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

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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

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1955

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Conference Program

Sessions

1. General

   Chairman: *Carey 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. Bovard, 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. Irvin, 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: *Carey 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.

Contents

The Biological Effects of Calcined Gypsum Dust

An Experimental Study on Animal Lungs

G. W. H. SCHEPERS, M.D., D.Sc.
T. M. DURKAN, M.E.
and
A. B. DELAHANT, Saranac Lake, N. Y.

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 m to avoid repetition of what has already b placed on record by Gardner, and though the sake of completeness and logic refere has to be made to such matter, most of material now presented will appear for first time, and the interpretation of expe mental records and slides are our own.

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.

MATERIALS

The calcined gypsum used in the experime was the standard product of plaster mills a being a commercial material, varied somewhat composition from time to time. The following proximate estimate of composition and particle-s range refers to the product received during early part of the experimental studies; for mater forwarded later the per cent of hemihydrate w higher and of calcite, lower:

Component	Per Cent	Approximate Particle Size: Range, μ	Avers μ
Hemihydrate $CaSO_4 \cdot \frac{1}{2} H_2O$	70	1—75	5
Anhydrite $CaSO_4$	10	1—40	4
Calcite $CaCO_3$	15	1—20	9
"Dead-burned gypsum"	3	1—30	8
Quartz SiO_2	<1	.....	..
$MgCO_3$, Fe_2O_3, Al_2O_3	2	.....	..
"Calcined gypsum"	100	1—40	5

The quartz was a commercial product supplied as finely ground powder with an SiO_2 content whi exceeded 99%. The tubercle bacilli used for t infection phase of the study were of the R_1 lo virulence human strain whose tuberculogenic pr pensities and cultural characteristics have be well documented.†

SCOPE OF EXPERIMENTS

The present report will deal with the re sults obtained in inhalation experiments i

† References 5 and 6.

Effort has been made
what has already been
ardner, and though for
s and logic reference
matter, most of the
will appear for the
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ides are our own.

RIALS

ised in the experiments
ct of plaster mills and,
rial, varied somewhat in
time. The following ap-
nposition and particle-size
luct received during the
ntal studies; for material
cent of hemihydrate was
er:

Per Cent	Approximate Particle Size: Range, μ	Average, μ
70	1—75	5
10	1—40	4
15	1—20	9
3	1—30	8
<1	.....	..
2	.....	..
100	1—40	5

cial product supplied as a
h an SiO_2 content which
rcle bacilli used for the
dy were of the R_1 low-
hose tuberculogenic pro-
naracteristics have been

PERIMENTS

will deal with the re-
lation experiments in

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_1 tubercle bacilli, and then calcined gypsum dust for 18 months more.

Calcined gypsum dust for 25 months, then infection with R_1 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_1 tubercle bacilli, and then the mixed dust for 27 months more.

Infection control R_1 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_1 strain of tubercle bacilli was achieved by means of the intratracheal insufflation technique perfected in The Saranac Laboratory.[7] Each animal received 6 puffs of the atomizer from a suspension of R_1 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: Focal Pigmentation	Lungs: Atelectasis	Pulmonary Lymph Nodes: Focal Pigmentation	Pulmonary Lymph Nodes: Enlarged Nodes
553-28	54	Died	Pneumonia	..	..	..	..
50	69	Died	Pneumonia	..	..	..	..
53	252	Killed	.....	..	..	..	..
82	263	Died	Pneumonia	..	..	..	..
81	284	Died	Pneumonia	..	..	..	..
64	285	Died	Pneumonia	..	..	..	..
49	290	Killed	.....	+	+	..	..
63	300	Died	Pneumonia	..	..	..	++
44	312	Died	Pneumonia	..	..	..	..
42	373	Killed	.....	+	..	..	..
70	374	Died	Pneumonia	..	..	..	++
43	426	Killed	.....	+	..	+	..
61	475	Died	Pleurisy	+	..	.	+
45	610	Killed	.....	+	+	..	..
47	610	Killed	.....	+	+	..	++
93	667	Killed	.....	..	..	..	++
55	688	Died	Pulmonary abscess	..	+	..	+++
76	715	Died	Pneumonia	+	+	..	+
48	725	Died	Pneumonia	..	+	..	++
54	732	Killed	.....	+	+	..	..
46	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: Focal Pigmentation	Lungs: Atelectasis	Pulmonary Lymph Nodes: Focal Pigmentation	Pulmonary Lymph Nodes: Enlarged Nodes
553-54	22	Killed	.....	..	+	..	+
46	22	Killed	.....	..	+	..	++
91	34	Died	(?)	+	+	..	..
59	44	Died	(?)	+	..	..	+
86	46	Died	Pneumonia	..	..	..	..
77	47	Died	Pneumonia	..	..	..	+
96	588	Killed	.....	+	..	..	..
78	666	Killed	.....	+	..	..	..
79	666	Killed	.....	+	..	..	++
80	666	Killed	.....	+++	..	+	++

