	Died	Pneumonia	..	..	..	..
68	378	Killed		+	..	..	..
70	574	Died	Pneumonia	..	..	..	++
71	425	Killed		+	..	+	..
72	475	Died	Plethory	+	..	..	+
73	510	Killed		+	+	..	..
74	510	Killed		+	+	..	++
75	557	Killed		..	..	..	++
76	585	Died	Pulmonary abscess	..	+	..	+++
77	716	Died	Pneumonia	+	+	..	+
78	725	Died	Pneumonia	..	+	..	++
79	732	Killed		+	+	..	..
80	732	Killed		+	+	..	..

Symbols: +, slight reaction; ++, moderate reaction; +++, advanced reaction.

detail later, but in summary it may be stated that although a diffuse cellular reaction ultimately ensued no fibrosis attended this process.

The lymph nodes showed irregular enlargement of a moderate degree, characterized by growth of the follicles more particularly. Only rarely could pigmentation be seen. There were no signs of degeneration, necrosis, or fibrosis.

Ten guinea pigs were left in normal air for periods up to 22 months after they had been exposed for 24 months in the calcined gypsum dust chamber. Only four of the animals died naturally, and in only two of them was pneumonia the cause (Table 2). Pigmentation persisted in the majority, but atelectasis soon disappeared though diffuse cellular proliferation could still be seen. In the lymph nodes a low-grade chronic inflam-

TABLE 2.—*Biological Action of Calcined Gypsum Dust*
Guinea Pigs Were Continuously Exposed by Inhalation to the Dust for Twenty-Four Months and Then Were Transferred to Normal Air Where They Remained Until Death

Guinea Pig No.	Exposure to Dust, Days	Fate	Cause of Death	Tissue Reaction in			
				Lungs		Pulmonary Lymph Nodes	
				Focal Pigmentation	Atelectasis	Focal Pigmentation	Enlarged Nodes
552-44	32	Killed		..	+	..	+
46	32	Killed		..	+	..	++
51	34	Died	(1)	+	+	..	..
54	44	Died	(1)	+	..	..	+
55	46	Died	Pneumonia	..	..	..	..
77	47	Died	Pneumonia	..	..	..	+
95	555	Killed		+	..	..	..
78	555	Killed		+	..	..	..
79	555	Killed		+	..	..	++
80	555	Killed		++	..	+	++

Symbols: +, slight reaction; ++, moderate reaction; +++, advanced reaction.

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matory reaction developed during the first two months the animals were in normal air, but during subsequent months this sign receded. Similar observations have, on occasion, been made on adult guinea pigs never intentionally exposed to dust. Until the precise and specific underlying histopathologic mechanism is appreciated in the case of the gypsum-exposed guinea pigs, the significance of the occurrence of these lymph node changes may be missed.

The results of this study are given in Table 3. It will be observed that only four of the animals died spontaneously. This rate of 23% for an 18-month period is actually lower than the average mortality trend of 21% per annum in our dusting experiments with an inert amorphous silicate. This virtually suggests that the gypsum exerts some measure of protection against the action of quartz. It must be recalled, though, that these animals represented the hardest speci-

TABLE 3.—Combined Biological Action of Calcined Gypsum Dust and Quartz Dust
Guinea Pigs Were Exposed by Inhalation to Calcined Gypsum Dust for Twenty-Four Months
and Thereafter to Quartz Dust Until Death

Guinea Pig No.	Quartz Dust, Days	Survival in Days	Cause of Death	Microscopic Evidence of Pneumoconiosis			Reaction in Pulmonary Lymph Nodes			
				Pigmentation	Atelectasis	Cellular Infiltration	Degeneration Fibrotic Necrotic	Enlargement	Pigmentation	Degeneration Hyaline Necrotic
554-00	80	Died	?	+	+	..	..	..	..	..
55	83	Killed		+	+	..	..	+	..	..
56	83	Killed		++	+	..	..	..	+	..
56	123	Killed		+	+	..	..	++	++	..
57	123	Killed		++	..	..	..	++	+++	..
55	124	Died	Pneumonia	..	+	..	..	++	..	..
59	154	Killed		++	..	..	..	..	..	..
59	164	Killed		+++	..	..	..	++	++	..
70	145	Killed		+++	+	..	..	..	..	..
57	201	Died	?	++	..	+	..	++	..	..
60	206	Killed		++	..	+	..	..	..	..
68	206	Killed		++	..	+	+	+	..	..
69	206	Killed		++	..	+	++	++	..	+++
71	423	Killed		++	..	+	++	+	++	..
72	423	Killed		+	..	++	++	++	..	+
73	487	Died	Pneumonia	+	..	++	+	++	+	..
74	543	Killed		++	..	++	+++	++	+	..

Symbols: +, slight reaction; ++, moderate reaction; +++, advanced reaction.

2. EXPOSURE TO CALCINED GYPSUM DUST FOR TWENTY-FOUR MONTHS FOLLOWED BY PROLONGED EXPOSURE TO QUARTZ DUST

In order to determine whether a prolonged period of exposure to calcined gypsum dust would modify the usual harmful effects of any quartz dust which might be inhaled later, an inhalation experiment to investigate this question was conducted. A group of 17 guinea pigs, after being exposed to a calcined gypsum aerosol for 24 months, was transferred to another room in which they inhaled a quartz aerosol for periods up to 18 months. The average value for the number of particles per cubic foot of air was 448,000,000 for the calcined gypsum dust and 120,000,000 for the quartz dust.

mens that survived the two years of gypsum exposure, and so protection may be only illusory.

That the gypsum does have a protective influence, however, is revealed by a study of the pulmonary tissue reaction. While pigmentation increased progressively, eventually attaining a geometric pattern and finally producing mustard-colored patches, it, nevertheless, was not as extreme as the pigmentation which occurs in animals exposed to quartz dust only.

Atelectasis was present in animals in the earlier phases of the quartz-dusting period and disappeared toward the end of the experiment. The atelectasis thus may have been a perpetuation of that seen in the later

phases of the experiment with calcined gypsum dust alone.

Consolidation, dominantly cellular in type, appeared toward the latter part of the quartz-dusting phase. From about 10 months onward, areas of cellular infiltration could be found. Strands of fibrous tissue appeared among these areas toward the end of the 12th month. Except in the guinea pig killed last of all, this fibrosis remained moderate in degree throughout the period of study. In this animal and in that one preceding it in the series, some abscess formation could be

changes and necrosis appeared first toward the eighth month and became increasingly more prevalent later.

Associated with these parenchymal pulmonary changes there was a marked catarrhal bronchiolitis in the quartz-exposed animals which was not seen in those which had first been exposed to calcined gypsum dust. The lymph nodes likewise showed a considerably enhanced and early expansion in the silicotic control guinea pigs, with progressive fibrosis and ultimate hyalinization.

TABLE 4.—*Biological Action of Quartz Dust*
Control Study: Uninfected Guinea Pigs Exposed by Inhalation to Quartz Dust Alone Until Death

Guinea Pig, No.	Exposure, Days	Date	Gross Evidence of Silicosis			Microscopic Evidence of Silicosis					Tissue Reaction in Pulmonary Lymph Node		
			Pigmentation	Pleural Abscesses	Pleural Plaques	Bronchiolitis	Cellular Infiltration	Degeneration			Macrophage Infiltration	Degeneration	
								Fibrous	Hyaline	Necrotic		Fibrous	Hyaline
602-44	43	K	..	..	..	+	+	..	..	+	..	..	
5	125	K	..	..	..	..	+	+	..	+	..	..	
5	154	K	+	..	..	..	+++	++	..	+++	..	..	
4	243	K	++	..	..	..	+++	++	+	+++	+	..	
9	306	K	..	..	+	..	+++	+++	+	++	++	..	
6	366	K	++	..	+	..	+++	+++	++	++	++	..	
8	428	K	++	+	..	..	+++	+++	++	+++	++	..	
12	533	K	++	..	+	..	+++	+++	+++	+	+++	+++	

Symbols: +, slight reaction; ++, moderate reaction; +++, advanced reaction.

seen. Necrosis was, however, conspicuous by its absence in earlier phases. No hyaline changes occurred in the lungs.

The pulmonary lymph nodes showed moderate enlargement only, with no tendency to increase in size toward the end of the experiment. Pigmentation remained minimal, but some hyaline fibrosis occurred toward the 14th month and in some instances was preceded by isolated areas of necrosis.

These changes are the more sharply shown to be indicative of the protective action of the gypsum when Tables 3 and 4 are compared. In the latter table, representing the control group exposed to quartz dust only, cellular infiltrates are recorded as having appeared within two months and were quite marked by the eighth month. Fibrosis could be discerned within 4 months, and it increased progressively, reaching a marked degree toward the 10th month. Hyaline

This comparison suggests that the prior inhalation of calcined gypsum dust not only retards the onset of the major effects of inhaled quartz dust by at least six months but also materially diminishes the degree to which they evolve and modifies the nature of the reaction to the quartz dust.

3. ALTERNATING WEEKLY EXPOSURE TO QUARTZ DUST AND TO CALCINED GYPSUM DUST

In the preceding study the guinea pigs inhaled calcined gypsum dust alone for a long period and then quartz dust alone during the remaining time they resided in the dust chamber. Some of the protective action of gypsum against quartz could, in theory perhaps, be explained on the basis of selection, for it must be recalled that quartz dusting was commenced only after 24 months of residence in an environment containing calcined gypsum dust in atmospheric suspen-

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sion, and after the weaker guinea pigs had died off.

A group of 10 guinea pigs was therefore exposed to calcined gypsum dust for three weeks and thereafter alternately to quartz dust for one week and to calcined gypsum dust for the next week. During each weekly period the animals were exposed to the dust for about 8 hours per day for five days and about 4 hours on the sixth day, or a total of 44 hours per week. This alternating weekly routine was kept up for two years.

the second year of exposure. The pulmonary lymph nodes likewise showed the same pattern of reaction as that which occurs in the silicotic guinea pig.

Unfortunately, animals were not killed prior to the eighth month; hence it is possible that a measure of early protection was exerted by the gypsum. The degree of reaction seen in the animal accidentally killed after three months was, however, less than that found in the quartz-exposed animal at two months, and at the eighth month the animal

TABLE 5.—Combined Biological Action of Calcined Gypsum Dust and Quartz Dust
Guinea Pigs Were Exposed by Inhalation to Calcined Gypsum Dust for Three Weeks and
Thereafter Were Exposed Alternately to Calcined Gypsum Dust and to Quartz
Dust for a Week at a Time Until Death

Guinea Pig No.	Expo- sure to Dust, Days	Fate	Cause of Death	Microscopic Evidence of Pneumoconiosis						Reaction in Pulmonary Lymph Nodes			
				Brachi- olitis	Cellular Infiltration		Degeneration			Cellular Infil- tration	Degeneration		
					Focal	Diffuse	Fibrous	Hya- line	Ne- crotic		Fibrous	Hyaline	Ne- crotic
553-12	95	D	Trauma	..	+	..	..	..	..	..	..	..	
8	254	K		+	+	..	..	..	..	++	+	+	
6	278	K		+++	++	..	+	..	..	++	..	++	
14	351	D	Chronic pneumonia	+++	++	+	++	..	..	++	..	++	
12	389	D	Chronic pneumonia	+++	++	+++	++	..	+	++	+++	+++	..
11	464	D	Chronic pneumonia	+++	++	+++	++	..	++	++	+++	+++	..
9	295	D	Chronic pleurisy	++++	+	+	++	..	..	+	+	..	..
7	423	K		+++	+++	++	+++	..	++	..	+++	+++	..
15	426	K		+++	+++	+++	+++	..	+	+	+	..	..
10	322	K		+++	+++	+++	+++	+	+	++	++	++	..

Symbols: +, slight reaction; ++, moderate reaction; +++, advanced reaction; +++++, very marked reaction.

During this period the average concentration of the calcined gypsum dust was about 448,000,000 and of the quartz dust about 128,000,000 particles per cubic foot of air. The results of the experiment are summarized in Table 5.

Four of the ten animals died of pulmonary causes toward the end of the first year, and the close grouping of these deaths suggests an intercurrent infection. The total pulmonary reaction was not unlike that seen in the animals exposed to quartz only (Table 4). Marked bronchiolitis was a prominent feature near the end of the first 12 months. Cellular infiltrates appeared focally and diffusely, and degenerative changes followed rapidly and reached a marked degree during

from the latter group showed a considerably greater degree of pulmonary and hilar node reaction than that observed in animals exposed to calcined gypsum dust for a comparable period.

The point which has not been settled by this study is whether this slight retardation of the pneumoconiotic response was due to the fact that the animals received a total dust load about half as great as that which the animals inhaled in the control experiment with quartz dust only. By comparison with the preceding experiment it would seem too that any inhibitory action which the gypsum may possess is not so much dependent on the concurrent presence of the gypsum and quartz in the lung tissue

as on the biological responses induced by the gypsum.

4. EXPOSURE TO A MIXTURE OF EQUAL PARTS OF CALCINED GYPSUM DUST AND QUARTZ DUST

Another aspect of the possible protective action of calcined gypsum dust was investigated in an experiment conducted with a mixture of equal parts (by volume) of calcined gypsum dust and quartz dust. A group of 35 guinea pigs was exposed to this mixed dust for periods up to 24 months, and at the end of that time 15 surviving animals were transferred to a normal atmosphere where they lived for periods up to 7 months. The average dust concentration of the mixed dust during the experiment was 318,000,000 particles per cubic foot of air, and the average concentration of the quartz particles in the mixture, determined by using dilute acid as a collecting fluid in the impinger flasks, was estimated to be about 124,000,000.

Although the material in the dusting machine was composed of approximately equal parts of quartz and calcined gypsum, that ratio was somewhat different for the aerosol derived from the mixture. Table 6 shows that the amount of quartz was less and the amount of gypsum greater in the atmospheric dust than in the parent mixture from which the aerosol was derived. For dust that had settled on top of the animal cages, the situation was reversed, and for this settled material the quartz content was higher and the gypsum content lower. This

TABLE 6.—Composition of Aerosol and of Settled Dust in Comparison with Parent Hopper Mixture Which Was Composed of Equal Volumes of Calcined Gypsum Dust and Quartz Dust

All Samples Were Dried at 110 C Before Analysis

Component	Hopper Mixture, Per Cent	Settled Dust on Top of Cages, Per Cent	Aerosol Inside Cages, Per Cent
SiO ₂	49.7	53.7	25.5
CaSO ₄	45.8	37.5	59.4
CaCO ₃ }	3.6	3.2	1.7
MgCO ₃ }			
Fe ₂ O ₃ , Al ₂ O ₃	0.8	0.9	0.8
Ignition loss	0.5	6.2	9.4
Total	100.6	100.5	100.6

condition was probably due in part to the larger average size, and therefore more rapid settling rate, of the quartz particles.

The results derived from this study are summarized in Table 7. Once again it was found that more than one-half (in this study 55%) of the animals died of pulmonary causes, the majority of these succumbing within the earlier phase of the experiment. In spite of this, there was very little evidence of a pneumoconiotic response before about the 15th month. From that stage on the total reaction was that of a dominantly cellular diffuse reaction. Atelectasis was a conspicuous feature in one instance, and bronchiolitis occurred in two later cases. But both fibrosis and necrosis were in abeyance until about the 19th month of exposure and even then remained limited in their extent or intensity.

The pulmonary lymph nodes likewise showed but minimal reaction. Though they exhibited a uniform tendency toward moderate enlargement, degenerative changes, such as fibrosis, hyalinization, and necrosis, ensued in but a few cases and to a minimal degree only.

The concurrent exposure to gypsum and quartz, therefore, appeared to have retarded and modified the influence of the quartz on the guinea pig lung.

When the 15 surviving animals were restored to normal air after a full 24-month period of residence in the gypsum quartz dust environment, the high rate of pulmonary deaths continued (Table 8). Over the nearly eight-month period of survival, 53% of the animals died of pulmonary causes. At the time of their death, the majority suffered from a chronic pneumonia which was partly based on the diffuse cellular quartz-induced infiltrates in the pulmonary parenchyma. At the same time there was a very marked type of fibrotic response, with hyaline changes in some instances. Unlike in the frankly silicotic cases, however, there was but little tendency toward necrosis, though a dust-engendered abscess was found in at least one instance toward the end of the experiment. The pulmonary lymph nodes were moderately enlarged and the scat

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TABLE 7.—Combined Biological Action of Calcined Gypsum Dust and Quartz Dust
Guinea Pigs Continuously Exposed by Inhalation Until Death to an Aerosol Derived from a
Mixture of Calcined Gypsum Dust and Quartz Dust in Equal Proportions

Guinea Pig No.	Exposure to Dust, Days	Fate	Cause of Death	Microscopic Evidence of Pneumoconiosis						Reaction in Pulmonary Lymph Nodes			
				Bronchi-olitis	Atelec-tasis	Cellular Infiltration		Degeneration		Macro-phage Infil-tration	Degeneration		
						Focal	Diffuse	Fibrous	Ne-crotic		Fibrous	Hya-line	Ne-crotic
500-22	0	Died	Pneumonia	..	..	..	..	..	..	++	..	..	..
41	20	Died	Pneumonia	..	..	..	..	..	..	+	..	..	..
49	187	Died	Pneumonia	..	..	..	..	..	..	++	..	..	..
76	228	Died	?	..	..	+	..	..	..	+++	..	..	..
83	229	Died	Pneumonia	..	++	..	++	..	..	+	..	..	..
37	269	Killed		..	..	+	..	+	..	++	..	..	..
56	442	Died	Empyema	..	..	..	..	..	..	+++	..	..	++
54	451	Died	Pneumonia	..	..	++	..	..	..	+	..	..	..
25	465	Killed		..	..	..	++	..	..	++	++	..	..
78	465	Killed		..	..	..	+++	..	..	+	++	..	..
80	466	Died	Pneumonia	..	..	++	..	+	..	+	..	+	..
43	487	Died	Empyema	..	..	+++	..	..	..	+++	..	..	..
39	493	Killed		..	..	..	+	..	..	++	..	..	+
47	494	Died	Empyema	..	..	..	+++	..	..	+	..	..	+
21	496	Died	Empyema	..	..	..	+++	..	..	++	..	..	..
44	518	Killed		++	..	++	..	..	..	+	..	..	..
56	543	Killed		++	..	++	++	..	..	++	..	..	..
29	574	Killed		..	..	++	++	..	+	+	..	..	+
25	650	Killed		..	..	+++	+++	+	+	++	..	++	..
22	728	Killed		..	..	+++	+++	+	..	+++	..	++	..

Symbols: +, slight reaction; ++, moderate reaction; +++, advanced reaction.

of moderate to marked diffuse hyalinization in the majority of cases.