Symbols: +, slight reaction; ++, moderate reaction; +++, advanced reaction.

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 hardiest 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.	Survival in Quartz Dust, Days	Fate	Cause of Death	Microscopic Evidence of Pneumoconiosis					Reaction in Pulmonary Lymph Nodes			
				Pigmentation	Atelectasis	Cellular Infiltration	Degeneration: Fibrotic	Degeneration: Necrotic	Enlargement	Pigmentation	Degeneration: Hyaline	Degeneration: Necrotic
553-60	30	Died	?	+	+	..	..	..	..	..	..	..
51	63	Killed	.....	+	+	..	..	..	+	..	..	..
52	63	Killed	.....	++	+	..	..	..	..	+	..	..
56	123	Killed	.....	+	+	..	..	..	++	++	..	..
57	123	Killed	.....	++	..	..	..	..	++	+++	..	..
65	134	Died	Pneumonia	..	+	..	..	..	++	..	..	..
62	184	Killed	.....	++	..	..	..	..	..	..	..	..
58	215	Killed	.....	+++	..	..	..	..	++	++	..	..
75	245	Killed	.....	+++	+	..	..	..	..	..	..	..
67	291	Died	?	++	..	+	..	..	++	..	.	..
66	306	Killed	.....	++	..	+	..	..	..	..	..	..
68	306	Killed	.....	++	..	+	+	..	+	..	..	+
69	306	Killed	.....	++	..	+	++	..	++	..	..	+++
71	428	Killed	.....	++	..	+	++	+	++	..	+++	..
72	428	Killed	.....	+	..	++	++	..	++	..	+	..
73	487	Died	Pneumonia	+	..	++	+	++	+	..	++	..
74	553	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 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 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

			Gross Evidence of Silicosis			Microscopic Evidence of Silicosis					Tissue Reaction in Pulmonary Lymph Node		
								Degeneration			Macrophage Infiltration	Degeneration	
Guinea Pig, No.	Exposure, Days	Fate	Pigmentation	Pleural Adhesions	Pleural Plaques	Bronchiolitis	Cellular Infiltration	Fibrous	Hyaline	Necrotic		Fibrous	Hyaline
602-44	63	K	..	..	..	+	+	..	..	..	+	..	..
3	123	K	..	..	..	..	+	+	..	..	+	..	..
2	184	K	+	..	..	..	++	++	..	..	+++	..	..
4	245	K	++	..	..	..	+++	+++	−	+	+++	+	..
9	306	K	..	..	+	..	+++	+++	+	+	++	++	..
6	366	K	+++	..	+	..	+++	+++	++	++	++	++	..
8	429	K	++	+	..	..	+++	+++	++	+++	++	++	..
22	553	K	++	..	+	..	+++	+++	+++	+++	+	+++	+++

Symbols: +, slight reaction; ++, moderate reaction; +++, advanced reaction.

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-

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

				Microscopic Evidence of Pneumoconiosis						Reaction in Pulmonary Lymph Nodes			
					Cellular Infiltration		Degeneration				Degeneration		
Guinea Pig, No.	Exposure to Dust, Days	Fate	Cause of Death	Bronchiolitis	Focal	Diffuse	Fibrous	Hyaline	Necrotic	Cellular Infiltration	Fibrous	Hyaline	Necrotic
553-13	96	D	Trauma	..	+	..	..	..	..	..	..	..	..
8	264	K	.....	+	+	..	..	..	..	++	+	..	+
5	378	K	.....	+++	++	..	+	..	..	++	..	..	++
14	381	D	Chronic pneumonia	+++	++	+	++	..	..	++	..	..	++
12	389	D	Chronic pneumonia	+++	++	+++	++	..	+	++	+++	+++	..
11	391	D	Chronic pneumonia	+++	++	+++	++	..	++	++	+++	+++	..
9	395	D	Chronic pleurisy	+++	+	+	++	..	..	+	+	..	..
7	403	K	.....	+++	+++	++	+++	..	++	..	+++	+++	..
15	426	K	.....	+++	+++	+++	+++	..	+	+	+	..	..
10	732	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	28.3
$CaSO_4$	45.8	37.5	59.4
$CaCO_3$ } $MgCO_3$ }	3.6	3.2	2.7
Fe_2O_3, Al_2O_3	0.8	0.9	0.8
Ignition loss	0.9	5.2	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 seat

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: Bronchiolitis	Atelectasis	Cellular Infiltration: Focal	Cellular Infiltration: Diffuse	Degeneration: Fibrous	Degeneration: Necrotic	Reaction in Pulmonary Lymph Nodes: Macrophage Infiltration	Degeneration: Fibrous	Degeneration: Hyaline	Degeneration: Necrotic
560-23	9	Died	Pneumonia	..	..	..	..	..	..	++	..	..	..
31	20	Died	Pneumonia	..	..	..	..	..	..	+	..	..	..
49	187	Died	Pneumonia	..	..	..	..	..	..	++	..	..	..
26	223	Died	?	..	..	+	..	..	..	+++	..	..	..
33	229	Died	Pneumonia	..	++	..	++	..	..	+	..	..	..
27	282	Killed	.....	..	..	+	..	+	..	++	..	..	..
56	442	Died	Empyema	..	..	..	..	..	..	+++	..	..	++
24	451	Died	Pneumonia	..	..	++	..	..	..	+	..	..	..
25	465	Killed	.....	..	..	..	++	..	..	++	++	..	..
28	465	Killed	.....	..	..	..	+++	..	..	+	++	..	..
30	468	Died	Pneumonia	..	..	++	..	+	..	+	..	+	..
43	487	Died	Empyema	..	..	+++	..	..	..	+++	..	..	..
39	493	Killed	.....	..	..	..	+	..	..	++	..	..	+
47	494	Died	Empyema	..	..	..	+++	..	..	+	..	..	+
32	496	Died	Empyema	..	..	..	+++	..	..	++	..	..	..
44	518	Killed	.....	++	..	++	..	..	..	+	..	..	..
54	543	Killed	.....	++	..	++	++	..	..	++	..	..	..
29	574	Killed	.....	..	..	++	++	..	+	+	..	..	+
35	690	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 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: Pulmonary Abscess	Atelectasis	Cellular Infiltration: Focal	Cellular Infiltration: Diffuse	Degeneration: Fibrous	Degeneration: Hyaline	Degeneration: Necrosis	Reaction in Pulmonary Lymph Nodes: Enlargement	Degeneration: Hyaline	Degeneration: Necrotic
560-36	33	Killed	.....	..	..	+	++	+	..	..	..	..	..
53	33	Killed	.....	..	..	++	++	++	+	..	++	++	..
41	48	Died	Pneumonia	..	..	+++	+++	++	+	+	++	+	..
29	61	Killed	.....	..	..	+++	++	+++	++	..	++	++	..
40	73	Died	Pleurisy	..	+	..	−	..	..	..	++	++	..
48	76	Died	Pneumonia	..	..	+	+++	+++	++	..	++	++	..
52	105	Died	Pneumonia	..	..	++	+++	++	..	..	++	..	..
37	114	Died	Pulmonary abscess	..	..	..	++	+++	++	..	++	..	..
38	118	Died	Pneumonia	..	..	.	+++	+++	..	..	++	+++	..
45	119	Died	Pneumonia	..	..	..	+++	+++	..	..	++	+++	..
42	120	Killed	.....	..	..	..	+++	+++	..	..	++	+++	..
55	132	Killed	.....	+	..	+	..	+	..	..	++	..	..
46	132	Killed	.....	..	..	..	+	+++	++	++	..	++	..
34	219	Died	Pneumonia	..	..	+	..	+	..	..	++	..	..
50	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 2½ : 1. In the experiment with the 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	31.4	35.4	17.7
$CaSO_4$	62.4	55.2	54.1
$CaCO_3$ } $MgCO_3$ }	5.2	5.6	8.7
Fe_2O_3, Al_2O_3	0.5	0.7	0.9
Ignition loss	0.2	3.1	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 animals 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