It would seem, therefore, that the concurrent inhalation of the calcined gypsum and quartz dust, though retarding the mitigating

effects of the latter as long as exposure is actively continued, ultimately leaves the lung tissue diffusely vulnerable to the effects of the quartz dust. Apparently after the exposed animals have resided for a period in normal

TABLE 8.—Combined Biological Action of Calcined Gypsum Dust and Quartz Dust
Guinea Pigs Were Exposed by Inhalation for Twenty-Four Months to an Aerosol Derived
from a Mixture of Calcined Gypsum Dust and Quartz Dust in Equal Parts
and Were Thereafter Kept in Normal Air Until Death

Guinea Pig No.	Survival After End of Dust Exposure, Days	Fate	Cause of Death	Microscopic Evidence of Pneumoconiosis						Reaction in Pulmonary Lymph Nodes			
				Pulmo-nary Abscess	Atelec-tasis	Cellular Infiltration		Degeneration		Enlarge-ment	Degeneration		
						Focal	Diffuse	Fibrous	Hya-line		Hyalos-crotic	Ne-crotic	
500-36	33	Killed		..	..	+	++	+	..	..	..	..	..
53	33	Killed		..	..	++	++	++	+	++	++	..	..
41	48	Died	Pneumonia	..	..	+++	+++	++	+	++	++	..	..
22	61	Killed		..	..	+++	++	+++	++	++	++	..	..
40	73	Died	Pleurisy	..	+	..	++	..	..	++	++	..	..
48	76	Died	Pneumonia	..	..	+	+++	+++	++	++	++	..	..
12	106	Died	Pneumonia	..	..	++	+++	++	..	++	..	..	..
27	114	Died	Pulmonary abscess	..	..	..	++	+++	++	++	..	..	..
26	118	Died	Pneumonia	..	..	..	+++	+++	..	++	+++	..	..
45	119	Died	Pneumonia	..	..	..	+++	+++	..	++	+++	..	..
42	120	Killed		..	..	..	+++	+++	..	++	+++	..	..
56	122	Killed		+	..	+	+	+	..	++	..	..	..
46	122	Killed		..	..	..	++	+++	++	..	++	..	..
34	140	Died	Pneumonia	..	..	+	..	+	..	++	..	..	..
40	227	Killed		..	..	++	++	+++	++	++	..	+	+

Symbols: +, slight reaction; ++, moderate reaction; +++, advanced reaction.

air, the protective action of the gypsum is withdrawn and the quartz particles then exert their usual harmful effect. The quartz and gypsum also appear to have been carried to the lymph nodes at a differential rate which favored the hyalinizing action of the quartz at these sites.

5. EXPOSURE TO A MIXTURE OF TWO PARTS OF CALCINED GYPSUM DUST AND ONE PART OF QUARTZ DUST

Since the experiment with a mixture of equal parts of quartz dust and calcined gypsum dust gave definite evidence of an early protective action of the gypsum, the observations were checked by conducting another experiment in which a mixture of 2 parts (by volume) of the gypsum to 1 part of the quartz was used. It was found that on a weight basis the ratio was closer to $2\frac{1}{2}:1$. In the experiment with the $2\frac{1}{2}:1$ mixture, 64 guinea pigs were exposed for periods up to 29 months, and the average dust concentration was 245,000,000 particles per cubic foot of air. As in the preceding experiment, the actual aerosol in the animal cages differed in composition from the hopper mixture, the ratio of calcined gypsum to quartz in the aerosol being approximately 3:1 (Table 9).

TABLE 9.—Composition of Aerosol and of Settled Dust in Comparison with Parent Hopper Mixture Composed of Two Volumes of Calcined Gypsum Dust and One Volume of Quartz Dust

All Samples Were Dried at 100 C Before Analysis

Components	Hopper Mixture, Per Cent	Settled Dust on Top of Cages, Per Cent	Aerosol Inside Cages, Per Cent
SiO ₂	52.4	35.4	17.7
CaSO ₄	42.4	55.2	54.1
CaCO ₃ }	5.2	5.6	8.7
MgCO ₃ }			
Fe ₂ O ₃ , Al ₂ O ₃	0.5	0.7	0.9
Ignition loss	0.2	2.1	18.8
Total	99.7	100.0	100.2

Of the 64 guinea pigs, 42% died of respiratory disease, in most cases of chronic pneumonia. These deaths were, however, evenly distributed over the full 29-month period and may therefore be of reduced statistical significance (Table 10). In the majority of ani-

mals that died of natural causes, distinct pigmentation had developed, and bronchiolitis of a moderate degree was in evidence. The latter condition may have been linked with the pneumonic process, as bronchiolitis was less common and less marked in those animals which were killed for sampling (Table 11).

Focal cellular proliferation due to dust could be discerned from about the 10th month onward, and diffuse cellular infiltrations commenced to appear after the 14th month. However, except in isolated cases, collagen deposition, hyalinization, and necrosis rarely were observed. Such degenerative changes were slightly commoner and more advanced in those animals that had died of pneumonia.

The hilar lymph nodes likewise underwent enlargement, mainly from cellular proliferation, with but moderate and considerably delayed fibrous changes and necrosis in isolated instances only.

It appears then that when the amount of quartz dust to which the animals were exposed simultaneously with the calcined gypsum dust was reduced to about one-third the level introduced in the preceding experiment the fibrogenic and necrotizing influences of the quartz dust were materially inhibited despite prolonged exposure. Perhaps degenerative changes might have ensued, as in the previous experiment, had the dusting been discontinued.

To show that the animals had actually trapped quartz dust in their pulmonary tissues, the lungs of guinea pigs exposed to dust of the gypsum-quartz mixture and to quartz dust alone were analyzed for their silica content. The results obtained for the gypsum-quartz-exposed animals are contrasted with the findings for the quartz control series (Table 12). It will be observed that, although considerably less dust was retained in the lungs of the gypsum-quartz animals than was trapped in the tissues of the control animals, sufficient quartz accumulated in the lungs to have had some fibrogenic influence. It should be noted, however, that at the 24th month there was but little more quartz in the lung ash of the animals exposed to the mixed dust than there was at 8 months. At the 22-month

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TABLE 10.—Combined Biological Action of Calcined Gypsum Dust and Quartz Dust
Guinea Pigs Were Exposed by Inhalation to an Aerosol Derived from a Mixture of Two
Volumes of Calcined Gypsum Dust and One Volume of Quartz Dust;
Exposure Was Continuous Until Death
Tabulation of Animals Which Died of Pneumonia or Other Natural Cause
During Course of Exposure

Guinea Pig No.	Exposure to Dust, Days	Cause of Death	Microscopic Evidence of Pneumoconiosis							Reaction to Pulmonary Lymph Nodes				
			Fig. mentation	Bronchioles	Atelectasis	Cellular Infiltration		Degeneration			Enlargement	Degeneration		
						Focal	Dilute	Fibrous	Hyaline	Necrotic		Fibrous	Hyaline	Necrotic
548-10	81	Pneumonia	..	..	..	..	..	..	..	..	..	..	..	..
26	106	Pneumonia	..	..	..	..	..	..	..	..	+	..	..	..
37	147	Tuberculosis	..	..	..	..	..	..	..	+++	+++	..	..	+++
47	229	Chronic pneumonia	..	+	..	..	..	..	..	..	++	..	..	..
5	280	Chronic pneumonia	..	+	..	..	..	..	..	..	..	..	..	..
28	376	Chronic pneumonia	++	+	..	..	..	..	..	..	++	..	..	..
60	381	Chronic pneumonia	++	+	..	..	..	..	..	..	+++	..	..	..
66	399	Chronic pneumonia	++	+	..	..	..	..	..	..	+	..	..	..
69	408	Chronic pneumonia	++	..	..	..	..	..	..	..	++	+	+	..
56	409	Chronic pneumonia	++	+	..	+	..	..	..	..	++	..	..	..
25	411	Chronic pneumonia	++	+	..	+	..	..	..	..	++	..	..	..
33	412	Chronic pneumonia	++	++	..	+	..	+	..	..	++	+	+	..
51	414	Chronic pneumonia	++	++	..	+	..	..	..	..	++	+	+	..
52	415	Chronic pneumonia	++	++	++	+	+	+	..	..	++	++	++	..
42	417	Chronic pneumonia	++	++	..	+	+	+	..	..	++	..	..	..
39	417	Chronic pneumonia	++	++	..	+	+	+	..	..	++	..	..	..
19	420	Chronic pneumonia	++	++	..	+	+	+	..	..	++	++	++	..
41	420	Chronic pneumonia	++	++	..	..	+	..	..	..	++	..	..	..
50	423	Chronic pneumonia	++	++	..	++	++	..	..	+++	++	..	..	..
13	429	Chronic pneumonia	++	++	..	++	++	+	..	+++	++	..	..	..
61	439	Chronic pneumonia	++	++	..	++	++	+	..	+++	++	..	..	..
63	439	Abscess	++	++	..	+++	++	++	..	+++	++	..	..	..
24	452	Chronic pneumonia	++	++	..	..	..	..	..	++	++	+	..	..
49	498	Abscess	++	++	..	+	++	..	..	..	..	..	..	++
31	487	Abscess	++	++	..	+	..	..	..	..	..	++	++	..
16	510	Chronic pneumonia	++	++	..	+	+	..	..	..	..	++	++	..
54	651	Chronic pneumonia	++	++	..	+	+++	..	..	..	..	..	..	..
90	902	?	++	+	..	+++	+	+++	+	+	+	+	+	..

Symbol: +, slight reaction; ++, moderate reaction; +++, advanced reaction.

period the animals which had breathed quartz dust only had nearly three times as much SiO_2 in their lung ash as had the animals exposed to the mixed gypsum and quartz dust for the same period. We may, therefore, not be dealing after all with any specific inhibiting action against the effect of quartz dust on tissue but merely with a reduction or dilution of the quartz component.

6. EXPOSURE TO CALCINED GYPSUM DUST, THEN INFECTION WITH TUBERCLE BACILLI, AND EITHER CONTINUATION OF THE DUST EXPOSURE OR REMOVAL TO NORMAL AIR

In this experiment, which was divided into two parts, the effect of inhaled calcined gypsum dust on a tuberculous infection was studied. In the first part, 20 guinea pigs, after having been exposed to the dust for 6 months

TABLE 11.—Combined Biological Action of Calcined Gypsum Dust and Quartz Dust
Guinea Pigs Exposed by Inhalation to an Aerosol Derived from a Mixture of Two Volumes
of Calcined Gypsum Dust and One Volume of Quartz
Study of Animals Killed for Sampling

Guinea Pig, No.	Expo- sure to Dust, Days	Microscopic Evidence of Pneumoconiosis							Reaction in Pulmonary Lymph Nodes			
		Pigmen- tation	Bronchi- tides	Cellular Infiltration		Degeneration			Enlargement	Degeneration		
				Focal	Diffuse	Fibrotic	Hya- lin	Ne- crotic		Fibrotic	Hya- lin	Ne- crotic
545-56	147	+	..	..	..	..	..	..	..	..	..	..
1, 2	244	+	..	..	..	..	..	..	++	..	..	..
3, 4	304	++	+	+	..	+	..	..	..	..	..	..
5	325	+	+	+	..	..	..	..	++	..	..	..
7, 8, 64	372	+	+	+	..	..	..	..	++	..	..	..
9, 22	402	++	..	+	+	+	..	+	+++	..	..	..
15, 18, 20, 27, 41, 50, 52	428	++	+	++	+	+	+	+	+++	+	+	+
10	489	++	+	++	++	+	..	..	+++	+	+	..
11, 12, 14, 17, 18, 23	465	+++	+	++	++	..	..	+	+++	+	+	+
27, 41, 50, 52	566	++	++	++	++	..	..	+	+++	+	+	+
21, 22, 29, 30	720	+++	++	++	+++	+	+	..	+++	++	++	..
24, 40, 53	870	+++	++	++	+++	++	..	..	+++	++	++	..

Symbol: +, slight reaction; ++, moderate reaction; +++, advanced reaction; A, atelectasis.

were infected with attenuated R_1 tubercle bacilli and thereafter immediately returned to the dust room for additional exposure, up to 18 months more. For the second part of the experiment, the preinfection period of exposure to the dust was longer, namely, 25 months instead of 6 months. After being infected, the 15 animals used were not returned to the dust room. Instead, they were transferred to a normal environment and allowed to live there for periods as long as 18 months.

As a control experiment, 12 guinea pigs were infected by R_1 bacilli but were not exposed to dust.

The results of these studies are summarized in Tables 13 and 14. Before the influence of inhaled calcined gypsum dust or quartz dust

on the course of experimental tuberculosis can be interpreted, the effect of R_1 tubercle bacilli on the guinea pig lung should be briefly reviewed (Table 15).

It will be noted that, of the 12 animals in the control experiment (Table 15), 6 died within a 22-month period of observation. In all cases the deaths were due to pulmonary causes, and in at least one instance the cause was spreading cavitary tuberculosis. However, only in this one case was there spreading tuberculosis. In all other instances there were either no signs of tuberculosis or but one to three small tubercles. In only four instances did these tubercles show any activity. Tuberculosis was detectable in the pulmonary lymph nodes in one instance, but it

TABLE 12.—Ash and Silica Content of Lungs of Guinea Pigs After Exposure to Aerosols Composed, Respectively, of Calcined Gypsum Dust and Quartz Dust in a Ratio of 2:1 and of Quartz Dust Alone

Exposure, Mo.	Guinea Pig No.	Gypsum: Quartz			Guinea Pig No.	Quartz Control		
		Silica				Silica		
		Ash, % of Dried Lung	% of Dried Lung	% of Ash		Ash, % of Dried Lung	% of Dried Lung	% of Ash
6	1, 2	7.65	1.34	17.45	2	9.58	2.73	35.63
11	3, 4, 6	7.80	0.95	12.44	11, 4	13.54	5.57	45.38
12	7, 8	6.67	0.76	11.52	73, 57	12.01	5.10	46.77
18	9	7.28	0.60	9.07	7	11.63	4.94	41.78
26	11, 12, 19	4.91	0.81	16.47	24, 18	9.59	2.80	27.74
17	17, 18, 23	5.11	0.78	15.18	64	10.82	3.66	33.90
18-19					22, 20	9.71	3.42	35.41
22	23, 27	5.14	0.72	13.97	58	10.72	4.22	39.36
24	22, 29, 30	5.19	1.07	18.87				

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TABLE 13.—Influence of Calcinced Gypsum Dust on the Course of Experimental Tuberculosis Guinea Pigs Were Exposed by Inhalation to Calcinced Gypsum Dust for Six Months, Were Then Infected with *R. Tubercle Bacilli*, and Were Immediately Returned to the Dust Room for Continuation of Their Exposure to Dust Until Death

Guinea Pig No.	Survival After Infection, Days	Fate	Cause of Death	Tuberculosis					Dissemination			
				Healed	Calcification	Fibrosis	Spread	Cavitation	Cavity	Pulmonary Lymph Nodes	Liver	Spleen
553-26	99	D	Pneumonia	..	..	..	..	+	..	..	F+	..
37	144	D	Pneumonia	..	..	..	..	+	..	C+	F+	..
16	230	E	..	..	..	++	++	..	..	F+++	F+++	F+++
17	230	K	..	+	..	+	++	..	..	F+	..	..
22	258	D	Tuberculosis	..	+	++	..	..	+++	FT+	C+	C+
38	275	K	..	+++	..	..	..	..	..	F+	..	PT
38	275	K	..	+	+	+	+	+	..	F+	..	..
19	307	K	..	..	..	++	+	+	..	..	..	..
23	306	D	?	+++	..	++	..	..	..	FT+	FT+	PT
20	320	D	Pneumonia	+++	..	++	..	..	..	FT+	FT+	..
24	446	D	?	++	..	..	++	+	..	F+	..	PCT
39	474	K	..	+++	+	++	..	..	..	..	..	..
34	480	D	Pneumonia	+++	+	++	..	..	..	N+++	..	..
27	482	D	Pneumonia	++	+	+	..	..	..	FT+	..	F+
41	505	K	..	+	..	..	..	+	..	FT+	..	F+
18	520	K	..	+++	..	++	..	..	..	FN+	..	..
25	520	K	..	+++	..	++	..	..	..	FN+	..	..
31	553	D	?	..	..	++	+++	..	++	HF	HF	HF
25	551	K	..	++	..	++	+++	..	..	FT+	..	PT
40	551	K	..	++	..	..	..	+	..	..	..	PT

Symbols: C, caseation; F, fibrosis; FN, fibrous nodules; FT, fibrous tuberculosis; FCT, fibrocaseous tuberculosis; HF, hyaline change; N, necrosis; +, slight reaction; ++, moderate reaction; +++, advanced reaction.

was inactive. In the guinea pig with spreading pulmonary tuberculosis, active tuberculosis could be found not only in the hilar nodes but also in the spleen and liver.

When the guinea pigs in one of the dusted groups (Table 13) had been exposed to

calcinced gypsum dust for 6 months, infected, and then further exposed to the gypsum dust for an additional 18 months, only 9 of the 20 animals died spontaneously. Of these deaths, only six were ascribed to pulmonary causes. While signs of healing were in evidence in

TABLE 14.—Influence of Calcinced Gypsum Dust on the Course of Experimental Tuberculosis Guinea Pigs Were Exposed by Inhalation to Calcinced Gypsum Dust for Twenty-Five Months, Infected with *R. Tubercle Bacilli*, and Transferred to Normal Air

Guinea Pig No.	Survival After Infection, Days	Fate	Cause of Death	Pulmonary Tuberculosis					Dissemination		
				Healed Tubercles	Calcification	Fibrosis	Spread	Cavitation	Pulmonary Lymph Nodes	Liver	Spleen
553-26	8	Died	Pneumonia	..	..	..	..	..	..	..	..
83	9	Died	Pneumonia	2	..	..	+	..	..	..	..
27	10	Killed	..	..	..	..	..	..	..	..	..
34	27	Died	Pneumonia	3	..	..	++	..	C+	..	..
35	41	Killed	..	25	..	++	+	..	C++	C+	C+
37	122	Killed	..	17	..	++	+	++	FT+	..	..
38	135	Killed	..	20	..	++	++	..	..	..	..
39	135	Killed	..	1	..	+	+	..	F+	..	..
90	144	Killed	..	0	..	..	..	..	..	..	..
92	144	Killed	..	0	..	+	..	..	..	..	..
94	160	Killed	..	4	+	++	..	..	..	..	..
96	168	Killed	..	1	..	..	..	..	..	..	..
98	169	Killed	..	2	..	+	..	..	..	..	..
99	161	Killed	..	25	+	++	..	++	..	..	..
100	161	Killed	..	13	..	++	..	..	F+	F+	..

Symbols: C, caseation; F, fibrosis; FT, proliferative tubercle; +, slight reaction; ++, moderate reaction; +++, advanced reaction.

TABLE 15.—*Fate of Guinea Pigs Infected with R₁ Tubercle Bacilli
Control Study: No Dust Exposure*

Guinea Pig, No.	Survival, Days	Fate	Cause of Death	Pulmonary Tuberculosis		Confluent Tuberculosis	Disseminated Tuberculosis		
				Arrested Tubercles	Caseation		Pulmonary Lymph Node	Liver	Spleen
432-12	62	Died	Pulmonary infarct	1	++	..	..	..	..
11	66	Died	Pneumonia	2	+	..	..	..	..
7	118	Died	Acute congestion	6	+	..	..	..	..
1	174	Died	Pneumonia	1	..	..	..	+	..
2	202	Killed		1	..	..	..	..	..
6	265	Killed		2 (7)	..	..	+	..	..
3	438	Died	Pulmonary abscess	..	..	..	..	..	..
6	445	Killed		2 (7)	..	..	..	..	..
9	685	Died	Tuberculosis	..	..	+++	+++	+++	+++
10	601	Killed		4	..	..	..	..	..
4	654	Killed		2 (7)	..	..	..	..	..
5	654	Killed		2 (7)	..	..	..	..	..

Symbols: +, slight reaction; ++, moderate reaction; +++, advanced reaction.

most instances, in a few cases with associated calcification, spreads occurred in six instances; two cases developed cavitary tuberculosis and one died from this disease. Fibrosis was a prominent feature in a majority of instances, but caseation persisted in eight cases. The tuberculous process had, however, spread to the pulmonary lymph nodes, liver, and spleen but in most instances was partly healed. Caseation occurred in isolated instances, and fibrocaseous tuberculosis in one case. There was a higher proportion of nodules in the animals surviving longer, and in these there was also associated hyaline fibrosis.