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

			Microscopic Evidence of Pneumoconiosis								Reaction in Pulmonary Lymph Nodes			
						Cellular Infiltration		Degeneration				Degeneration		
Guinea Pig, No.	Exposure to Dust, Days	Cause of Death	Pigmentation	Bronchiolitis	Atelectasis	Focal	Diffuse	Fibrous	Hyaline	Necrotic	Enlargement	Fibrous	Hyaline	Necrotic
648-20	81	Pneumonia	..	..	..	..	..	..	..	..	..	..	..	..
26	106	Pneumonia	..	..	..	..	..	..	..	..	+	..	..	..
57	147	Tuberculosis	..	..	..	..	..	..	..	+++	+++	..	..	+++
47	229	Chronic pneumonia	..	+	..	..	..	..	..	..	++	..	..	..
5	289	Chronic pneumonia	..	+	..	..	..	..	..	..	..	..	..	..
25	376	Chronic pneumonia	+–	+	..	..	..	..	..	..	++	..	..	..
59	381	Chronic pneumonia	+–	+	..	..	..	..	..	..	+++	..	..	..
66	399	Chronic pneumonia	+–	+	..	..	..	..	..	..	+	..	..	..
											++	..	..	..
39	408	Chronic pneumonia	++	..	..	..	..	..	..	..	++	+	+	..
55	409	Chronic pneumonia	+–	+	..	–	..	..	..	..	++	..	..	..
35	411	Chronic pneumonia	+–	+	..	+	..	..	..	..	++	..	..	..
33	412	Chronic pneumonia	+–	+–	..	+	..	+	..	..	++	+	+	..
31	414	Chronic pneumonia	+–	+–	..	+	..	..	..	..	++	+	+	.
52	415	Chronic pneumonia	+–	+–	++	+	–	+	..	..	++	++	++	
42	417	Chronic pneumonia	+–	+–	..	+	+	+	..	..	++	..	..	..
26	417	Chronic pneumonia	+–	++	..	+	+	+	..	..	++	..	..	..
19	420	Chronic pneumonia	+–	+–	..	+	+	+	..	..	++	++	++	..
41	420	Chronic pneumonia	+–	+–	..	..	+	..	..	..	++	..	..	..
56	423	Chronic pneumonia	+–	++	..	++	++	..	..	+++	++	..	..	..
12	429	Chronic pneumonia	+–	+–	..	++	++	+	..	+++	++	..	..	..
61	439	Chronic pneumonia	+–	++	..	++	++	+	..	+++	++	..	..	..
65	439	Abscess	+–	+–	..	+++	++	++	..	+++	++	..	+	..
24	452	Chronic pneumonia	+–	++	..	..	..	..	..	++	++	+	..	..
49	468	Abscess	+–	+–	..	+	++	..	..	..	..	..	..	++
31	487	Abscess	+–	+–	..	+	..	..	..	..	..	++	++	..
16	513	Chronic pneumonia	+–	+–	..	+	+	..	..	..	..	++	++	..
54	651	Chronic pneumonia	++	++	..	+	+++	..	..	..	..	..	..	..
36	862	?	++	+	..	+++	+	+++	+	+	+	+	+	..

Symbols: +, 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.	Exposure to Dust, Days	Pigmentation	Microscopic Evidence of Pneumoconiosis: Bronchiolitis	Cellular Infiltration: Focal	Cellular Infiltration: Diffuse	Degeneration: Fibrotic	Degeneration: Hyaline	Degeneration: Necrotic	Reaction in Pulmonary Lymph Nodes: Enlargement	Degeneration: Fibrotic	Degeneration: Hyaline	Degeneration: Necrotic
848-58	147	+	..	..	..	..	..	..	..	..	..	..
1, 2	244	+	..	..	..	..	..	..	++	..	..	..
3, 4	304	++	+	+	..	+	..	..	..	..	..	..
6	335	+	+	+	..	..	..	..	++	..	..	..
7, 8, 64	372	+	+	+	..	..	..	..	..	..	..	..
9, 32	402	++	..	+	+	+	..	+	+++	..	..	..
15, 43, 60, 37, 44, 38, 62	429	++	+	++	+	+	+	+	+++	+	+	+
10	480	++	+	++	++	+	..	..	+++	+	+	..
11, 12, 14, 17, 18, 23	555	+++	+	++	++	..	..	+	+++	+	+	+
27, 54, 50, 63	665	++	++	++	++ A+	..	..	+	+++	+	+	+
21, 22, 29, 30	730	+++	++	++	+++	+	+	..	+++	++	++	..
34, 40, 53	870	+++	++	++	+++	++	..	..	+++	++	++	..

Symbols: +, 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 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.	Gypsum: Quartz: Guinea Pig, No.	Gypsum: Quartz: Ash, % of Dried Lung	Gypsum: Quartz: Silica: % of Dried Lung	Gypsum: Quartz: Silica: % of Ash	Quartz Control: Guinea Pig, No.	Quartz Control: Ash, % of Dried Lung	Quartz Control: Silica: % of Dried Lung	Quartz Control: Silica: % of Ash
8	1, 2	7.65	1.34	17.45	2	9.58	2.73	28.53
11	3, 4, 6	7.80	0.95	12.64	11, 6	12.34	5.57	45.13
12	7, 8	6.67	0.76	11.52	73, 57	12.01	5.50	45.77
13	9	7.28	0.66	9.07	7	11.83	4.94	41.73
16	11, 12, 13	4.91	0.81	16.47	24, 18	9.59	3.80	32.75
17	17, 18, 23	5.11	0.78	15.13	64	10.82	3.66	33.90
18-19	.....	....	....	.....	22, 20	9.71	3.42	33.41
22	63, 27	5.14	0.72	13.97	58	10.72	4.22	39.39
24	22, 29, 30	5.59	1.07	18.87				

nd Quartz Dust
re of Two Volumes

Reaction in Pulmonary Lymph Nodes			
	Degeneration		
alarge-ment	Fibrotic	Hya-line	Ne-crotic
..	..	..	..
++	..	..	..
..	..	..	..
-+	..	..	..
..	..	..	..
-++	..	..	..
-++	+	+	+
-++	+	+	..
-+	+	+	+
-+	+	+	+
-+	++	++	..
-+	++	++	..

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pig lung should be
15).
of the 12 animals in
(Table 15), 6 died
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e instance the cause
tuberculosis. How-
e was there spread-
ther instances there
tuberculosis or but
rcles. In only four
les show any activ-
tectable in the pul-
one instance, but it

sure to Acrosols
ust in a

ntrol

Silica	
% of Dried Lung	% of Ash
2.73	28.53
5.57	45.13
5.50	45.77
4.94	41.73
3.80	32.75
3.66	33.90
3.42	33.41
4.22	39.39

TABLE 13.—*Influence of Calcined Gypsum Dust on the Course of Experimental Tuberculosis* Guinea Pigs Were Exposed by Inhalation to Calcined Gypsum Dust for Six Months, Were Then Infected with R_1 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	Caseation	Cavity	Pulmonary Lymph Nodes	Liver	Spleen
553-36	99	D	Pneumonia	..	..	..	..	+	..	.....	F+	.....
37	144	D	Pneumonia	..	..	..	..	+	..	C+	F+	.....
16	230	K	.....	..	..	++	++	..	..	F+++	F+++	F+++
17	230	K	.....	+	..	+	++	..	..	F+	.....	.....
32	258	D	Tuberculosis	..	+	++	..	..	+++	FT+	C++	C++
33	275	K	.....	+++	..	..	..	..	..	F++	.....	FT
38	275	K	.....	+	−	+	..	+	..	F+	.....	.....
19	307	K	.....	..	..	++	−	+	..	.....	.....	.....
23	386	D	?	+++	..	++	..	..	..	FT++	FT++	FT
30	393	D	Pneumonia	+++	..	++	..	..	..	FT++	FT++	.....
24	446	D	?	++	..	..	++	+	..	F++	.....	FCT
39	474	K	.....	+++	−	++	..	..	..	.....	.....	.....
34	480	D	Pneumonia	+++	+	++	..	..	..	N+++	.....	.....
27	482	D	Pneumonia	++	−	+	..	..	..	FT+	.....	F+
41	505	K	.....	+	..	..	..	+	..	FT+	.....	F+
18	520	K	.....	−++	..	++	..	..	..	FN+	.....	.....
22	520	K	.....	+++	..	++	..	..	..	FN+	.....	.....
31	553	D	?	..	..	++	+++	..	++	HF	HF	HF
35	561	K	.....	−+	..	++	+++	..	..	FT+	.....	FT
10	561	K	.....	−+	..	..	..	+	..	.....	.....	FT