The occurrence of 34% spreads in the gypsum-dusted guinea pigs indicates a dis-

tinct excess over that which occurred in the control series (8.3%). However, it should be recalled that the control group was relatively small. Added to this tendency to spread, there were in the dusted animals the signs of caseation, cavitation and fibrosis, and metastatic dissemination to the hilar nodes and abdominal organs. All these changes indicate some stimulatory effect of the calcined gypsum dust on the tuberculous process. There was no indication, however, that the tuberculosis promoted any pneumoconiotic process.

When the infection by means of the R₁ tubercle bacilli was initiated at the end of a 25-month period of exposure to the calcined gypsum dust (Table 14), the influence of

TABLE 16.—*Influence of Calcined Gypsum and Quartz Dust on the Course of Experimental Tuberculosis*
Guinea Pigs Were Exposed by Inhalation to Calcined Gypsum Dust for Three Weeks and Thereafter Alternately to Quartz Dust and to Calcined Gypsum Dust for a Week at a Time; After 171 Days Pigs Were Infected with R₁ Tubercle Bacilli, and Then Alternating Dust Exposure Continued

Guinea Pig, No.	Survival After Infection, Days	Fate	Cause of Death	Pulmonary Tuberculosis				Dissemination			
				Spread	Cavity	Tuberculo-silicosis	Calcification	Pulmonary Lymph Nodes	Tuberculo-silicosis	Liver	Spleen
432-4	161	Died	Tuberculosis	+++	+++	+	..	++	++	TS+	S++
6	265	Killed		+++	+	+++	..	..	+	..	..
1	368	Died	Chronic pneumonia	+	..	..	+	++	++	T+	..
2	393	Killed		..	+	+++	+	+++	+++	T++	..
3	405	Killed		..	+	+++	++	+++	+++	T++	..

Symbols: TS, tuberculo-silicosis; T, tuberculosis; S, silicosis; +, slight reaction; ++, moderate reaction; +++, advanced reaction.

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the dust on the course of the infection was entirely benign. But 3 of the 15 animals died of pneumonia within the first month after infection and none thereafter. Mild spreads were found in six of the animals killed before the sixth month and none in the later stages. Caseation was found twice only in the lungs and twice also in pulmonary lymph nodes. Pulmonary fibrosis was quite common in the healing tubercles. No pneumoconiosis occurred.

This study therefore indicates that the prior two-year period of inhalation of calcined gypsum dust modified the native susceptibility of the guinea pigs to the R_1 tubercle bacillus adversely, though not materially so. The localization of the lesions was affected, and for their normal tendency to heal by resolution there was substituted a process of healing by fibrosis, with calcification in a few instances.

7. ALTERNATE WEEKLY EXPOSURES TO CALCINED GYPSUM DUST AND TO QUARTZ DUST AND INFECTION WITH R_1 TUBERCLE BACILLI

In the first part of the third phase of the infection experiment, five guinea pigs were exposed alternately to quartz dust and to calcined gypsum dust for weekly sessions after a preliminary course of gypsum inhalation for three weeks. At the end of about 6 months they were infected with R_1 tubercle bacilli, and the alternating quartz-and-gypsum regimen was continued for an additional period of 13½ months. The results of this study are summarized in Table 16.

Spreading and cavitary tuberculosis was rapidly induced in three specimens within the first year after infection, while tuberculosilicosis within the pulmonary tissues dominated the scene, particularly in the later phases of the study. Foci of tuberculosis could be discerned in the liver, and silicotic nodules occurred in the hilar lymph nodes in all cases and once in the spleen.

These results and their relatively prompt occurrence leave no doubt that alternating gypsum and quartz exposures influence the course of tuberculosis adversely. The result is greatly modified, however, by the degree to which silicosis develops concurrently.

In the second part of this experiment, 21 guinea pigs were infected with R_1 tubercle bacilli after 3 months of exposure to an aerosol derived from a mixture of equal parts of calcined gypsum and quartz, the dusting procedure being continued for 27 months after the infection was initiated. Half of the animals died from pneumonia during this protracted period, the spontaneous deaths occurring slightly more frequently toward the end of the experiment (Table 17).

Signs of pneumoconiosis were slow to develop, but from the 13th month after infection (16 months from the start of the dusting) marked and diffuse cellular infiltration supervened, with hyaline changes in many of these lungs. Pulmonary tuberculosis of a confluent type and of moderate extent made an early appearance and persisted throughout the long period of the study. Caseation, cavitation, or calcification, however, was limited to isolated instances, especially in the latter months of the study.

The pulmonary lymph nodes showed an early tendency toward fibrosis and tuberculosilicosis. Necrosis became a rather constant finding at a later stage. Necrotic foci occurred also in the liver, occasionally with tuberculosis. Rather more commonly, tuberculous metastases were found in the spleen, and in a number of cases tuberculosilicosis likewise occurred in that organ.

Once more, therefore, the concurrent exposure to quartz dust and calcined gypsum dust in equal proportions promotes the development of tuberculosis in the infected guinea pigs. However, the disease does not reach a destructive and fatal stage like that seen when the dust exposure is to quartz dust alone (Table 4). It will be observed from this record that exposure to quartz dust converts the infection with R_1 tubercle bacilli into a spreading tuberculous process associated with tuberculosilicosis and a high and early mortality rate.

COMMENT

Since in previous experiments the intraperitoneal injection of even an excessive quantity of calcined gypsum particles did not pro-

TABLE 17.—Influence of Calcined Gypsum Dust and Quartz Dust on the Course of Experimental Tuberculosis

Guinea Pigs Were Exposed by Inhalation for Three Months to an Aerosol Derived from a Mixture of Equal Volumes of Calcined Gypsum Dust and Quartz Dust and Were Then Infected with *R. Tubercle Bacilli*; After Infection the Animals Were Immediately Returned to the Dust Room Where Their Dust Exposure Was Continued Until Death

Guinea Pig No.	Survival After Infection, Days	Cause of Death	Con- sistance	Pulmonary Tuberculosis				Dissemination		
				Degeneration		Pneumoconiosis		Pulmo- nary Lymph Node	Liver	Spleen
				Cavita- tion	Hyaline Necrosis	Focal	Diffuse			
400-9	173	E	+	..	+	..	..	F++	..	..
17	230	K	+++	..	+	+	..	TF+	F+	..
11	277	D	Pneumonia	+++	..	+	..	..	..	T+
16	287	D	Pneumonia	+++	OL+	..	+	..	N+	..
1	336	K	+	+	+	+	..	ST+	..	..
2	356	K	+++	+	..	..	..	ST++	..	..
10	358	D	Pneumonia	+++	OL+	..	..	ST++	..	T+
13	399	K	+++	..	..	+	+	..	..	..
5	401	K	+	..	+	..	+++	N+	F+	F+
10	428	K	+++	+	+	+	..	..	..	F+
8	438	K	+++	..	+++	+	+++	N++	..	T+
21	432	D	Pneumonia	+++	+++	..	..	N+	..	F+
16	482	D	Pneumonia	+++	OL+	+	..	F++	N+	TF+
6	508	K	+++	OL+++	+++	..	+++	N++	N+	TF+
19	510	D	Pneumonia	+++	OL+++	+	..	N++	T+	TF+
7	549	D	Pneumonia	+++	+++	..	+	N+	T+	TF+
14	565	D	Pneumonia	+++	+++	..	+++	N+	..	..
12	570	K	+++	CA++	..	..	+++	N+	N+	T+
8	578	D	Pneumonia	+++	+++	..	+++	N+	N+	T+
4	491	K	+++	+++	..	+	+++	F++	..	T+
20	800	D	Pneumonia	+++	OL+	+++	+	N++	T+	..

Symbols: +, slight reaction; ++, moderate reaction; +++, advanced reaction; CA, cavitation; OL, calcification; F, fibrosis; H, hyaline change; N, necrosis; ST, silicotuberculosis; T, tuberculosis; TF, tuberculous fibrosis.

duce progressive fibrosis, it was anticipated that the inhalation of those particles would have no serious effect upon the lungs. That assumption has been verified by the studies reported in this paper. It has been demonstrated that the small increments of fine calcined gypsum particles inhaled into the lungs largely disappear, apparently as a result of solution in the tissues. Very little anatomic evidence of their presence can be discovered. Evidences of reaction in the fixed tissues of the lung are minimal, even after exposures to high concentrations for a period of two years.

In the hilar lymph nodes, which must have received the greater part of the gypsum that was spirited away from the lung parenchyma in this series of guinea pigs, there is an almost specific pattern of reaction comprising medullary hyperplasia in the nodes and their follicles which is unaccompanied by any increase

in the lymphoid tissue. Fibrosis was, however, conspicuous by its absence.

It is to be hoped that this interesting finding may mean that it would be inconceivable that the inhalation of calcined gypsum dust will produce significant reactions in otherwise healthy lungs of industrial personnel, perhaps even regardless of atmospheric concentrations. This circumstance would therefore conclusively eliminate calcined gypsum per se as the cause of the pulmonary lesions which have already been reported in respect of deceased gypsum-industry employees.⁸

It is difficult to evaluate the high pneumonia rate in these guinea pigs. By comparison with other studies conducted in The Saranac Laboratory, it is excessive (Table 18). However, these latter investigations have been conducted in more recent years when it has been possible to control epizootics more effectively by ultraviolet-light radiation

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TABLE 18.—Comparison of Number of Spontaneous Deaths of Guinea Pigs in Inhalation Experiments with Various Dusts

Kind of Dust	Animals Exposed to Dust, No.	Animals Found Dead, No.	Mortality Rate, Per Cent
Quartz	84	19	23
Silica fume	708	80	11
Amorphous Silica A	404	48	12
Amorphous Silica B	192	44	23
Amorphous Silica C	209	44	21
Amorphous Silica D	235	54	23
Volcanic glass	81	6	7

and antibiotics. Perhaps no further attention need be given to the matter. However, the high pneumonia rates and the emphasis of this phenomenon on certain phases of the study suggest that the matter is at least worth further investigation.

The experiments demonstrated that guinea pigs are protected against ordinarily dangerous concentrations of quartz dust by the concurrent presence of calcined gypsum dust in the same atmosphere. Under the conditions of the experiments, in which the ratio of quartz to gypsum was relatively high, the protection was not absolute or uniform for all the exposed animals. The protective action of the calcined gypsum completely prevented the development of fibrosis in the majority of cases and retarded or modified the character of the dust reaction in the remainder. The degree of protection was not defined wholly by the length of exposure but was affected to some extent by other factors not clearly understood. Sporadic cases of nodular fibrosis developed in some animals exposed for shorter periods than in other animals which failed to manifest this type of reaction. Possibly host factors involving individual susceptibility were involved.

The protection was most evident in respect to the degree to which the prevalence or severity of bronchiolitis was reduced in the animals exposed to both gypsum and quartz; to the retardation of the pulmonary cellular reaction and the diminution of its extent; to the limited amount of fibrosis, hyalinization, or necrosis which ensued, and to the inhibition of dissemination of the dust to abdominal organs and even to the regional lymph nodes.

Several possible explanations for this condition should be entertained. The first concerns the possibility of chemical or physical interaction between the gypsum and the quartz, either in the hopper mixture or even after deposition in the guinea pig tissues. Next should be considered the factor of biological antagonism to quartz which may be induced by the gypsum. To these observations should be added the fact that the dose of quartz was actually decreased through dilution with the gypsum and that the quartz was administered to older guinea pigs and to the hardiest survivors of earlier phases of the experiment. It is even possible, though unlikely, that the quartz dust itself may have "aged" with the passage of time, thus not being quite as potent as at earlier phases of the experiment.

The latter question cannot receive an answer until we have more information concerning the influence of aging of powdered quartz on its biological properties. The problem whether quartz has a greater or a less propensity for damaging the tissues of older laboratory animals compared with its effects on the younger specimens usually selected for study has never been properly examined. Linked with this question is the possibility that mere survival against all the forces which naturally or artificially may tend to decimate the ranks of laboratory animals may signify a hardy stock perhaps also more resistant to quartz dust. There is no answer to this, but it should be entertained as one of the possible mechanisms which influenced the results in this investigation.

The fact that the quartz dose was actually decreased through dilution may have relevance. Over the years, experiments with quartz dust have been carried out in The Saranac Laboratory in a great diversity of dosage levels. Except in extreme ranges of particle concentration, the tissue reaction to quartz does not vary too obviously. To be precise, however, no systematic body of knowledge exists to enable one to make comparisons with complete assurance. The great differences observed in the present series of experiments suggest decidedly that the ex-

TABLE 19.—Effect of Varying the Amount of Gypsum on the Solubility of Particulate Quartz Suspended in a Buffer Solution

Quartz Particle Size: 1 μ to 3 μ
 Buffer Solution: H₂BO₃-NaOH pH 6.90
 Incubation: 37 C for Twenty Hours

Gypsum Suspension, Mg.	Soluble SiO ₂ , Mg/100 Cc.	Increase in Soluble SiO ₂ , Per Cent	pH at End 24 Hr.
0	0.55		6.70
20	0.70	22.5	6.75
50	0.78	39.9	6.75
100	0.90	62.1	6.75
500	1.25	125.7	6.75
750	1.28	127.0	6.87
1,000	1.33	144.4	6.95
2,000	1.36	135.7	7.23
3,000	1.36	135.8	7.45
5,000	1.35	111.3	7.15
Control: No Quartz			
5,000	0.12		7.50

planation does not rest merely with the question of dilution. In The Saranac Laboratory, experience has also been gained with dilution as a factor in relation to "inert" substances, such as iron oxide, and the results of these studies serve as further confirmation that the inhibition achieved by the calcined gypsum dust is real and not merely a function of quartz dosage. That the quartz dust actually did enter into the lung tissues in a dosage ratio bearing some relation to that according to which it was administered was adequately shown by the chemical analyses of guinea pig lungs recorded in Table 12.

That the influence of the gypsum on the quartz may have been due to some form of physicochemical interaction is suggested by Tables 19 and 20 and the known fact that gypsum particles have a positive electrical charge while the charge of quartz particles is negative. In Table 19 it is shown that the presence of gypsum in a buffered solution increases the solubility of suspended quartz particles considerably without substantially changing the pH. Table 20 confirms the latter observation and shows that the presence of gypsum raises the pH of the solution markedly when 1% gypsum and 1% quartz are incubated together in a buffered solution at 37 C for 24 hours. If the theory of Holt* that silica exerts its necrotizing and fibrogenic action by virtue of silicic acid polymers,

which can form only in an acid pH range, be acceptable, the reduction in the influence of the quartz in the presence of gypsum may find an explanation. Such a chemical theory receives further confirmation from the observation that when quartz and gypsum were administered in alternating weekly doses the resultant pneumoconiosis was much worse than when an equivalent amount of calcined gypsum dust was introduced into the guinea pig lungs simultaneously with the quartz dust. Owing to the apparently rapid elimination of the gypsum and the tardiness with which koinophores make an appearance in response to its introduction, this would mean perhaps that in the alternating exposure experiment the gypsum had practically been eliminated at the end of each week end, so that the quartz had an unimpeded opportunity to act on the tissues in focal and later diffuse regions where a low pH prevailed. The elimination experiment in which the animals were left in fresh air after a prolonged period of exposure to quartz dust and calcined gypsum dust also indicates the same chemical explanation. By the progressive loss of gypsum from the lungs, the local tissue pH could have been progressively reduced, thus liberating the full action of the accumulated quartz. The answer to these enigmas can come only through further research.

That the total result may have been simply one of biologically antagonistic effects of gypsum and quartz and even perhaps merely

TABLE 20.—Effect of Varying pH Values on the Solubility of Particulate Quartz When Suspended with Calcined Gypsum in a Buffer Solution

Quartz Particle Size: 1 μ to 3 μ
 Buffer Solution: H₂BO₃-NaOH
 Incubation: 37 C for Twenty-Four Hours

Buffer Solution, pH	Suspension 1% Quartz + 0% Gypsum		Suspension 1% Quartz + 1% Gypsum	
	Soluble SiO ₂ , Mg/100 Cc.	pH After 24 Hr.	Soluble SiO ₂ , Mg/100 Cc.	pH After 24 Hr.
6.1	1.18		1.25	
7.1	0.28	6.65	1.50	6.85
7.4	0.54	6.94	1.75	6.90
8.5	0.66	7.62	2.51	7.45
9.5	1.62	8.70	2.10	8.32
10.2	2.45	9.11	1.14	9.50

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a matter of tissue or cellular competition cannot be dismissed as a possibility without due consideration. The paucity of koinophores in the gypsum-drenched lung may mean not only that calcined gypsum does not exert a chemotropism for these cells, such as quartz exerts markedly,¹⁰ but even that the presence of gypsum repels these cells. Silicosis does not ensue until quartz particles have been phagocytosed by the alveolar macrophages and transported to sites where their cumulative action can provoke local lesions. If gypsum blocks the approach of these cells, the quartz particles will simply not be picked up.

It is possible too that the absence of alveolar macrophages in the early phase of the exposure to calcined gypsum dust may signify merely that they do not need to enter the alveoli to ingest the gypsum. The latter, being somewhat soluble, could be picked up after penetration of the alveolar walls. As the gypsum is not likely to prove immediately toxic to the macrophages, there would be no barrier to their transportation to distant parts and disappearance from the lungs. In such circumstances they would not be available to pick up the quartz particles.

The influence of flocculation on the accessibility of the quartz should also be examined. It was shown by Gardner⁴ that when calcined gypsum dust and quartz dust are suspended in the dust room simultaneously there is a marked tendency to flocculation. Gardner suspected that this might prevent the actual inhalation of many of the suspended particles. However, his tabulation shows that more than 52% of the clumps measured less than 5 μ in diameter. These would be respirable. What was not settled was whether these clumps of particles remained as aggregates even within the cells of the lung or lymph nodes.

Biological antagonism naturally goes further than these simple mechanistic speculations. Until we know more about all these issues, we must keep an open mind about the possible antagonistic influences and even, perhaps, specific synergisms between calcined gypsum and quartz in terms of tissue and cellular enzyme and energy transfer systems.

A final point of direct practical application might be stressed here; namely, that where a series of pulmonary reactions do result when calcined gypsum and quartz are administered either together (successively, simultaneously, or alternately) or in conjunction with a tuberculous infection, the final histopathological result achieved is not a mere quantitative expression of the relative component action of each of these three etiological agents but actually, in a sense, is a new type of lesion, a form of holistic synthesis. This is the problem of the mixed pneumoconioses which are being encountered in increasing numbers in industry today. Their precise nature cannot be simply predicted by reference to the known properties of the separate component mineral substances. More research is needed about all these matters.

SUMMARY

In a series of long-term inhalation experiments, guinea pigs were exposed to calcined gypsum dust alone and to mixtures of quartz dust and calcined gypsum dust; in addition, the influence of the gypsum and of the gypsum mixed with quartz on the course of experimental tuberculosis was studied.

The effect of calcined gypsum dust on the lungs of guinea pigs exposed to the dust for two years was too insignificant to be classified as a pneumoconiosis.

The presence of calcined gypsum dust in atmospheric suspensions with quartz dust offered to exposed guinea pigs a substantial degree of protection against the usual harmful effects of the quartz dust. The protection, however, was lost when the exposures ceased, enabling the gypsum to be removed from the lung tissue and liberating the full effect of the accumulated quartz; but to a lesser degree.

The inhalation of calcined gypsum dust alone influenced the course of experimental tuberculous infection in guinea pigs to a moderately disadvantageous degree only, manifested chiefly by interference with the process of healing after initial spread of the infection.

The course of a tuberculous process in guinea pigs infected with R₁ tubercle bacilli was adversely affected to a slighter degree

by exposure to a mixture of quartz dust and calcined gypsum dust than by exposure to quartz dust alone.

Chemical analysis of lung tissues of guinea pigs that had been exposed to a mixture of quartz dust and calcined gypsum dust shows that the quartz is actually retained in the lung tissue but in less than half the concentration which may be achieved when the exposure has been to quartz dust only.