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 calcined 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 Calcined Gypsum Dust on the Course of Experimental Tuberculosis* Guinea Pigs Were Exposed by Inhalation to Calcined Gypsum Dust for Twenty-Five Months, Infected with R_1 Tubercle Bacilli, and Transferred to Normal Air

Guinea Pig, No.	Survival After Infection, Days	Fate	Cause of Death	Pulmonary Tuberculosis					Dissemination		
				Healing Tubercles	Calcification	Fibrosis	Spread	Caseation	Pulmonary Lymph Nodes	Liver	Spleen
553-86	8	Died	Pneumonia	..	..	..	..	..	..	..	..
83	9	Died	Pneumonia	2	..	..	+	..	..	..	..
97	10	Killed	.....	..	..	..	..	..	..	..	..
84	27	Died	Pneumonia	3	..	..	+	..	C+	..	..
85	61	Killed	.....	23	..	++	+	..	C++	C+	C+
87	122	Killed	.....	17	..	++	+	++	PT+	..	..
88	185	Killed	.....	20	..	++	++	..	..	..	..
89	185	Killed	.....	1	..	+	+	..	F+	..	..
90	241	Killed	.....	0	..	..	..	..	..	..	..
92	244	Killed	.....	6	..	+	..	..	..	..	..
94	386	Killed	.....	4	+	++	..	..	..	..	..
95	368	Killed	.....	1	..	..	..	..	..	..	..
98	368	Killed	.....	3	..	+	..	..	..	..	..
99	541	Killed	.....	25	+	−−	..	++	..	..	..
100	541	Killed	.....	13	..	−−	..	..	F+	F+	..

Symbols: C, caseation; F, fibrosis; PT, proliferative tubercle; −, slight reaction; ++, moderate reaction; +++, advanced reaction.

TABLE 15.—*Fate of Guinea Pigs Injected with R, Tubercle Bacilli*
Control Study: No Dust Exposure

Guinea Pig, No.	Survival, Days	Fate	Cause of Death	Pulmonary Tuberculosis: Arrested Tubercles	Caseation	Confluent Tuberculosis	Disseminated Tuberculosis: Pulmonary Lymph Node	Liver	Spleen
553-12	89	Died	Pulmonary infarct	1	++	..	..	..	..
11	98	Died	Pneumonia	2	+	..	..	..	..
7	118	Died	Acute congestion	6	+	..	..	..	..
1	174	Died	Pneumonia	2	..	..	..	+	..
2	202	Killed	.....	1	..	..	..	..	..
8	255	Killed	.....	3 (?)	..	..	+	..	..
3	438	Died	Pulmonary abscess	—	..	..	..	..	..
6	445	Killed	.....	2 (?)	..	..	..	..	..
9	585	Died	Tuberculosis	..	..	+++	+++	+++	+++
10	601	Killed	.....	8	..	..	..	..	..
4	654	Killed	.....	2 (?)	..	..	..	..	..
5	654	Killed	.....	2 (?)	..	..	..	..	..

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 distinct 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 R_t 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 R_t Tubercle Bacilli, and Then Alternating Dust Exposure Continued

Guinea Pig, No.	Survival After Infection, Days	Fate	Cause of Death	Pulmonary Tuberculosis: Spread	Cavity	Tuberculosilicosis	Calcification	Dissemination: Pulmonary Lymph Nodes: Tuberculosis	Silicosis	Liver	Spleen
553-4	101	Died	Tuberculosis	+++	+++	+	..	++	++	TS+	S++
6	255	Killed	.....	+++	+	+++	..	..	+	..	..
1	368	Died	Chronic pneumonia	+	..	..	+	++	++	T+	..
2	393	Killed	.....	..	..	+++	+	+++	+++	T++	..
3	405	Killed	.....	..	+	++	++	+++	+++	T++	..

Symbols: TS, tuberculosilicosis; T, tuberculosis; S, silicosis; +, slight reaction; ++, moderate reaction; +++, advanced reaction.