The most likely explanation for the inhibitory effect of calcined gypsum on quartz appears to be in the realm of physical chemistry, though biochemical factors and biological antagonism have not been excluded.

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Effect of Inhaled Commercial Hydrous Calcium Silicate Dust on Animal.

An Experimental Study

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Commercial hydrous calcium silicate is one of the products that have been studied by long-term inhalation experiments at The Saranac Laboratory. These studies were commenced in 1943 under the direction of Dr. L. U. Gardner and with the assistance of two of us (T. M. D. and A. B. D.) who carried the work to its completion after Dr. Gardner's death. Guinea pigs, rats, and hamsters were used, and the experiments were designed to reveal the nature of the pulmonary tissue reaction to inhaled dust of the material in normal animals and in those harboring an experimentally induced tuberculous infection.

From experience with other siliceous materials one would expect to find that a product composed only of calcium silicate would be relatively inert in its effect on tissue. Extensive clinical studies of industrial workers exposed to cement dust in high concentration have, for instance, shown that the effect of the inhaled dust of that material on the lungs is insignificant. Portland cement is composed principally of two calcium silicates, namely, dicalcium silicate and tricalcium silicate. Recognition must be given, however, to the possibility that any poten-

tially hazardous raw material might not be to a nonhazardous form during the manufacturing process and, appear to a greater or less extent in an unchanged condition in the final product. The clay and shale used in making cement often have a quartz content of 20% to 30% or more, but chemical reactions, occurring when the raw mixture is heated, convert practically all the hazardous free-silica mineral to a relatively harmless silicate. In most samples of cement the amount of quartz that has come through the manufacturing process unchanged is less than 0.1%.

The hydrous calcium silicate product used in The Saranac Laboratory studies was made from calcium hydroxide and silica plus a moderate amount of asbestos, which was incorporated in the mixture to impart certain desirable physical properties to the finished product. Analysis of one sample of this finished product disclosed that approximately 80% of the raw mixture had been converted to hydrous calcium silicate and that about 15% was magnesium silicate (Table 1). About 1% quartz persisted in the final product. Probably the greater part of the magnesium silicate was present as the fibrous mineral chrysotile, although a portion may have been in the form of serpentine, a mineral similar to chrysotile in chemical composition but one which is nonfibrous.

EXPERIMENTAL METHOD

To determine the effect of inhaled dust of the product on pulmonary tissue, an inhalation experiment was conducted. In that experiment groups of guinea pigs, rats, and hamsters were exposed in a cubical dust room, 8 ft. in dimension, in which

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TABLE 1.—Composition of Commercial Hydrous Calcium Silicate

Component Analysis	Per Cent	Component Analysis	Per Cent (Approx.)
SiO ₂	45.5	Hydrous calcium silicate	80
Fe ₂ O ₃ , Al ₂ O ₃ , TiO ₂	3.5	Calcium carbonate	5
CaO	25.0	Magnesium silicate	15
MgO	7.1		
Na ₂ O, K ₂ O	0.8		
Ignition loss	19.7		
Total	99.7	Total	100

an atmospheric suspension of the hydrous calcium silicate product was created by the action of a paddle which rotated inside a hopper containing the material in finely divided form. The dust cloud generated in this manner floated out into the room where it was maintained for eight hours on five days of the week and for four hours on Saturdays. Some of the animals were exposed to the dust for periods as long as three years. At regular intervals during the experiment a few animals were killed, and the organs examined grossly and microscopically to determine the nature and the extent of the tissue reaction to the calcium silicate product. The tissue was also analyzed chemically to estimate the amount of the inhaled dust that was retained in the lungs of animals exposed for definite periods of time. Only guinea pigs were used in the studies dealing with infected animals. The R₁ low-virulence strain of the tubercle bacilli was introduced intratracheally by means of the insufflation technique.

Dust counts of atmospheric samples collected in the dust room were made regularly by means of the midget impinger. The concentration of the hydrous calcium silicate aerosol to which the uninfected animals were exposed was generally within the range of 100,000,000 to 125,000,000 particles per cubic foot of air by light-field count, and the overall average was 115,000,000. In the studies on infected animals the concentration was higher, the average being 205,000,000.

EXPOSURE OF UNINFECTED ANIMALS

Three species—guinea pig, rat, and hamster—were employed in this phase of the investigation. Summaries of the findings are given in Tables 2, 3, and 4. Attention should first be drawn to the relatively high mortality rate reflected in Table 2. That these deaths were due to intercurrent epizootic infection was almost certain in the case of the guinea pigs and is emphasized the more forcefully by the fact that the animals died not only of pneumonia but also of pericarditis, peritonitis, and cervical adenitis with abscess formation. That all the hamsters which died did so within the first year may also have some bearing on the question. In the case of the rats, on the contrary, no animals died within the first year, and the rate at which animals succumbed increased with the passage of time. In view of the progressive nature of the pulmonary disease which ensued as a result of the exposure to the dust of the hydrous calcium silicate product, there is some presumptive evidence that the deaths and dust exposures bore some relation to each other in this instance.

TABLE 2.—Biological Action of Commercial Hydrous Calcium Silicate Dust
Guinea Pigs, Hamsters, and Rats Were Exposed by Inhalation to an Aerosol of Commercial
Hydrous Calcium Silicate Dust Until Death
Record of Animals, Exposed to the Dust Alone, Which Died Spontaneously

Species	Cause of Death									
	Pneumonia		Pericarditis		Peritonitis		Cervical Adenitis		Total	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
Guinea Pig	51 ¹	49.2	7	5.6	12	9.6	3	2.4	73	56.8
Hamster	101	50.5	..	..	..	..	..	..	124	60.0
Rat	221	55.6	..	..	..	..	..	..	50	60.0

¹ 40.5% died within first year of experiment.

² 100.0% died within first year of experiment.

³ 10.0% died within first year of experiment.

⁴ Two deaths from other causes.

The three species of experimental animals reacted somewhat differently to the dust, though the difference was more one of degree than of quality. The most marked lesions were provoked in the guinea pigs, but this was probably largely due to the fact that dusting was carried on for a total of 36 months in the case of this species, while the procedure was terminated at the end of the 18th month in the case of the rats and hamsters. When cognizance is taken of this fact, it appears that, stage for stage, the latter two animal groups actually suffered greater pulmonary damage sooner than did the guinea pigs. This difference is brought out by a comparison of Tables 3 and 4, in the construction of which the same scales of values were used.

Pigmentation of the pulmonary tissue or of pulmonary lymph nodes never became prominent features in these animals. It increased diffusely as a light brown discoloration which was most marked along the anterior margins of the lungs in the guinea pigs. As it became macroscopically detectable at the 12th month of exposure only, its absence in the case of the rats or hamsters before the 18th month may have no true significance. It would seem that the pigment was almost entirely due to hemosiderin, as shown by Prussian blue staining. Pigmented koinophores and giant cells became a prominent feature toward the terminal phase of the experiment on guinea pigs, and clusters of such cells could even be found in rat lungs where they were grouped around the smaller blood vessels.

Lymphoid hyperplasia was a prominent and persistent feature of the reaction in the guinea pigs. There was mild hyperplasia about the main bronchi in some of the rats, but this was not an impressive observation for this species. No lymphoid hyperplasia was seen in the hamsters.

The hyperplasia consisted almost entirely of lymphoid cell proliferation without any evidence of central macrophage accumulation such as may occur as a result of exposure to certain amorphous siliceous dusts. Mostly the lymph deposits remained spherical in shape and were thus well defined from sur-

rounding structures. Occasionally, however, there was some lymphoid invasion of the walls of adjacent alveoli. At a later stage macrophages tended to accumulate around these lymph foci.

In spite of this tendency toward intrapulmonary lymphoid hyperplasia, the pulmonary lymph nodes showed no consistent corresponding change. In some of the animals there was early lymphoid hyperplasia, but in the majority the nodes enlarged slightly or moderately only at the start. After the animals had been in the dust atmosphere for two years, the nodes became more consistently enlarged, and in the instances in which this occurred the cause was almost always infiltration of the medullary zones by macrophages, which no doubt migrated thence from the pulmonary tissues. The cortical follicles did not enlarge and often showed signs of atrophy. In both the rats and hamsters the reaction in the pulmonary lymph nodes was even less marked.

Undoubtedly the most prominent lesion discovered in this series of animals was present as chronic bronchiolitis and bronchial ulceration, with emphasis on the former. The disease was progressive in nature and destructive in its effects, although the tendency to epithelial desquamation, so characteristic of the reaction to quartz dust, was not present.

The bronchiolar lesions commenced early in the guinea pigs and hamsters but were delayed in the rats. In neither of the latter groups were the severe grades of obliterative bronchiolitis or bronchiolitis deformans, which characterized the guinea pig response, observed. In the rat the stress was rather on bronchiolar ulceration and peribronchiolitis.

As the dusting proceeded beyond the first year of experiment, the inflammatory reaction in the bronchioles gave way to progressive distention and distortion. This change was brought into sharp focus by the increasing cellular deposits around the air passages. Toward the end of the second year the crenated outlines of the bronchiolar lumina were thrown into sharp relief by a

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marked tendency to peribronchiolar atelectasis, with epithelialization of the walls of the shrinking alveoli and cellular infiltration among these minute cystic spaces. This change produced a microscopic sectional effect resembling multiple adenomatosis, but as there is no lack of differentiation of the cellular components, no neoplastic change could be postulated. This adenomatoid pattern was seen only in the guinea pigs, but as its evolution was in the nature of a delayed phenomenon, it is possible that it would also have appeared in the rats and hamsters had exposure been continued in their cases beyond the 18th month.

Phagocytosis of the inhaled dust could be demonstrated in all animals from the commencement of the experiment. It was most marked in the case of the guinea pigs and least prominent as a feature in the case of the hamsters. The phagocytes were dominantly mononuclear macrophages until about the end of the first year of the exposure when multinucleated giant cells commenced to be substituted in progressively greater numbers. At the same time these giant cells grew in size so that they often filled the alveoli completely, and toward the end of the third year of exposure the giant cells replaced the mononuclear cells almost completely, especially around the distorted bronchioles. As time passed, their cytoplasm became increasingly more acidophilic and their centers more charged with ingested particles. There was no evidence of necrosis of these cells, such as occurs in experiments with finely divided quartz dust and silica fume, which provoke similar giant cells.

Interstitial cellular proliferation and infiltration are a late sign in all three species. It commences first toward the end of the ninth month of exposure, and for the succeeding six months it is almost entirely limited to macrophage accumulations around smaller blood vessels and bronchioles, at the angles between adjacent alveoli, and in the interlobular septa. Among these macrophages may be found isolated eosinophiles and plasmacytes. Fibrocytes first make an appearance between the 15th and the 18th month of dust

inhalation, and soon after this strands of collagen may be perceived among the cells. Fibrosis proceeds slowly, however, before the end of the 30th month of dust exposure. Thereafter it is detectable in increasing amounts, particularly in relation to the adenomatoid areas around the bronchioles. Fibrosis also appears prominently in local areas of consolidation, which become progressively commoner toward the end of the third year of exposure. In animals killed, respectively, at 33 and 36 months from the start of the dusting, extensive areas of lobular consolidation could be found, and similar consolidation associated with cystic distention of trapped bronchi could be seen in several of the rats killed at the 15- and 18-month periods. No acute inflammatory process was demonstrable to account for these results.

Asbestos bodies of an elongated, slender, tapering, minute variety were demonstrable by oil-immersion microscopy from about the 15th month onward in rats and hamsters and from the 18th month onward in the guinea pig. Occasionally opaque clubbed bodies could be found, but in most instances the bodies were difficult to bring into focus and tended to be curved and spindle-shaped. Often they were intracellular, being partly engulfed by one or more macrophages. None were found lying free within alveoli. They were so constantly found in association with the areas of fibrosis that the conclusion of a causal relationship between these phenomena is almost inescapable.

Emphysema of the hypertrophic variety appeared as an early sign in the hamsters, in which it was present to a quite marked and widely distributed degree at the end of the 18 months of dust exposure. In the rats the lesions were also consistently present from an early stage but to a lower degree than in the hamsters. In the guinea pigs, on the contrary, hypertrophic emphysema was contrastingly absent during the first two years of the experiment. In the final 12 months, compensatory emphysema was manifested as a prominent lesion silhouetted against the foci of cellular proliferation and peribronchiolar atelectasis.

Unlike in many other dust experiments, there was no marked tendency toward subpleural congregation of the hydrous calcium silicate dust. Consequently the reaction at this site was minimal and delayed. The most conspicuous changes occurred in the rats where there were occasional subpleural cellular condensations and a recurrent tendency to the formation of interlobular adhesions. In some of the guinea pigs which outlasted three years of exposure to the dust, foci of subpleural cellular proliferation attended by giant-cell accumulation were demonstrable.

The relatively marked macrophage infiltration of the pulmonary lymph nodes contrasted sharply with the paucity of giant cells among them, with the minimal amount of interstitial fibrosis which ensued, and with the absence of asbestos bodies. Periadentitis of a mild degree became a consistent finding in a majority of animals beyond the end of the first year of dust inhalation. Deposition of fibrous strands around the lymph nodes followed successive phases of afferent lymphangiectasia and macrophage transportation along these channels, with littoral arrest of increasing numbers of these cells.

The lack of fibrosis, except at sites where asbestos bodies occur with greatest prevalence, is indeed remarkable, the more so when regard is had to the dense cellular infiltrations which ultimately ensue. One is led to the conclusion, therefore, that the hydrous calcium silicate dust alone, except for its chrysotile component, is nonfibrogenic though it provokes a cellular reaction.

EXPOSURE OF TUBERCULOUS ANIMALS

There are three types, or phases, of investigation that have been found invaluable for studying the effect of inhaled dust on the course of experimentally induced tuberculosis in animals. These three types of experiment are sometimes called the simultaneous phase, the reactivation phase, and the predisposition phase. In the simultaneous phase, normal animals are infected with attenuated tubercle bacilli of the R₁ strain by an inhalation method and then are immediately transferred to the dust room. Thus the tuber-

culous disease and the tissue reaction to the inhaled dust will develop simultaneously. In the reactivation-phase experiment, the animals, after being infected with the tubercle bacilli, are allowed to live in a normal atmosphere for several months before being exposed to dust. During this period the tuberculous lesions generally regress, and in some instances complete healing by resolution may take place. Following this interval, the exposure of the animals to some dusts has no significant effect on the usual course of the tuberculous process, and the lesions continue to regress, while exposure to other dusts may cause the tuberculous process to become active and to spread. A predisposition-phase experiment is one in which animals are exposed to dust for several months, are then infected with the tubercle bacilli, and are immediately returned to the dust room where their exposure to dust is continued. In this phase the effect of a previous dust exposure on the early course of a tuberculous process can be studied.

SIMULTANEOUS PHASE: REACTION IN GUINEA PIGS INFECTED WITH TUBERCLE BACILLI AT ONSET OF DUST INHALATION

In the first experiment in which animals were infected with tubercle bacilli at the time that their exposure to the dust was started, 25 guinea pigs were used, but an epidemic of pneumonia during the first 10 months reduced to 16 the number of animals available for study. Two of these died at fourteen months, apparently from progressive tuberculosis, and two others died from undetermined causes but not from tuberculosis. In the remaining 12 animals the course of the tuberculous disease was followed by killing 1 or 2 animals at 1, 6, 9, 12, 15, 18, and 24 months after infection. In 9 of the 25 animals the lesions were multiple, isolated, and healed, often with central calcification. In six of the remaining animals the lesions were still circumscribed but showed neither a tendency to heal nor to spread even at the end of 18 months. In six other animals there was a moderate tendency to local spread of the tuberculous process, while in the remaining

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TABLE 5.—Causes of Death in Guinea Pigs Exposed by Inhalation to Commercial Hydrous Calcium Silicate Dust and Also Infected with Tubercle Bacilli of the R₁ Strain

Type of Experiment	Exposed Animals, No.	Cause of Death								Total	
		Pneumonia		Pericarditis		Peritonitis		Other Causes			
		Deaths, No.	Per Cent	Deaths, No.	Per Cent	Deaths, No.	Per Cent	Deaths, No.	Per Cent	Deaths, No.	Per Cent
Simultaneous phase	20	6	30.0	1	5.0	7	35.0	2	10.0	16	80.0
Reactivation phase	25	2	8.0	1	4.0	..	..	1	4.0	4	16.0
Predisposition phase	20	6	30.0	..	..	..	..	..	..	6	30.0
Control: Group A	54	4	11.7	..	..	..	..	..	..	4	11.7
Group B	25	3	12.0	1	4.0	2	8.0	..	..	6	24.0

animal, which was killed at 15 months, the lesions were widespread throughout the lung but fibrosis had been produced. In an attempt to develop a strain of guinea pig resistant to the infection that had caused the pneumonia, some of the animals were used for breeding during this experiment. The two animals that died from progressive tuberculosis (at 14 months) and the single animal (killed at 15 months) that exhibited

widespread lesions were all used as breeders during the experiment, as were also four other animals in the experiment, which had failed to show extensive disease. Owing to the element of uncertainty introduced by this factor of breeding, and also because of the high mortality from pneumonia and to verify the suggestive evidence of stimulating action of the inhaled dust upon tuberculosis, the experiment was repeated.

TABLE 6.—Course of Tuberculosis Induced in Guinea Pigs by Infection with Tubercle Bacilli of the R₁ Strain

Control Study: Infection Only; No Dust Exposure

Guinea Pig No.	Survived After Infection, Days	Fate	Pulmonary Lesions					Reaction in Pulmonary Lymph Nodes			
			Arrested Tubercles, No.	Spreading Tuberculosis	Caseation	Calcification	Pleuritis	Enlargement	Tubercle Formation	Dissemination	
										Liver	Spleen
05	05	Died	8	..	..	..	..	+	..	..	..
07	05	Killed	6	..	+	..	..	++	+	T+	T+
08	05	Killed	15	..	+	..	..	++	+	T+	T+
23	120	Killed	7	..	..	..	..	++	..	..	..
24	120	Killed	6	..	..	..	..	+++	++	..	T+
25	120	Killed	2	..	..	..	..	++	+	..	..
26	120	Killed	5	..	..	..	+	++	+	..	..
72	125	Died	..	+++	++	..	..	++	++	T+++	T+++
73	100	Died	2	..	..	..	++	+	..	..	..
15	100	Killed	4	..	..	+	..	++	+	..	..
30	100	Killed	11	..	..	+	..	++	..	..	..
38	105	Died	2	..	..	..	..	++	..	..	..
41	100	Killed	0	..	..	..	..	++	..	..	..
71	120	Killed	4	..	..	..	..	++	+	..	..
28	115	Died	1	..	..	++	..	+	..	..	..
70	125	Killed	7	..	..	..	..	++	..	..	..
20	125	Killed	18	..	..	+	..	++	..	..	..
07	120	Killed	4	..	..	..	..	+	..	..	..
09	120	Killed	5	..	..	..	..	+	..	..	..
08	120	Killed	3	..	..	..	..	++	..	..	..
70	120	Killed	1	..	..	..	..	++	..	..	..
71	120	Killed	5	..	..	..	..	++	..	..	..
72	120	Killed	5	..	..	..	..	++	..	..	..
73	120	Killed	2	..	..	..	..	+	..	..	..
74	120	Killed	2	..	..	..	..	+	..	..	..
77	120	Killed	8	..	..	..	..	++	..	..	..
78	120	Killed	5	..	..	..	..	++	..	..	..
79	120	Killed	2	..	..	..	..	++	..	..	..
20	120	Killed	5	..	..	..	..	++	..	..	..
21	120	Killed	6	..	..	..	..	++	..	..	..
22	120	Killed	4	..	..	..	..	++	..	..	..
23	120	Killed	2	..	..	..	..	++	..	..	..
24	120	Killed	4	..	..	..	..	++	..	..	..
25	120	Killed	3	..	..	..	..	++	..	..	..
26	120	Killed	0	..	..	..	..	++	..	..	..

Symbols: +, slight reaction; ++, moderate reaction; +++, advanced reaction; T, tubercle formation.

TABLE 7.—Influence of Inhaled Commercial Hydrous Calcium Silicate Dust on the Course of Experimentally Induced Tuberculosis in Guinea Pigs
Simultaneous Phase: Animals Received Their Tuberculous Infection and Started Their Period of Dust Exposure Simultaneously

Guinea Pig, No.	Exposure to Dust, Days	Pate	Pulmonary Lesions				Dissemination			
			Arrested Tubercles, No.	Spreading Tubercles	Cavitation	Pleuritis	Pulmonary Lymph Nodes		Liver	Spleen
							Enlargement	Tuberculous		
1	60	Died	2	..	..	+	++	..	..	..
2	60	Killed	0	+	..	..	+	+	..	..
3	60	Died	10	+	..	..	+	+	..	..
4	111	Died	2	++	..	..	+	..	N+	..
5	120	Killed	6	..	..	..	+	..	..	..
6	120	Killed	6	..	..	..	+	+	..	..
7	135	Died	..	+++	..	++	++	++	N+	N+++
8	160	Died	..	++	++	..	+	+	..	..
9	176	Died	3	..	..	+++	++	..	..	..
10	180	Killed	..	..	..	++	++	+	..	..
11	180	Killed	7	..	..	+	++	..	..	..
12	185	Died	1	..	..	+++	..	..	..	..
13	204	Died	2	..	..	+++	++	..	..	..
14	320	Died	..	..	..	++	..	..	..	..
15	240	Killed	7	+	..	..	++	+	..	..
16	240	Killed	6	+	..	..	++	+	..	..
17	245	Died	..	+++	..	..	+	+	T++	T+++
18	265	Killed	..	+++	..	..	+	+	T+	T+++
19	265	Killed	9	..	..	..	+++	++	..	..
20	415	Died	..	..	..	..	++	+	..	..
21	420	Died	..	..	..	+++	..	..	..	..
22	420	Killed	8	+++	..	+++	..	..	..	..
23	450	Killed	6	..	..	+++	+	+	..	..
24	517	Died	..	..	..	++	+	+	..	..
25	560	Died	..	++	..	+++	++	..	..	..
26	580	Died	..	++	..	..	+	+	..	..
27	660	Died	2	..	..	++	++	..	..	..
28	720	Killed	2	..	..	..	++	..	..	..
29	720	Killed	6	..	..	++	++	..	..	..
30	720	Killed	..	++	..	..	++	+	..	..

Symbols: +, slight reaction; ++, moderate reaction; +++, marked reaction; P, fibrils; N, necrosis; T, tuberculosis.

When conducted a second time, 30 guinea pigs, instead of 25, were used in this simultaneous infection experiment. The animals were killed in pairs for study at 2, 4, 6, 8, 12, 15, and 24 months after infection. Again the incidence of pneumonia was unusually high, six of the animals dying from that cause during the first 8 months of exposure and two more during the following 16 months. An additional three died of pericarditis, one of peritonitis, and two more of other causes (Table 5). This left a balance of 16 animals which were killed as planned.

The results are assembled in Table 7 which should be compared with the control study recorded in Table 6, in connection with which the same culture batch of tubercle

bacilli was used but the animals were not exposed to dust.

As may be seen in Table 5, the mortality rate among the control group was but 11.7% as against the high rate of 46.6% found in the animals which were caused to inhale dust. As these experiments were conducted simultaneously and in the same laboratory, except that the animals receiving dust exposure were even better protected from outside contacts, the different death rates may have some significance after all.

The numbers of tubercles which developed in the control series did not differ materially from those which were discovered in the animals exposed to dust after infection. In one control animal there was a marked spread which caused the death of the guinea

pig. Massive caseating lesions were found in the lungs, the liver, and the spleen. It was suspected that this animal may have been accidentally infected with virulent human tubercle bacilli. Consequently, bacilli were recovered, cultured, and subinoculated into the groins of four healthy guinea pigs. These animals developed local abortive lesions characteristic of the R_1 bacillus, and no systemic tuberculosis ensued. By this study it was fairly satisfactorily demonstrated that Guinea Pig 73 was unduly susceptible to tuberculosis.

In the guinea pigs which were caused to breathe the hydrous calcium silicate dust after infection, localized spreads of the tuberculosis occurred in 13 out of the 30 cases. In four of these the tuberculous process was quite advanced, and in four others it was moderately marked at the time of autopsy. It should be noted too that five of these spreads occurred during the second year of the experiment, i. e., long after the tubercles should have been arrested and healed. Attention should also be drawn to the presence of cavitation within two tuberculous pneumonic areas in Guinea Pig 25.

Pleural adhesions of a chronic tough variety were also quite common in the animals receiving the dust exposure. The pulmonary lymph nodes showed a greater prevalence of late active tuberculous foci, such lesions in the control animals having usually disappeared from the nodes before the end of the first year.

From this simultaneous phase experiment it would seem, therefore, that the hydrous calcium silicate had a mild to moderately adverse effect on the course of the R_1 tubercle infection.

REACTIVATION PHASE: COURSE OF TUBERCULOSIS
IN GUINEA PIGS WHICH WERE EXPOSED TO
HYDROUS CALCIUM SILICATE DUST
SEVERAL MONTHS AFTER INFECTION
WITH R_1 TUBERCLE BACILLI

Infected guinea pigs were placed in the dust chambers at intervals of two months, i. e., 10 at two months, 8 at four months, and 8 more at six months after infection. In order to follow the course of the tissue reac-

tion, a pair of animals of the first subgroup (two months in normal air) was killed after only 2 months of dust exposure, and, in addition, animals from all groups were killed in pairs after 4, 8, and 12 months of exposure to the dust. Examination of the tissue of the dusted animals failed to reveal a significant reactivation of the tuberculous disease by the inhaled dust (Table 8). Only five animals showed evidence of spreading pulmonary tuberculosis. In three the disease was minimal in extent, and in two others there was moderately extensive local spread. Caseation persisted in one animal to the end of a year, and slight to moderate foci of fibrosis could be discerned in a few animals, suggesting that not all the tubercles healed by resolution. Chronic pleuritis and pleural adhesions were present in 10 of the guinea pigs, which was considerably in excess of what is customarily found in a typical reaction to the introduction of R_1 tubercle bacilli. Dissemination of the tuberculous process to abdominal organs and to the pulmonary lymph nodes did not occur in any but exceptional cases. Guinea Pig 52 was probably one of these "sports." The term "sport" is given to a guinea pig in which the inhalation infection with the attenuated bacilli is not confined principally to the lungs and pulmonary lymph nodes but extends also to other organs and produces in them tuberculous changes of sufficient extent to be recognized macroscopically. Since "sports" represent a departure from the normal pattern of tissue reaction to attenuated tubercle bacilli, whether the infection is combined with dust exposure or not, such animals must be excluded in assaying the effect of an inhaled dust upon a tuberculous infection. It is believed that "sports" are animals whose native resistance to the attenuated R_1 organism is unusually low. Support for this belief is given by experience with quartz dust, a definitely hazardous material which reactivates an inhalation infection produced by attenuated R_1 bacilli but ordinarily is not associated with tuberculous extension to organs other than the lungs and pulmonary lymph nodes.

TABLE 8.—Influence of Inhaled Commercial Hydrous Calcium Silicate Dust on the Course of Experimentally Induced Tuberculosis in Guinea Pigs

Reactivation Phase: Animals, After Receiving Their Tuberculous Infection Were Allowed to Live in a Normal Environment for a Period of Two to Six Months Before They Were Exposed to Dust

Guinea Pig, No.	Exposure to Dust, Days	Fate	Pulmonary Lesions				Dissemination				
			Arrested Tubercles, No.	Spread- ing Tuber- culoids	Cavita- tion	Fibroids	Pleuritis	Pulmonary Lymph Nodes		Liver	Spleen
								Enlarge- ment	Tuber- culoids		
Exposure to Dust Was Started Two Months After Infection											
47	0	Died	5	+	+			+	+	T+	T+
48	11	Died	..	..	..	..	..	+	..	..	..
49	40	Died	2	..	..	..	+	+	..	..	..
50	80	Killed	5	..	..	..	..	++	+	..	..
51	80	Killed	8	..	..	..	..	++	+	..	..
52	120	Killed	3	..	..	..	..	+	+	..	..
53	120	Killed	4	..	..	..	+	+	+	..	..
54	240	Killed	7	..	..	..	..	++	+	..	..
55	240	Killed	2	..	..	..	+++	+	+	..	..
56	240	Killed	6	..	..	..	..	++	..	..	..
57	240	Killed	19	++	..	+	..	++	+	..	..
58	240	Killed	9	++	..	++	..	++	+	..	..
Exposure to Dust Was Started Four Months After Infection											
45	120	Killed	2	..	..	..	++	++	+	..	..
46	120	Killed	2	..	..	..	..	++	+	..	..
47	240	Killed	2	..	..	..	..	++	..	..	..
48	240	Killed	6	..	..	..	+++	++	+	..	..
49	240	Killed	7	..	..	..	..	++	+	..	..
50	240	Killed	2	..	..	..	..	++	..	..	..
Exposure to Dust Was Started Six Months After Infection											
49	117	Died	5	..	..	..	++	+	..	..	..
50	120	Killed	5	+	..	+	++	++	+	..	..
51	120	Killed	7	+	..	+	..	++	+	..	T+++
52	240	Killed	1	..	..	..	+++	++	+	..	..
53	240	Killed	9	..	..	..	..	++	..	..	..
54	240	Killed	..	..	..	..	+	++	..	..	..
55	240	Killed	5	..	+	++	..	++	..	..	..

Symbols: +, slight; ++, moderate; +++, advanced; T, tuberculosis.

PREDISPOSITION PHASE: REACTION IN GUINEA PIGS INFECTED WITH TUBERCLE BACILLI THREE MONTHS AFTER THEIR EXPOSURE TO DUST WAS STARTED

An experiment of this type is a severe test, because a dust that is only very slightly toxic may produce tissue changes which, though minor in character, may be sufficient to alter profoundly the development of a fresh tuberculous infection. In this experiment, which was designed to study the effect of the dust accumulated in the lung upon a newly developing tuberculous disease, 30 guinea pigs were exposed to the dust for three months and then were infected with attenuated tubercle bacilli. The dust exposure was immediately resumed and carried on for another 21 months.

The over-all death rate in this series of animals was relatively low (Table 5). It may

be of some significance that the majority of the eight animals that died from pneumonia did so during the latter half of the dusting phase. It is also significant perhaps that local and diffuse spreads of the tuberculous process had occurred most commonly in these animals prior to their terminal fatal illness.

The prevalence of such spreads in this series of guinea pigs does indeed appear to be significant (Table 9). Six animals showed marked local or diffuse extension of the disease, and in seven more this spread was of moderate severity. In an additional 9 cases there was slight spread of the process, so that a total of 22 animals reacted unfavorably. Cavitation occurred in 2 instances, and pleural extension in 10 of the 30 guinea pigs. One animal died from a pneumonic tuberculous process.

EFFECT OF INHALED HYDROUS CALCIUM SILICATE

TABLE 9.—Influence of Inhaled Commercial Hydrous Calcium Silicate Dust on the Course of Experimentally Induced Tuberculosis in Guinea Pigs

Predisposition Phase: Animals, After Being Exposed to the Dust for Three Months, Were Infected with Tubercle Bacilli of the R₁ Strain and Then Were Immediately Returned to the Dust Room Where Their Dust Exposure Was Continued Until Death

Guinea Pig, No.	Further Exposure to Dust After Infection, Days	Fate	Pulmonary Lesions				Dissemination			
			Arrested Tubercles, No.	Spreading Tuberculosis	Cavitation	Pleuritis	Pulmonary Lymph Nodes		Liver	Spleen
							Enlargement	Tuberculosis		
207	0	Killed	..	..	..	..	..	..	..	..
8	0	Killed	..	..	..	..	..	..	..	..
9	0	Killed	..	..	..	..	..	..	..	..
10	0	Killed	..	..	..	..	..	..	..	..
21	0	Killed	..	..	..	..	..	..	..	..
91	30	Died	..	..	..	..	++	+	..	..
92	60	Killed	17	+	..	..	..	..	..	..
93	60	Killed	21	+	..	..	++	+	..	..
94	120	Killed	16	+	..	..	++	+	..	..
95	120	Killed	34	+	..	..	++	+	..	..
99	180	Killed	7	++	..	..	++	+	..	..
97	180	Killed	11	+	..	..	++	+	..	..
114	210	Died	6	+++	+++	++	+	..	..	..
205	230	Died	2	++	..	+++	+	..	..	..
112	240	Killed	6	..	..	..	+	+	..	..
113	240	Killed	20	+	..	..	++	+	..	..
58	300	Killed	2	++	..	++	++	+	..	..
206	300	Killed	5	++	..	++	++	+	..	++
115	345	Died	..	+++	..	++	+	..	..	..
99	365	Killed	2	++	..	..	+++	+	..	..
100	365	Killed	4	..	..	..	+++	+	..	..
119	405	Died	..	+++	++	+	+	+	..	..
117	420	Died	..	+++	..	+	++	+	..	..
103	450	Died	..	++	..	..	+	..	..	..
104	465	Died	..	+++	..	+	++	+	..	..
116	480	Killed	..	+++	..	..	+	+	..	..
120	480	Killed	..	++	..	++	+	+	..	..
107	520	Killed	4	+	..	..	+	..	..	..
102	530	Killed	5	+	..	..	++	+	..	..
118	530	Killed	2	+	..	++	+	+	..	..

Symbols: +, slight or incipient reaction; ++, moderate reaction; +++, marked reaction; T, tuberculosis.

It is of interest to note that the extension of the disease was almost entirely confined to the pulmonary tissues, tuberculous foci being detected in the spleen of one animal only. The reaction in the pulmonary lymph nodes was not of a significant nature or degree.

These findings indicate that a tuberculous infection which originates in guinea pigs several months after a prolonged exposure of the animals to dust of the hydrous calcium silicate product was initiated may be unfavorably influenced by the inhaled dust. A separate control experiment was set up, using 25 guinea pigs, as the predisposition-phase experiment was started at a later stage than the preceding studies so that a fresh R₁ culture had to be employed. The results ob-

tained were so similar to those given in Table 6 that the latter may suffice for the purpose of this paper.

ANALYSIS OF TISSUE OF EXPOSED ANIMALS

Chemical analysis of lung tissue of uninfected guinea pigs that had inhaled the hydrous calcium silicate dust for periods up to 36 months yielded the data reported in Table 10. It will be noted that as the period of exposure became longer the values for the tissue ash gradually increased, thus showing that mineral matter was accumulating in the lungs. There was a pronounced increase in the silica component up to about 30 months and then a slight decrease. This phenomenon is illusory, as it is due to the relatively rapid rate at which inorganic matter was deposited

in the lung at this stage when the tissue reaction suddenly blossomed forth into the full-blown disease process. Comparable results have been obtained in The Saranac Laboratory in inhalation experiments with other dusts.

The total amount of silica which accumulated in the lung was about a third of that which may be demonstrated in the pulmonary tissue of guinea pigs exposed to quartz dust for a comparable period.

COMMENT

The first point which may be considered is that the commercial hydrous calcium sili-

As the chrysotile dust is capable of provoking fibrosis in guinea pigs, it may also in the case of the present study have been the cause of the focal fibrogenic response, so that the hydrous calcium silicate component may have to be exonerated. It seems likely that the giant-cell reaction was largely an effect provoked by the latter component. Attention should be directed to the lack of obvious necrosis in these cells. In this respect the dust differs quite markedly from quartz dust and silica fume. Indeed, necrosis was seldom a feature in this experimentally induced disease even in the presence of tuberculosis. It is possible, therefore, that at-

TABLE 10.—Analysis of the Lungs of Guinea Pigs Exposed to Commercial Hydrous Calcium Silicate Dust

Period of Exposure, Mo.	Ash, Per Cent of Dried Lung	Mineral Components of Dried Lung			Mineral Components of Lung Ash		
		SiO ₂ , Per Cent	CaO, Per Cent	MgO, Per Cent	SiO ₂ , Per Cent	CaO, Per Cent	MgO, Per Cent
1	4.22	0.22	0.07	0.07	4.31	1.64	1.80
4	4.45	0.30	0.08	0.08	4.55	1.94	1.94
8	4.44	0.35	0.08	0.08	4.59	2.34	2.09
8	4.45	0.29	0.12	0.09	4.63	2.59	2.10
16	4.67	0.42	0.14	0.14	9.37	2.63	2.66
12	4.92	0.62	0.16	0.15	10.62	2.90	3.12
16	4.23	0.72	0.10	0.22	10.49	1.96	6.92
21	5.19	0.60	0.17	0.10	11.42	3.22	1.74
24	4.20	0.53	0.13	0.07	12.61	2.76	1.45
27	4.65	0.64	0.15	0.17	12.74	2.49	3.12
30	5.47	1.11	0.14	0.05	19.91	2.42	0.92
33	5.44	0.76	0.12	0.19	14.05	2.26	2.31
36	5.47	0.68	0.14	0.16	12.49	2.92	2.34

cate product, studied in the experiments just described, really provoked two underlying pathological processes ascribable, respectively, to the calcium silicate and to the chrysotile components. The terminal syndrome of peribronchiolar atelectasis, fibrosis, and adenomatoid change was, in fact, of the same kind as that which has been repeatedly produced in The Saranac Laboratory by means of inhaled asbestos dust. The lesion of experimental asbestosis has somewhat more fibrosis to it and shows less of a cellular reaction and the giant cells seen in the present case are less commonly observed. In character with the asbestos lesion is the absence, in the present experiments, of fibrosis of the pulmonary lymph nodes in which no asbestos bodies could be found either.

though the hydrous calcium silicate dust stimulated the proliferation or local accumulation of cells it did not kill these cells. This point is well illustrated in the case of the bronchial epithelium, which proliferated as part of the process of chronic bronchiolar inflammation but did not readily necrose or become desquamated as in animals exposed to quartz dust. In many of the worst seeming adenomatoid or cystic lesions, the bronchial epithelium even retained its ciliated epithelial surface.

The evolution of the adenomatoid reaction is clearly revealed to comprise cryptic distention of the bronchioles, secondary papillomatous ingrowths into these distended lumina, and peripheral epithelialization of atelectatic alveoli.

EFFECT OF INHALED HYDROUS CALCIUM SILICATE

Why the alveolar ducts and bronchioles should have dilated at an early phase in the rats was not clearly revealed. No proximal obstruction could be displayed which could account for the distention on mechanical principles. Possibly the cause may be related to the tendency to peribronchiolar atelectasis. Perhaps a neurogenic mechanism was at the root of it all. To be true, the larger cystic distentions were usually found within areas of chronic diffuse consolidation, and it is possible that in such instances the distention of the trapped air passages resulted mechanically from cicatricial contraction.

The origin of two types of emphysema which were discovered may have similar explanations. While that which developed in the guinea pigs was definitely compensatory to the foci of atelectasis and fibrosis which it surrounded and the emphysema found in the rats and hamsters was of the hypertrophic variety, both may have had a common origin in the damage to the bronchioles.