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_t 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	Fate	Cause of Death	Pulmonary Tuberculosis						Dissemination		
				Confluence	Degeneration			Pneumoconiosis		Pulmonary Lymph Node	Liver	Spleen
					Caseation	Hyaline	Necrosis	Focal	Diffuse			
560-9	172	K	.....	+	..	..	+	..	..	F++	..	..
17	239	K	.....	++	..	+	+	+	..	TF+	F+	..
11	277	D	Pneumonia	+++	..	+	..	..	..	..	..	T+
18	287	D	Pneumonia	+++	CL+	..	+	++	..	..	N+	..
1	359	K	.....	+	..	+	+	++	..	ST+	..	..
2	359	K	.....	+++	+	..	..	..	..	ST++	..	..
15	368	D	Pneumonia	+++	CL+	..	..	..	..	ST++	..	T+
13	399	K	.....	+++	..	..	..	++	+	..	..	..
5	401	K	.....	+	..	+	..	..	+++	N+	F+	F+
10	408	K	.....	++	+	++	+	..	..	..	..	F+
3	428	K	.....	++	..	++	++	..	+++	N++	..	T+
21	482	D	Pneumonia	++	+++	+++	..	..	..	N+	..	F+
16	482	D	Pneumonia	++	CL+	++	..	..	..	F++	N+	TF+
6	508	K	.....	+++	CL+++	+++	..	..	+++	N++	N+	TF+
19	510	D	Pneumonia	++	CA++ CL++	++	..	..	++	N++	T+	TF+
7	549	D	Pneumonia	++	++	+++	..	..	++	N+	T+	TF+
14	555	D	Pneumonia	+++	..	+++	..	..	+++	N+	..	..
12	570	K	.....	+++	CA++	..	..	..	+++	N+	N+	T+
8	618	D	Pneumonia	+++	+++	..	..	..	+++	H+	N+	T+
4	651	K	.....	+++	++	..	..	+	+++	F++	..	T+
20	800	D	Pneumonia	+++	CL+	+++	+	..	+++	N++	T+	..

Symbols: +, slight reaction; ++, moderate reaction; +++, advanced reaction; CA, cavitation; CL, 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 employes.[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

Course of

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Dissemination		
ilmo- ary mph ode	Liver	Spleen
++	..	..
P+	F+	..
..	..	T+
..	N+	..
T+	..	..
++	..	..
—	..	T+
..	..	..
—	F+	F+
..	..	F+
++	..	T+
N+	..	F+
++	N+	TF+
++	N+	TF+
++	T+	TF+
—	T+	TF+
+	..	..
+	N+	T+
+	N+	T+
++	..	T+
++	T+	..

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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	268	86	32
Amorphous Silica A	305	48	16
Amorphous Silica B	192	64	33
Amorphous Silica C	209	44	21
Amorphous Silica D	285	64	22
Volcanic glass	91	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: 1μ to 3μ
Buffer Solution: H_3BO_3-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 20 Hr.
0	0.55	....	6.70
20	0.70	22.6	6.75
50	0.76	36.9	6.75
100	0.90	62.4	6.75
500	1.25	122.7	6.75
750	1.28	127.0	6.87
1,000	1.38	144.4	6.95
2,000	1.36	135.7	7.03
3,000	1.30	116.8	7.05
5,000	1.28	111.3	7.16
Control: No quartz			
5,000	0.12	....	7.00

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 [9] 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 koniophores 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 enigmata 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: 1μ to 3μ
Buffer Solution: H_3BO_3-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	1.16	....	1.25	....
7.1	0.28	6.65	1.50	6.55
7.4	0.54	6.94	1.75	6.60
8.0	0.66	7.42	2.51	7.45
9.0	1.62	8.70	2.10	8.32
10.2	2.45	9.11	1.14	9.50

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psum in a

μ to 3μ
-NaOH
Four Hours

Suspension 1% Quartz + 1% Gypsum	
luble SiO_2, 100 Cc.	pH After 24 Hr.
25	....
50	6.85
75	6.60
51	7.45
10	8.32
14	9.50

a matter of tissue or cellular competition cannot be dismissed as a possibility without due consideration. The paucity of koniophores 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 Gardner [4] 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 5μ 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 alternatingly) 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.

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 R_1 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.

Acknowledgement is made to Stanislaw P. Kaszer, M.E., E.E., Biostatistician, for tabulating and analyzing the data from which Table 18 was constructed.

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