The mild to moderate tuberculogenic effect of the hydrous calcium silicate dust manifested itself in local or even diffuse spreads, delayed healing, and dissemination to other organs. It is not yet possible at this stage to attribute this phenomenon definitely to either the chrysotile or hydrous calcium silicate components. The fact that the tuberculous process did not persist in the pulmonary lymph nodes, whereas it was activated in the lungs, parallels the observation that only in the lungs were asbestos bodies found. It

must be presumed that the hydrous calcium silicate dust was transported from the lungs to the lymph nodes, to judge by macrophage accumulation at the latter sites, and it is probable that the dust was more densely concentrated in the lymph nodes than in the pulmonary tissues. This suggests that the stimulation to perpetuation and spread of the tuberculous process may have derived from the chrysotile fibers rather than from the hydrous calcium silicate. Such a conclusion naturally requires further confirmation through experimental investigation.

SUMMARY

Inhalation studies have been conducted using a commercial product composed of hydrous calcium silicate and chrysotile on normal guinea pigs, rats, and hamsters and on guinea pigs infected with tubercle bacilli of the R_1 strain.

The dust caused marked chronic bronchiolitis, with terminal peribronchiolar focal fibrosis, bronchiectasia, and epithelialization of atelectatic alveoli. The final lesions closely resembled those found in experimental asbestosis and included asbestos bodies.

The course of experimentally induced tuberculosis was mildly to moderately adversely affected by the prolonged inhalation of the dust.

It seems likely that the chrysotile component of the commercial product, rather than the hydrous calcium silicate, was the cause of the deleterious effects on the tissues of the experimental animals.

Relationship of Particle Count, Weight, Shape, and Size of Air-Borne Dusts

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In experimental studies at The Saranac Laboratory, animals are exposed to air-borne dust in rooms 8 by 8 by 8 ft. in dimension. A dusty atmosphere is created in the rooms with mechanical dust disseminators to simulate the environment that might exist in a mine or an industrial plant where the material under study is being handled, with the exception that concentrations in the dust rooms are usually maintained at a higher level. During the experiments numerous determinations of the concentration and particle-size distribution of the air-borne dust are made, and certain studies of the parent material also are carried on. From the determinations made on quartz dust and on several varieties of submicron amorphous silica dust, data have been compiled to show relationships between the count, weight, and size of the dust particles and to compare results obtained with certain sampling methods.

QUARTZ DUST

The quartz dust used in the experiments was a commercial product with a silica content greater than 99%. The material was finely pulverized, and 98%-99.5% of the air-borne particles seen at a magnification of 1000 times were smaller than 10μ and 88%-95% were smaller than 5μ in size.

PARTICLE SHAPE

When observed at a magnification of 1000 times, quartz particles that had been settled

on slides placed in the dust room have the appearance seen in Figure 1A. Here the small particles, 1μ to 2μ in size, seem to have a fairly regular outline. An electronmicrograph (Fig. 1B) of quartz particles from the same dust room reveals, however, that the small particles are really quite irregular in shape.

SIZE-FREQUENCY DISTRIBUTION

Measurements of the particle size of air-borne quartz dust were made on samples collected by means of the electrostatic precipitator and examined at 1000 $\times$ magnification, and from those measurements size-frequency graphs were constructed. Representative graphs, shown in Figure 2, indicate that the median particle size ranged from about 1.5μ to 2.0μ . A graph representing the particle-size distribution of the parent material is also shown (Fig. 2).

PARTICLE COUNT TO WEIGHT RATIO

Numerous samples of the atmospheric quartz dust in the dust room were collected simultaneously by means of the midjet impinger and the electrostatic precipitator. The dust concentration on a count basis was determined from the impinger samples and on a weight basis from the precipitator samples. From these findings the number of particles per milligram of dust was calculated. A summary of the results is given in Table 1. The values reported for the number of particles per milligram of the atmospheric quartz dust depend upon the optical system employed for counting the particles. When the standard light-field technique was used, the average count for the samples was about 100,000,000 particles per milligram, although values as high as 164,000,000 and as low as 61,000,000 were obtained. Eighty per cent of all of the

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PARTICLE COUNT, WEIGHT, SHAPE, AND SIZE



Fig. 1.—Quartz dust. A, settled dust; one division equals $1/2\mu$. B, air-borne dust; $\times 25,000$.

Room 4 QUARTZ DUST SIZE FREQUENCY

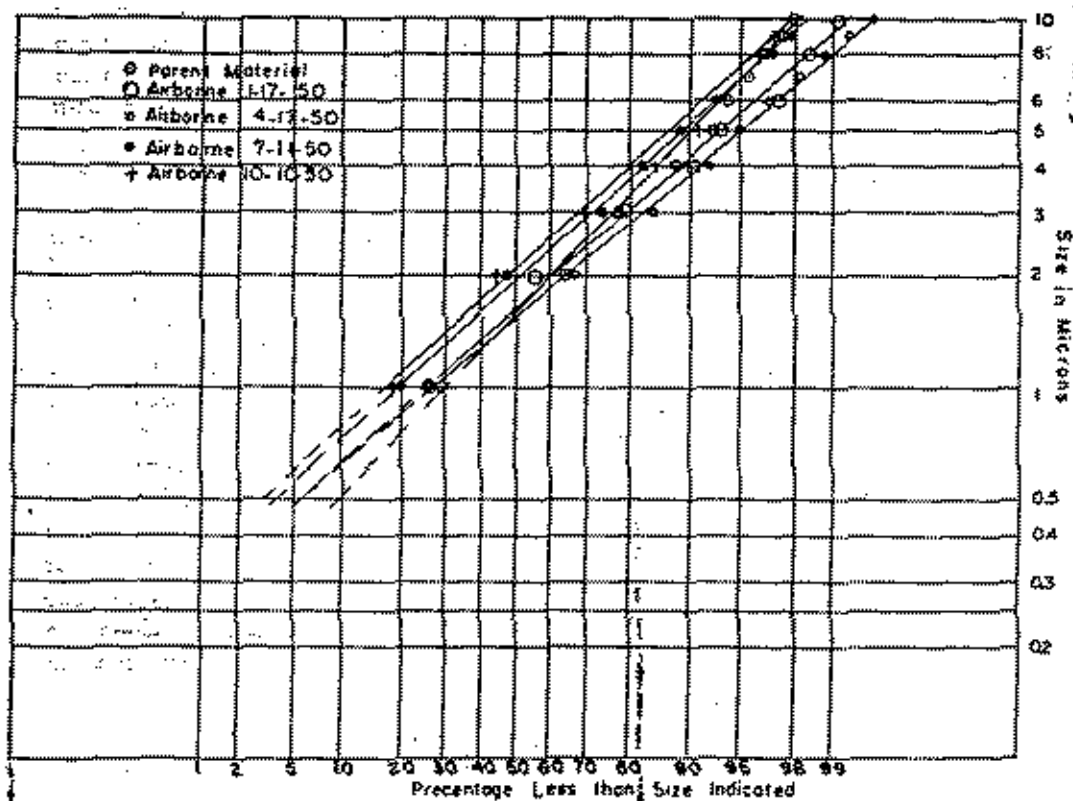


Fig. 2.—Size-frequency graph of quartz dust.

TABLE 1.—Number of Particles per Milligram and Average Particle Size of Air-Borne Quartz Dust

Dust Room	Year	Samples	Range of Values of No. of Particles per Mg.	No. of Particles per Mg.		Average Computed Particle Size		
				Light-Field Count, Millions	Dark-Field Count, Millions	Light-Field Count, μ	Dark-Field Count, μ	Size-Frequency Graph, μ
A	1949	1	Maximum	184	...	1.5	...	1.5
		1	Minimum	42	...	2.2	...	1.5
	1950	1	Typical	104	...	1.9	...	1.7
		12	Average	93	250	2.0	1.4	1.8
B	1951	1	Maximum	132	...	1.5	...	...
		1	Minimum	87	...	2.0	...	1.4
	1952	1	Typical	104	...	1.9	...	1.7
		10	Average	100	220	1.9	1.4	1.6
C	1953	1	Maximum	113	...	1.8	...	...
		1	Typical	94	...	2.0	...	1.9
	1954	1	Minimum	74	...	2.1	...	1.7
		9	Average	93	250	2.0	1.4	1.8
D	1954	1	Maximum	124	...	1.8	1.3	1.4
		1	Minimum	73	...	2.2	1.3	1.9
	1955	1	Typical	104	...	1.9	1.4	1.6
		10	Average	94	...	2.0	1.4	1.8
E	1954	1	Maximum	108	...	1.9	...	...
		1	Minimum	73	...	2.2	...	1.9
	1955	1	Average	94	225	2.0	1.4	1.9
		10	Average	90	...	2.0	...	...
F	1955	1	Maximum	160	...	...	...	...
		1	Minimum	102	...	...	...	...
	1956	1	Average	125	...	...	...	...
		1	Maximum	150	...	1.8	...	1.6
G	1955	1	Minimum	80	...	2.0	...	...
		10	Average	126	233	1.6	1.3	1.6
	1956	1	Maximum	127	...	1.8	...	...
		1	Minimum	83	...	2.0	...	1.4
H	1956	1	Typical	92	...	...	...	...
		5	Average	103	156	1.9	1.3	1.4
	1957	10	Average	114	...	...	...	...
		10	Average	92	207	1.9	1.4	1.4
I	1958	1	Maximum	135	...	...	...	1.9
		1	Minimum	83	...	2.0	...	2.0
	1959	12	Average	91	240	2.0	1.4	1.4
		1	Maximum	120	...	...	...	...
J	1959	1	Minimum	89	...	...	...	...
		12	Average	99	254	1.9	1.4	2.0
	1960	24	Average	90	229	1.9	1.4	...
		109	Average	101	213	1.9	1.4	...

values determined were within plus or minus twenty per cent of the average value. For an optical system yielding a semidark field, the average count was increased to about 270,000,000 particles per milligram, and in a series of tests with a condenser that produced a darker field, counts as high as four times the light-field counts were obtained. Even higher ratios of dark-field to light-field count, up to 34:1 for industrial dusts, have been reported by Hatch,¹ who showed that the ratio of dark-field to light-field count depends upon the percentage distribution of the particles in a sample above and below the size

corresponding to the limit of visibility in the light-field microscope. In the studies at The Saranac Laboratory the age of the dust cloud was brief, and the samples were collected within a few feet of the dust source. Thus the per cent of particles less than the limit of visibility of the light-field microscope was at a minimum. This condition is comparable to that found in a crushing plant or other industrial concern where dust is being continually created within an enclosed area.

For a number of years impinger samples to control dust concentrations in the experimental dust rooms of The Saranac Labora-

PARTICLE COUNT, WEIGHT, SHAPE, AND SIZE

tory were counted by both a light-field and a dark-field technique. A review of samples collected in the rooms in which quartz dust was dispersed disclosed that the ratio of dark-field count to light-field count had an average value of 2.7:1, with a maximum variation of about 20% above or below that value. Since the practice of making routine dark-field counts has recently been discontinued, only light-field counts are available for many samples. In compiling data for Table 1, therefore, the dark-field count for all samples was taken equal to 2.7 times the corresponding light-field count.

AVERAGE PARTICLE SIZE

The average size of the quartz particles, assuming them to be spherical in shape, can be calculated from the number of particles per milligram and the specific gravity. Values for the average size computed from the light-field count and from the dark-field count are listed in Table 1. In addition, the average size taken from size-frequency graphs (Fig. 2) is shown in the Table. The dimension obtained from the graph represents the size of the "average" particle on a count basis, 50% of the number of particles being larger and 50% being smaller than the "average" particle. The size calculated from both the light-field count and the dark-field count, however, is that of the particle having the average weight of all the particles. Nevertheless, in spite of these entirely different methods of estimating the average particle size, the values obtained for this particular quartz dust are of the same order of magnitude.

EFFECT OF ADDED SUBMICRON OR LARGE PARTICLES ON PARTICLE COUNT AND AVERAGE PARTICLE SIZE

If a series of 20 spherical particles are arranged in a size-frequency distribution similar to the distribution determined for the quartz dust in these studies, the series would be 1 μ , 1 μ , 1 μ , 1 μ , 1.5 μ , 1.5 μ , 1.5 μ , 1.5 μ , 2 μ , 2 μ , 2 μ , 2.5 μ , 2.5 μ , 3 μ , 3 μ , 4 μ , 5 μ , 6 μ , and 8 μ . By calculation⁷ the average size of the spherical particle in the series by count/weight

determination is 3.73 μ , the average (median) size by the count method is 2.0 μ , and the ratio of the first value to the second value is 1.86. If 380 particles of a size less than the limit of visibility of the light-field microscope are added to the 20 particles, the light-field count will not be changed, but the dark-field count will be raised from 20 to 400, and the ratio of the dark-field count to light-field count will be raised from 1:1 to 20:1. If for the purpose of calculation a size of 0.5 μ is assigned these 380 particles and their weight added to the original series of 20 particles, the average-size particle on a weight basis is increased only from 3.73 μ to 3.80 μ , the average-size particle by count remains 2.0 μ , and the ratio between the two values is 1.9. If 10 μ size particles are added progressively to the original series of 20 particles, the ratio of the average particle size by count/weight to the size of the average (median) particle by count increases to a maximum of about 2.8 and then decreases as the average particle size by count approaches the larger size. This ratio would be greatly increased by adding to the total weight of the series without significantly increasing the number of counted particles. This can be accomplished by the addition of a giant-size particle (30 μ -50 μ) to the original series or by the addition of a tremendous number of submicron particles. In practice a giant-size particle would not be air-borne very far from its source.

SUBMICRON SILICA DUST

The new amorphous silica products composed of particles submicron in size have become important commercial materials. Owing to the extremely small size of the particles and the low density of the bulk material, the collection and measurement of this submicron dust present real problems to the industrial hygiene engineer, and further study of such finely divided material is needed.

VARIATION IN PARTICLE SIZE

The typical appearance of submicron silica dust that had settled on a glass slide in a dust room is shown in Figure 3A. The particles

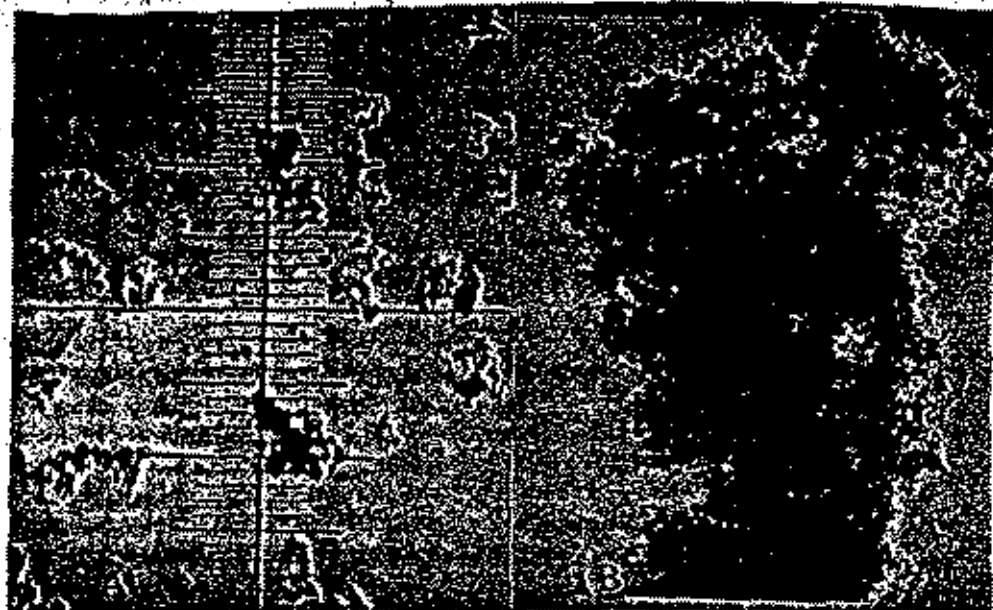


Fig. 3.—Silica dust. *A*, settled submicron amorphous dust; one division equals 12 μ . *B*, submicron dust; $\times 50,000$.

appear to range in size from about 1 μ to more than 10 μ , and seemingly the dust particles could be collected and counted in the accepted manner by the light-field technique. When the same material is examined with the electron microscope at 50,000 times magnification, it

is clear that the units seen (Fig. 3B) are not single particles but rather are aggregates composed of many extremely small particles. Much of the air-borne material is segregated in these clumps. In contrast electronmicrographs of other submicron silica dust may exhibit an abundance of small aggregates (Fig. 4). Since the particles are only a fraction of a micron in size and even the aggregates, in many cases, may be below the resolving power of the microscope employed in the standard light-field technique, the reliability of the usual dust-counting methods when applied to the submicron dust is immediately questioned.

Fig. 4.—Submicron silica dust; $\times 50,000$.



COMPARISON OF AGGREGATES AND PARTICLES

Data concerning the aggregates and individual particles of several varieties of submicron amorphous silica dust are given in Table 2. The values on the left refer to the aggregates, and those on the right to the particles. The first column lists values for the number of aggregates per milligram of air-borne dust, based on the assumption that all the dust is present as aggregates and that all the aggregates are revealed by the light-

PARTICLE COUNT BY LIGHT FIELD

Table 2. Relationship between particle count and weight of quartz dust aggregates. The relationship between particle count and weight of quartz dust aggregates. The relationship between particle count and weight of quartz dust aggregates.

Relationship of Aggregates					Relationship of Individual Particles		
No. of Aggregates per Mg. (Counted)	Average Size of Aggregates (microns)	Volume of Aggregates (cc)	Weight of Aggregates (mg)	Specific Gravity (Computed)	No. of Particles per Mg. (Computed)	Specific Gravity	No. of Particles per Mg. (Computed)
1000	0.01	0.0001	0.0001	2.2	1000	2.2	1000
100	0.01	0.0001	0.0001	2.2	100	2.2	100
10	0.01	0.0001	0.0001	2.2	10	2.2	10
1	0.01	0.0001	0.0001	2.2	1	2.2	1
1000	0.01	0.0001	0.0001	2.2	1000	2.2	1000
100	0.01	0.0001	0.0001	2.2	100	2.2	100
10	0.01	0.0001	0.0001	2.2	10	2.2	10
1	0.01	0.0001	0.0001	2.2	1	2.2	1
1000	0.01	0.0001	0.0001	2.2	1000	2.2	1000
100	0.01	0.0001	0.0001	2.2	100	2.2	100
10	0.01	0.0001	0.0001	2.2	10	2.2	10
1	0.01	0.0001	0.0001	2.2	1	2.2	1

field examination. The apparent density of the aggregates in Column 2, was taken equal to the apparent density of the unpacked bulk material. The average size of the aggregates was estimated from measurements of settling dust. Values for average size (Column 3) were computed from the number of aggregates (Column 1) and their apparent density (Column 2) and values in Column 4 were obtained from size-frequency graphs, similar to Figure 2, of dust aggregates that had settled on glass slides placed in the experimental dust room. Using the observed average size of aggregate (Column 4), corresponding values for the number of aggregates per milligram (Column 5) were computed. The large difference between the number of aggregates per milligram obtained by count (Column 1) and by computation (Column 5), the large difference between the size of the average particle obtained by the count method and by the count/weight method, and the variation in the values for the number of aggregates per milligram obtained by count may arise from several sources. Possible errors were the assumption that the density of the aggregates was the same as that of the unpacked bulk material and the assumption that substantially all the dust was in the form of aggregates visible by light-field examination. The ratio of the size of average aggregate obtained by the count method and the size of average aggregate obtained by the count/weight

method is much greater than similar ratios observed for quartz dust. It has been shown in a preceding section that the presence of a few giant-size aggregates or of a very great number of uncounted submicron particles in the sample will affect the ratio in this manner. It should be noted, however, that for the sample of submicron dust studied very few aggregates larger than 10 μ were reported in the standard counting procedure or in the size-frequency plots.

The size of the individual particles of sub-microscopic silica determined by measurement of electronmicrographs is given in Column 6 of Table 2. The actual density of those particles is assumed to be 2.2, the same as that of vitreous silica. Calculation of the number of individual particles per milligram of dust yielded the tremendously high values in the last column of Table 2.

Thus it becomes clear that when dealing with submicron silica dust the material cannot be accurately identified and counted by the standard light-field technique. A study of electronmicrographs of dust samples would yield information about the size and relative numbers of individual particles and aggregates, but application of the technique is somewhat restricted.

SUMMARY

Values are given for the relationship between the particle count and weight of quartz

dust obtained in experimental studies with the dust. Dimensions representing the average particle size of the quartz dust on a count basis and on a weight basis, although different, are of the same order of magnitude.

Values were determined for the relationship between the particle count and weight of submicron amorphous silica dust by methods similar to those used for the quartz study. Values representing the average size of particle and of aggregate on a count basis and on a weight basis were determined for the dust.

Large differences in these values indicate the unsuitability of the midget impinger and light-field counting technique for the counting and measuring of the submicron silica dust.

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Personal Impressions of Dr. E. L. Trudeau and Dr. E. R. Baldwin

HUGH M. KINGHORN, M.D., Saranac Lake, N. Y.

I met Dr. Edward Livingston Trudeau for the first time early in 1895. I had come to Saranac Lake and to the Adirondack Cottage Sanatorium, as it was then called, to be under his medical care for a pulmonary disease which I contracted in the Montreal General Hospital. At this time he was at the peak of his medical practice. His pulmonary disease seemed to be well under control, and he not only practiced medicine but also worked in his laboratory—the famous Saranac Laboratory.

Dr. Trudeau was born in New York on Oct. 5, 1848. His father, Dr. James Trudeau, was a member of a well-known New Orleans family, and his mother's father, Dr. François Éloi Berger, was a French physician whose ancestors had been physicians for many generations. Dr. Trudeau's mother, Cécile Berger, was Dr. Berger's only daughter. Dr. Trudeau had a brother and a sister, both older than himself. His father and mother separated shortly after his birth, and when Dr. Trudeau was 3 years old, he went abroad with his mother, brother, and grandparents. While they were abroad, his mother obtained a divorce and married a French officer—Capt. F. E. Chiffart. She and her husband lived in Fontainebleau until her death in 1900.

Dr. Trudeau remembered little about his father. During the Civil War his father was an officer in the Southern army. He was wounded and went back to New Orleans,

where he partly recovered and practiced his profession for a few years before his death. Before the war he married Miss Marie Bringier, who belonged to a well-known New Orleans family.

My first contact with Dr. Edward R. Baldwin and The Saranac Laboratory was in April, 1895. At that time I was an intern in the Montreal General Hospital, and, as I had been appointed for a second year as intern, I visited Saranac Lake before beginning my second year in hospital. Dr. Trudeau was away, and when I visited The Saranac Laboratory, Dr. Baldwin was the sole worker. He was there working on the albumoses of the tubercle bacillus, thinking that if he could immunize animals with the albumoses a cure might result. Three years later I became a regular worker in the laboratory.

In December, 1892, a slender and pale young man rang Dr. Trudeau's doorbell one morning and told him that he was a physician, that he had contracted tuberculosis, and that he wanted to go to the sanatorium. He said that his name was Edward R. Baldwin and that he was from New Haven, Conn. A great friendship developed between Dr. Trudeau and Dr. Baldwin, and some time later Dr. Baldwin took over the work of The Saranac Laboratory.

About the year 1898 I started to work in The Saranac Laboratory. At that time (1898), Dr. Trudeau and Dr. Baldwin were testing the effect of Robert Koch's old tuberculin on the rabbit's eye. The plan of the experiment was to inject living tubercle bacilli into the rabbit's eye and then, when well-marked tuberculosis had developed, to

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Fig. 1.—Left, Edward Livingston Trudeau, founder of the Adirondack Cottage Sanatorium (later Trudeau Sanatorium) and of The Saranac Laboratory. Right, Edward R. Baldwin, successor to Dr. E. L. Trudeau as Director of the Trudeau Sanatorium and as Director of The Saranac Laboratory.

Fig. 2.—Left, "Little Red," the first of the Adirondack Sanatorium cottages built by Dr. E. L. Trudeau to receive tuberculous patients. Right, "The Phoenix"—Dr. E. L. Trudeau working in a corner of The Saranac Laboratory, which arose from the ashes of his private laboratory through the generosity of Mr. George C. Cooper.



start treating the rabbit with Koch's old tuberculin. I gave the injections. The tuberculin solution was injected subcutaneously into the abdomen, and a dose of sufficient strength was given to produce a well-marked local reaction in the diseased eye. The reaction consisted of an intense redness of the eye. On the eighth or ninth day after the tuberculin injection, all redness had disappeared from the eye and the area of disease seemed to be less. The same dose of tuberculin, or a dose slightly stronger, was then given, and there was again marked redness of the diseased eye. This dose was again given eight or nine days later, and this was repeated until no reaction appeared. The dose of tuberculin was then increased. Constant clearing of the disease occurred, until finally the eye seemed to be free of disease.

Toward the end of the First World War, a trained nurse was referred to me, suffering from tuberculosis of the eye, which she had contracted in France. I told her of our experience with tuberculosis of the rabbit's eye, and she consented to take treatment for the disease in her eye. I followed the same procedure as we had used for the rabbit, and the disease in the nurse's eye disappeared. I don't think that I would have the courage to treat another human eye in the same way, that is to produce violent local reactions. A short time later I treated a man with tuberculosis of the eye with Koch's old tuberculin, but I used the slow method, that is, I increased the doses slowly and avoided local reactions. This patient also recovered from his eye tuberculosis.

Early in the 20th century—1901—Robert Koch produced his last and best vaccine for tuberculosis and called it "bacillary emulsion." This vaccine was prepared from a culture of tubercle bacilli. The bacilli were dried and ground up into a fine powder in an agate mill. The germs were held in suspension in 0.5% phenol and 0.86% saline solution. The powder was not sterilized by heat, as Koch assumed that the constant grinding would kill all germs.

We followed Koch's directions in The Saranac Laboratory and did not kill the vaccine by heat. When, however, we injected the vaccine into guinea pigs, we found that well-marked tuberculosis was seen as far as the spleen. After this we always sterilized our bacillary emulsion by heat and then inoculated our vaccine into guinea pigs so as to be sure that all germs were killed.

In order to find out at what intervals he should give the doses of bacillary emulsion, Robert Koch used the agglutination test; he found that agglutination was at its height from the 7th to the 14th day following a dose of vaccine. This is important, and it confirmed our work on the tuberculous eye of the rabbit, when we used Koch's old tuberculin, namely, that the local reaction had ceased by the eighth day.

In our work in The Saranac Laboratory, we followed Koch's directions but could not convince ourselves that the agglutination test was sufficiently accurate or practical to use routinely after a dose of bacillary emulsion.

About this time we began our work with the tuberculo-opsonic test for tuberculosis, as used by Sir Almroth Wright, of London. This test was used by Dr. Wright to control the giving of vaccines, including the vaccine for tuberculosis. We found it to be a very difficult and time-consuming test and not reliable. The margin of error was great, and with 100 as a fixed point the test might be 14 below or 14 above 100. Other observers found this also to be true. Wright found that after a dose of a vaccine there is always a negative phase which lasts about three days and that there then sets in a positive phase. The negative phase represents a period of depression, and no dose should be given while it lasts. He found that the opsonic index went constantly higher after the dose of the vaccine and that the time to give the next dose was on the fourth day, that is, at the peak of the positive phase.

In The Saranac Laboratory the opsonic test was found to be so unreliable that it was not used as a practical test to govern the giving of tuberculin injections. It was,

however, systematically studied, and a large number of tests were made, and the results were given at the Sixth International Congress on Tuberculosis, which was held in Washington, D. C., in September, 1908.

At this important meeting almost all the leading scientists of the world interested in tuberculosis were present. Dr. Koch was the honored guest. An open meeting was held to discuss the tuberculo-opsonic test. Five laboratories took part in the discussion, and The Saranac Laboratory was one of the five so honored. Dr. Koch was the guest of honor at the meeting and was seated on the platform; he was only a few yards from us when we gave our results. The experience to be so near this distinguished man and to be able to mention some of his results to illustrate some of our conclusions was thrilling. Our remarks were directed to him and not to the large assembly. We mentioned the negative and positive phases which Dr. Wright found after a dose of vaccine, and then we mentioned the work of Dr. Koch with his agglutination test as a control to giving his bacillary emulsion.

Dr. William H. Welch, of the Johns Hopkins Medical School, was chairman; the following day he stopped us to tell us that Dr. Koch had said to him, "Those men from Saranac Lake speak *Thatschen* (facts)." These were only some of the tests which we were doing at this time in The Saranac Laboratory.

Dr. Trudeau's last published paper appeared in the *British Journal of Tuberculosis and Diseases of the Chest* (1914) and was entitled "Relative Immunity in Tuberculosis and the Use of Tuberculin." The following year he died—1915. He showed by experiment that the living tubercle bacillus affords much better protection than the dead bacillus. He regarded this relative protection as not a "real immunity" but an increased resistance to superinfection. The relative immunity produced by small inoculations of attenuated bacilli in guinea pigs is an increased resistance but is not a real immunity. What Dr. Trudeau meant by real immunity is an immunity such as occurs in smallpox and in other infectious diseases, that is, an immunity which is shown by the fact that, after the disease had been entirely cured, any amount of exposure to the infection will not reproduce it. Such an immunity is not attainable experimentally in tuberculosis.

Dr. Trudeau's faith in the possibilities of chemotherapy for tuberculosis was based on what Ehrlich had demonstrated for syphilis. He saw no reason why what had been accomplished for syphilis should not be attained in tuberculosis.

I feel greatly honored to be able to tell you something about the work of these two outstanding physicians, and I thank you most heartily for the privilege of speaking to this splendid association.

Memories of Leroy Upson Gardner

PAUL S. RICHARDS, M.D., F.A.C.S., Salt Lake City

When the opportunity to prepare a memorial address on Leroy Upson Gardner was presented to me, my mind was flooded with thoughts making the approach to this subject difficult. Whether to admire more the man or the things he accomplished, I never could decide for myself.

I have read a great many of the tributes that have been paid to Roy and I would like to consider him from the closeness with which we were associated. Our relationship began at the Harvard Medical School in 1916. It was carried through with a warmth of friendship that I have known with very few men during my lifetime.

Contentment permeated his very being. No mechanical or fatalistic philosophy could ever be detected in him. He was the essence of the old saying that "knowledge is power and wisdom is liberty." He was dominated by only one code and that was to search out the truth. He was perfectly balanced within his knowledge, his mechanisms, and his purposes in life. His mind was stabilized by a warm religious faith. His scientific pursuits were kept in accord with his youthful training and guidance, and he always had a finely proportioned balance in his general perspective of things about him. Life never became too complex, for he held it calmly within his grasp, unifying all its ramifications into a pattern of perfect significance. None of the modern concepts offered him any entanglements. He lived in the various circles of life with calmness. The circle of the universe was harmonized into his pattern of living. His clutch never slipped; his transmission was always shifted with smoothness—no grating, grinding, or growling.

The world of the sky, the stars, the trees, and the plants held him in his first enchantment. The social world, or the world of people of all types, was magnetically drawn to him. The world of communion, which in its osmosis-like state of establishing equilibrium interpenetrated the physical and social realms, established a fine enduring relationship to temper his life. (There are very few who really knew Roy in this atmosphere.) And last, there was the world of his own creation—the environment of his work and his daily activities. I feel most fortunate that I knew Roy in all these phases of his life. And it brought to me a warmth and closeness of friendship which is even closer than kinship. Going along with him in his daily activities, getting acquainted with the sincerity of his heart and the magnificent work which he was doing and the great broad potential of the aspect of its application brought me close to a man that I wanted to know and really finally knew.

In one of our early meetings at Saranac Lake, one of the speakers in self-defense made the following statement, "When you take stuff from one writer, it is called plagiarism; when you take it from many writers, it is called research." If I may approach the ideas of others or possibly unconsciously quote them, I trust that you will keep me in the proper category.

Knowing how to live is the greatest of all arts. With all of Roy's scientific accomplishments, with his studying of nature and learning the pattern of the universe, he really acquired an art of living that could be called a way of life for anyone to follow. That which may have been considered a calamity by some in his life was really the beginning of his great success, and with it all he developed a supreme type of judgment, a

determination, a source of energy unequalled, a mirth, and a sense of fine humor and cheer. He acquired those qualities that go to make up the strong, happy person and became the type of man we all admire and whom we are glad to be with because of his fine, wholesome, beckoning stimulation—the kind of person who leads us on to greater heights and attainments. He had the qualities that lead and make up leadership—the qualities that have made the world a much finer place



Fig. 1.—Leroy Upson Gardner, M.D., as a young research worker on pulmonary tuberculosis and pneumoconiosis.

to live in. He had a fine balance between mind, emotion, and will. He was systematically developed—a man with a keen intellect, a great heart, and a conscience that kept him constantly at his duty. His ability of judgment, clear thinking, and determination seemed to stabilize him with an acuity that brought results in practically all his outlined efforts. His faculty for accurate observation was most outstanding, and his conclusions were always wisely drawn. He proceeded from a strong foundation of facts, because

he held to the truth which was the guiding inspiration of his scientific background.

It has been wisely said:

Science is only one small approach to life: it is one approach to truth, but in its own domain it is supreme; it can brook no rivals, it knows no mercy, it is utterly unhuman; it knows no friends, and it knows no enemies. It has no heart, no emotion, and no passion except one; that is, the passion to think straight and the passion never to be fooled and not to fool anyone else. There is nothing mysterious about it all. Indeed, its whole passion is to remove mystery, to replace mystery with knowledge. When the scientific attitude of thinking lays hold of a man's life, it never lets go. From that hour on he is a changed man. He may be going forward slowly, but he is always going forward. He is always journeying toward greater truths, deeper insights, and a sounder philosophy—a philosophy based on things as they are, as critical intelligence has been able to discover them, instead of a philosophy drawn from the false world which the wishful thinking of mankind is forever erecting in order to avoid or to escape reality.

Roy's scientific background never made him hard or harsh. It was only a cornerstone in helping him to lay one of the most beautiful philosophies of life I have ever known. He merged his scientific background into his philosophies of life, so that today we can consider him one of the greatest benefactors to humanity in the field of industrial medicine.

During his period of disability he learned the philosophy of his great predecessor, Edward Livingston Trudeau, who taught his patients

to cease to rebel and struggle and learn to be content with part of a loaf when one cannot have a whole loaf. This is a hard lesson to learn, but it is a good philosophy for the tuberculous individual, and to his astonishment he often finds what he considers the half loaf, acquiesced in, proves most satisfying.

When Dr. Trudeau stated this, he set forth principles which have carried on down through all the great men who have followed him here at Saranac. His teaching is a good one for all people to know. Trudeau told others only what he had learned himself in the school of experience. This philosophy

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made Roy's mind superior to the state of his body, and he turned himself into one of the most notable creative workers of his day and one who contributed much in correcting the environmental hazards of the industrial worker. He had the ability of dealing with intricate problems on the level of the cell, molecule, or atom and interpreting these into the reaction of the whole organism in relationship to the environment. Roy had the conviction that we can overcome industrial disease just as completely as we have overcome diphtheria and typhoid and many other ravaging conditions. He was outstanding in removing the hysterical aspects that have arisen in industrial disease, and he was a great factor in bringing management and labor to a common viewpoint in making safe the working conditions of the laborer and establishing laws that can be executed with justice. Certainly, to my way of thinking, he has been the greatest factor in bringing us to an equanimity of thought and purpose. This has fully demonstrated his humanitarian tendencies which were justly activated and driven by his scientific investigations. From all his observations in nature and his scientific research he developed a philosophy of life which was as consistent and pleasant as nature herself. In all his investigations he established an outstanding consistency.

His way of life shows a plan of tranquility, pleasantness which exists in all living things, and, because of these things which he acquired unto himself, his life had such a leavening effect that everyone he encountered has felt or has been better for having had his association. This all made him an outstanding teacher—a teacher among all classes, noted for his simplicity and clarity of presentation and most convincing in all his conclusions. Roy was not only one of the greatest scientific and research investigators of his period; he was one of the greatest of all humanitarians to ever enter the immortal annals of the medical profession. To actually have known him is to understand the truthfulness of that statement.

We all are composites of the people with whom we associate. We all have the self-same nature of the living things in this world to observe. The melodies in all creation play to all of us the same tune, and the one great outstanding difference in life is how each one of us responds to this. Roy seemed to have the outstanding ability of absorbing the best of everything and incorporating it into his way of living. It was because of these abilities that he always held my admiration. For that reason he has been one of the greatest contributing forces that has ever entered into my life. It has helped me in establishing those things that I consider to be a justifiable way of living.

While we were close to the same age, I admired him from the time I first saw him in the Pathology Laboratories that face out onto Longwood Avenue in Boston. At that time there were a number of large, two-story homes on the opposite side of the street. Several of us were standing by one of the large windows gazing out when Roy approached, and without saying a word he stood by the window and seemed to be absorbed in something. My eye caught him. I looked out, and across the street there was a large Newfoundland dog looking up and down the avenue, with his paws on top of the gate. When the dog seemed to feel that the highway was sufficiently clear, he stepped forward, pushed the gate, then backed up a step or two. After repeating this act various times, the gate finally swung open far enough for the dog to walk out on the sidewalk. I had seen this performance many times, but apparently it was Roy's first time of seeing the dog go through his act. He stood there with his shoulder against the window frame, clenched his pipe in his teeth, and with a bare smile on his face, I heard him say: "That is my idea of love's labors lost." From that moment on I decided that there was a man of keen observation and keen sense of humor and that I must get more thoroughly acquainted with him. That is when our friendship really began.

Roy gave us a great deal of assistance in the State of Utah relating to our occupational

disease laws. He went there on several occasions to testify before our Industrial Commission on problems pertaining to silicosis and its complications. The entire State of Utah and the medical profession feel indebted to Roy for the educational program which he brought to our Industrial Commission, with the type of laws which we established and the simplicity with which these laws have operated and are still operating. All the industries and labor organizations of our state still remember the great service he rendered to us.

The Chairman of our Industrial Commission and Utah Labor Relations Board, Otto A. Wiesley, in a letter addressed to me, had the following to say:



Fig. 2.—Leroy Upson Gardner, M.D., in the role of industrial hygienist on tour of mines in Utah.

You will recall that I met Roy Gardner on several occasions, and each revealed a different facet of his splendid character. He participated in the medical symposium which you conducted in Salt Lake City in 1943. Again I saw him in the witness chair during the Frank hearings, which was our first all-out formal hearing of a silicosis case. My final contact with him was at your summer cottage in Cottonwood Canyon. Although we discussed medical problems, the gathering was primarily social.

Brief though my acquaintance was with him, nevertheless I arrived at some unalterable conclusions—all highly favorable.

Roy was always truthful, a man of great moral courage, and as a medical witness he met my standards in every respect. He was a scientist always. He did not testify for or against anyone. In the Frank case he did a remarkable job. He deftly tied the testimony of a medical doctor, highly qualified, into his findings and conclusions so that

no conflict was apparent. In fact, he laid a foundation for medical testimony which we have always followed.

As a participant in the symposium, he exhibited the same traits. He was fearless, truthful, factual and gave the impression that he was a master of his subject.

Socially, he impressed me greatly. With his ever-present pipe, his kindly smile, his pleasing voice, and his obvious love for humanity, he appealed to me as a fitting occupant for a "House Beside the Road"—the kind of man a wayfarer would love to meet on a long journey.

Once you met him he became a beacon light along the highway of life—one of those rare individuals whose living image finds a resting place on the walls of one's memory's picture gallery. And then, when the highway of life becomes steep and tortuous and the storms break, what a blessing it is to take that living image from the walls of memory's picture gallery and find new hope, new courage to survive the storms!

Such a man was Roy Upson Gardner.

One of our prominent industrialists had the following to say about Roy:

He was a scientist but, above all, a humanitarian—asking little for himself but giving much. He had a great appreciation of beauty and was deeply impressed by nature's lavishness. He was especially impressed by the rugged grandeur of the western mountains. His work made him known to the mining industry throughout the world. He spoke easily, slowly, deliberately. He thought logically and expressed himself convincingly. His logic prevailed. His work will live as long as men seek the truth.

When I started to practice medicine, I became very closely associated with the mining industry in Utah. Many of my patients were miners of long standing. I soon recognized what poor surgical risks they were. I became interested in silicosis and sent some of the first patients to Saranac in 1923. Again, my contacts with Roy Gardner became close, and I followed through all the investigative work performed there. It was these contacts and the association with Homer Sampson and later Donald Cummings and numerous others that made Saranac Lake such a rendezvous for us seekers of knowledge to come and be fed. With this as a background, Roy made numerous visits into our locality, and it was upon these visits that we had ample time to become extremely well acquainted. He learned to

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love the West. He loved our mountains with the self-same passion that he loved the mountains here. All the letters that I received from him were in his handwriting, and they always started out: "The Adirondacks salute the Wasatches!"

Roy loved to visit at the home of my parents, who were among the original pioneers that came into the State of Utah. From them he gleaned much of the western history, of the privations and hardships they went through. On all his visits to Utah there were two things that he always requested—to visit our old homestead and for me to take him into the mountains. On numerous trips we exchanged our philosophies, and we talked over our most inward thoughts, our views of life, the purposes of living, the necessities of courage, faith, and confidence, the types of qualities that make men best fitted to meet their responsibilities and duties. Before taking him into the Uintas, the only part of the Wasatch Range that runs due east and west, I read him a piece that I have memorized over the years. This piece is entitled "God Meets Me in the Mountains."

God meets me in the mountains when

I climb alone and high

above the wrangling sinners and
the jangling devotions.

Up where the tapered spruce will

guide my glance to the sky

and canyon walls will mutely

preach their mighty homilies

In hush so dense that I can sense—

Is it my pulses drumming?

Or God's light footfall coming

through the silvery aspen trees?

Some way I seem to lose Him in the

joists of the street,

But on the twisty deer trail

A mystic presence in the forest

often strays my feet—

No vision borrowed from a saint,

but awesomely my own.

I feel it unite my spirit white,

the prophet's timeless passion.

As ancient as the fashion of the

pine tree's rugged cone.

Where pines reach up the mountains and

the mountains up the blue,

And, tense with some expectancy

the lifting ledges frown.

The high desire of the hills is my
desire too,

for there my spirit laughs to fling
its worldly duffie down

And, shaking free exultantly, calls

to its great companion!

God meets me in the canyon when

I miss him in the town.

—BADGER CLARK

The Wasatch Mountains became a very important part of my early life. My father took his family there in 1896, and we homesteaded. Of all the companions that I have had in the mountains, I have never had one whose companionship compared with Roy's. I was just as anxious as he was to go into the lofty altitudes and spend a few days. There he really knew how to relax—the mountains seemed to bring an atmosphere of tranquillity about him. After two or three days, he seemed to be completely rejuvenated. I assure you that all our time on these trips was not spent in relaxation. We climbed the lofty peaks to altitudes of 14,000 ft. or more. I have one spot on Old Baldy that I took him to on many occasions. From this spot, in turning through an arc of 180 degrees, we could count 35 lakes as we looked down into the valleys below. I called that spot my point of communion. The first time I took Roy to that point we left our camp at an elevation of approximately 9500 ft. about 2.30 a.m. We reached this selected point just at daybreak. It was there I recited for him "The Salutation of the Dawn."

Listen to the exhortation of the dawn!

Look to this day!

For it is life, the very life of life!

In its brief course lie all the

Varieties and realities of your existence;

The bliss of growth,

The glory of action,

The splendor of beauty.

For yesterday is but a dream,

And tomorrow is only a vision,

But today well lived makes

Every yesterday a dream of happiness,

And every tomorrow a vision of hope.

Look well, therefore, to this day!

Such is the Salutation of the Dawn!

—FROM THE SANSKRIT

Roy said, "I have read that quite a few times in my life, but this is the environmental place to bring out its full significance." By that remark I was amply repaid for bringing him to that point of inspiration at that hour of the day.

Growing old gracefully is one of life's greatest accomplishments. I have reached the age when the great events in my past, like those with Roy, echo back and amplify and touch with splendor the present every-



Fig. 3.—Leroy Upson Gardner, M.D., as Director of The Saranac Laboratory and as Director of the Trudeau Foundation for the study of tuberculosis and other pulmonary diseases.

day events of life. That is how Roy's life has affected me. He really never died when he passed the horizon and was taken from our sight. He lives with me as much as my father and mother do on my visits to the old homestead, which still stands after some 80 years of the type of living which really makes a place home. I am just as much an admirer of nature in our mountains today as ever. And much of it is done in the

fashion of the solitude of Thoreau, because I have never met a friend or companion of Roy's simplicity. In the creation of my imagination I travel with him in the realities of paths and byways of our mountainous retreats.

Many will recall that Don Cummings (Industrial Hygiene Engineer to the Saranac Laboratory) met his death in an airplane accident a very few miles from my point of practice. Roy had called me early that morning about 6:30 and told me it had been reported to him that the plane was lost. Don had left Salt Lake City to go to Las Vegas. I spent the entire day in the search, and it happened that I was one of the first persons to arrive at the scene of the accident, and I helped to remove Don's body. That night I reported all the details to Roy, and the gratitude that was in his heart is far beyond my expression to relate to you.

A few months following Don's death, Roy came and spent five days with me. During that time I had had a very close friend pass away, and I was asked to conduct his funeral or at least take charge of it. My friend happened to be a Mason, and, of course, the part of the program which rested upon my shoulders was arranging for the speaker, singers and type of services I thought would be appropriate. I told Roy that I had this responsibility to perform and asked him what he would like to do—whether he would like to stay home or whether he would like to go with me? He said, "Paul, I want to go with you."

The deceased was a member of one of our largest industrial organizations, and I asked the vice-president of the company to say a few words. I had given the man a few of our very personal associations, and he delivered one of the finest practical sermons I have ever heard. During the entire service I could not take my eyes off of Roy as he sat in the back of the auditorium, and I could tell that he was greatly burdened with sorrow. As soon as I had carried out my responsibilities, I went to him and he was still weeping bitterly. "Roy," I said, "you don't have to tell me what is going through

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your mind, because I know you are thinking of Don." He said, "Yes, Paul, I was so impressed with this service that I wished someone could have organized something like this for Don; I have sat here and have tried to readjust the sorrows of Don's departure by imagining now that I was going to his funeral and having someone say as fine things about him as the speaker here today has said about your close friend."

We went back home and sat in his room and talked over the problems of death and exchanged our ideas pertaining to it. I told him, "Roy, your heartstrings have been pulled on very severely today," and I said, "In my beliefs and faith and confidence I am sure that you will receive comfort where heretofore you have received nothing but sorrow in the way Don was buried." I told him the story of the little boy who had purchased a kite during a stormy day. This kite was of ordinary proportions, and he purchased about 4000 ft. of strong, durable, heavy twine. There was no difficulty in getting the kite into the air, and soon he let out all his string and walked up and down the roadside, maneuvering his kite which was entirely lost and enveloped in the clouds. A stranger came along and said, "My boy, what are you doing?" He answered, "Well, sir, I'm flying my kite." The stranger looked and looked and looked and looked, and he said, "My boy, I can't see any kite." "No," said the boy, "neither can I, but I'm flying my kite anyway." The stranger questioned, "How can you tell your kite is up there somewhere?" The boy said, "Well, I can just tell you by one thing, and that is by the pull on the string." With that Roy looked up, and he had one of his very choice smiles of satisfaction; he said, "Paul, I understand."

To me, Roy's remark, showing his greatness, was determined by the flexibility of his

adaptability which showed the true measure of Don. He was humble, simple, sincere and always capable of partaking of the life of all the people he met. He had a beautiful way of presenting it to the world and gave the world such a fine example.

I have frequently said that Roy represented in his general make-up three great men: From the standpoint of his philosophy and diplomacy, he was a Benjamin Franklin; in the field of research, he was a Louis Pasteur, and in the field of the general application of the principles of medicine in the industrial world, he was a Sir William Osler and a full exemplification of Osler's master word.

ROY

Teacher, leader, friend—my friend,

He was greater than most men.

From the soul of him poured

Love, truth, faith, and inspiration.

He has taught men the way of life

Through humility and joy.

His great gratitude and quick

Compassion have made hearts happy.

He gave of himself eternally

And of life asked little.

He loved the mountains, the pines,

And the canyon stream's prattle.

Here we would open wide the

Garden of our thoughts, Roy and I.

And all the while we talked,

God was the only one who passed by—

In memory, my friend and I take

The paths we made "yesterday,"

And those mountainous retreats

Turn back and magnify our joy!

Roy, on this occasion "The Wasatches salute the Adirondacks!"

Memorial Medical Center, 2000 So. Ninth St. E.

**ANNUAL REPORT OF THE MCINTYRE RESEARCH FOUNDATION
FOR YEAR ENDED DEC. 31, 1954**

Herewith is submitted the Annual Report of the McIntyre Research Foundation for the year ended Dec. 31, 1954.

The Foundation continued in active operation during the year. The mining and industrial companies licensed for aluminum therapy continued its use as an aid to the known medical and engineering controls of silicosis.

The financial support of our licensees in four different countries, including 15 states in the United States and 6 provinces of Canada, enabled the Foundation to pursue the following program:

(1) Progressive sponsorship of the research project covering the preparation and study of the Gough Large Lung Sections under the direction of the Ontario Department of Health.

(2) The maintenance of limited services to licensees and the dissemination of general information in response to many personal and written inquiries.

(3) Successful research in the Foundation's laboratories on the manufacture of an improved McIntyre Aluminum Powder of consistently finer particles, looking toward greater efficiency in treatment values.

(4) Providing a forum at the 1954 Conference where many interesting papers on research were presented and subsequently released for distribution by the Foundation.

More specifically, last year's Conference at Toronto featured the following:

(1) Practical demonstration of silicosis control.

(2) Aspects of aluminum therapy in the mines under license in Canada, Mexico, and Australia and in foundry and ceramic industries under license in the United States.

(3) Official statistics on lung fibrosis and silicosis chest x-ray ratings among working

miners in mines in Ontario and Western Australia. Incidentally, statistics on lung fibrosis and the number of new cases of disabling silicosis are rarely kept and more rarely published. We suggest that such statistical studies provide the only reliable basis for appraising silicosis prevention.

(4) Presentation of three papers on x-ray-film classification of the pneumoconioses. One of these by Dr. Ian McCallum, of the University of Durham, England, paid particular attention to coal mining. Fifty copies of this paper have been forwarded to the United Mine Workers Union at their request.

(5) Demonstration of the technique in the preparation of Gough Large Lung Sections by Dr. A. J. Blanchard, Pathologist at the Sunnybrook Hospital in Toronto. Dr. Blanchard is working under the direction of Dr. A. R. Riddell, Senior Medical Specialist of the Ontario Department of Health, and they demonstrated some of these sections at the 1955 Conference held in conjunction with The Saranac Laboratory at Saranac Lake, N. Y., on Feb. 7, 8, and 9 of this year.

ALUMINUM THERAPY

At Mines.—Mass change-room dispersal of McIntyre (Aluminum) Powder was continued at mines in the six Canadian metal-mining provinces and territories, in Mexico, in Western Australia, and at the Geevor Tin Mine in England. Two of the Canadian mines, Gaspé Copper in the east and United Keno, of Yukon, are 4000 miles apart by travel routes.

In Ontario alone, an average of 10,000 miners have had those daily prework treat-

ments for the past 10 years. In Western Australia, the Mines Department of the Government continues as the Foundation licensee. By law the employer in that country must provide aluminum-powder dispersals for the employees.

As in the previous year, we received a copy of the 1954 report of the chest x-ray fibrosis and silicosis ratings of the more than 6000 mining employees of Western Australia, as made at their second complete survey by the Commonwealth Health Board.

The Tristate Mines of the United States continued to offer individual mill and therapy-room treatment to all employees in dust exposure.

In northern Michigan, the new 12,500-ton-per-day White Pine Copper Company was licensed to use aluminum in its specially built therapy room accommodating more than 50 men at a time. As with all mines and plants licensed, White Pine met the Foundation requirements as to medical services and dust control, the latter as certified by the state. On our visit it was a pleasure to note White Pine's medical services and modern hospital and, in ventilation, its 15 ft. diameter, concrete-lined ventilation shaft, 350 ft. deep.

The new uranium mines in Blind River Area, Ontario, also have well-advanced programs for ventilation and medical services. Since their ores are siliceous, they plan to use aluminum therapy, as now do the Canadian Government's two Eldorado Uranium Mines in northwest Canada.

One licensed gold mine closed from lack of ore; another discontinued for change-room alterations. Two new and larger base-metal mines maintained the number of mine licenses.

All miners at licensed mines have pre-employment and periodical medical chest x-ray examinations. That eliminates cases of tuberculosis. While the general medical opinion is that aluminum has no effect one way or the other on tuberculosis, yet it is

reassuring to note that in the largest Canadian gold-mining center, Timmins of the Porcupine Area, both the death and the incidence rates of tuberculosis have been dropping steadily since 1945, which is the year aluminum therapy came into general mining use there.

At Industrial Plants.—The industrial plant licensed users are practically all in the United States. There individual treatments from small grinding mills supervised by nurses continue to be offered to employees in operations which may have a silica hazard. As in mining, periodical chest x-rays are a must in all such, as well as approval of the ventilation and dust-control program from the appropriate state authority. One difficulty at industrial plants is that the success of the campaign against silicosis makes it more difficult to maintain interest in individual treatments.

General.—Contacts with industrial plant licensees in the United States were maintained by the Foundation's Medical Director, Dr. J. W. G. Hannon, who also visited the Porcupine Mining Area in connection with the manufacturing methods of producing the improved aluminum powder.

Dr. W. D. Robson, Medical Consultant, visited mines in British Columbia.

Dr. Hannon and Dr. Rohde, Medical Director for Mexico, will report separately to the President and Directors on medical aspects.

I had in Canada personal committee-meeting contacts with the Canadian Mining Institute and with Provincial Company Mining Associations, and in the United States with the Mining Section of the National Safety Council.

Most of the past year's outside laboratory research, and animal experimentation concerning our work, has been concerned with pneumoconioses other than silicosis. The 1954 closing of the Trudeau Sanatorium, at Saranac Lake, is one evidence of the success of tuberculosis research.

In Ontario, encouraging results are being obtained by the Department of Health in research on the use of "Killed Vole Vaccine" in place of BCG in immunization against tuberculosis. That research was commenced several years ago under the auspices of the mining companies. Dr. D. A. Irwin, a Foundation Director, then of Banting Institute, Toronto, did the early research.

Of particular interest to the Foundation is animal research stated to be under way in South Africa. There monkeys, rabbits, and guinea pigs are reported under test by quartz dusting to produce silicosis and by aluminum dusting to prevent it. Results have not yet been reported.

1955 MCINTYRE-SARANAC CONFERENCE

The Seventh Foundation Conference was held jointly with The Saranac Laboratory on Feb. 7, 8, and 9. Unfortunately Dr. Lanza was unable to act as General Chairman, but Dr. Carey P. McCord substituted for him very ably.

The two organizations, having been engaged in research along parallel lines, were naturally anxious to pool their knowledge and resources.

Our opportunities as Canadian miners to dip into the pool of knowledge afforded by our connection in the medical profession recall our earlier experiences.

Meeting in 1933 at Toronto with the National Tuberculosis Association and allied bodies, our pioneers participated in a remarkable silicosis session, with the late Dr. L. U. Gardner, of Saranac Lake, presiding and presenting a paper.

Under the auspices of the Ontario Mining Association, a luncheon was provided for the 9 medical specialists presenting papers on silicosis and for 12 other Ontario physicians from the Department of Health, the University of Toronto, the Workmen's Compensation Board, the mines, and the Banting-Best Institute, Dr. (Sir) Frederick Banting being among those present. Along with 22 physicians, four mining engineers were present, namely, Mr. A. C. Bateman, of the Ontario Mining Association, and R. J. Ennis,

Balmer Neilly, and myself representing McIntyre Porcupine Mines, Limited. Also included in the group were mine medical directors, Dr. H. Moore, of the Hollinger Consolidated Gold Mines, and Dr. W. D. Robson, of the McIntyre Porcupine Mines.

That particular silicosis session went a long way to consolidate Ontario's program of silicosis prevention through the cooperation of the medical authorities and mine management. Outlined at that time for the purpose of studying prevention was the fact that silica (quartz dust) caused silicosis, with tuberculosis as a complicating factor. The preventive measures indicated were engineering control of the silica by ventilation and dust control and medical control of tuberculosis by x-ray diagnosis—control of contacts—sanitarium treatment.

The idea was suggested too that certain antidotal rock dust discouraged silicosis production. The resultant follow-up by the McIntyre Research team of Denny and Robson in cooperation with the Banting-Best Institute, particularly through Dr. D. A. Irwin, was the emergence of the discovery that aluminum was an inhibitor of the toxic action of silica in the test tubes and with rabbits.

The McIntyre Research Foundation developed from such a beginning.

Of the 26 persons present at the luncheon, at least 14 remain active in their interest in silicosis prevention. Four presented papers and discussion at the 1955 Conference, including Dr. Riddell, of the Ontario Department of Health, who gave a paper in 1933, and Drs. Irwin and Franks; the former who was formerly with the Banting Institute is now the Medical Director of the Aluminum Company of America, and the latter is still associated with the Banting Institute. Dr. A. J. Lanza, present in 1933, was unfortunately unable to contribute this year.

The successors of three others in that group, Dr. Schepers, Dr. Dworski, and Mr. Parkinson, also took an active part in the 1955 symposium.

Silicosis prevention is a long-time effort. There has been, however, since 1933, and

ANNUAL REPORT OF MCINTYRE RESEARCH FOUNDATION

particularly in the past 10 years, positive proof of a drastic decrease in the incidence of new cases of silicosis and of tuberculosis at our mines. There is also a remarkable increase in the life expectancy of those who have contracted silicosis.

In 1933 the average age at death of the three McIntyre miners, then dying each year through silicosis, was 40 years. Now the average age at death of Ontario silicosis cases is 62 years—an increase in life expectancy of 22 years in the past 22 years! We cannot, of course, project into the future such an increase in life expectancy.

On the Foundation's part, research is being continued and sponsored, as in the case of the Large Lung Section Project presented at the McIntyre-Saranac Conference. In 1954, as previously, the research

of others was presented and published at the Annual Conference. The papers of the Joint Conference of 1955 will be published in bound Proceedings.

The Foundation's basic interest continues to be in silicosis prevention. It believes that aluminum therapy has a place in that prevention, until engineering control can successfully remove all silica dust from the working atmosphere at all places and at all times. That time is not yet.

The Foundation also continues its interest in the other pneumoconioses.

We thus look forward confidently to many mutual benefits from the McIntyre-Saranac Conference and to increased protection of the health of all workers in dust.

ANGUS D. CAMPBELL,
B.A.Sc., M.E., Manager.

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