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Bridgeport, Conn.
November 10, 1936

Mr. F. H. Schluter, President,
Thermoid Rubber Co.,
Trenton, N. J.

My dear Mr. Schluter:

The writer and Mr. Vandiver Brown, of Johns-Manville, had a conference with Dr. Leroy Gardner, of Saranac, New York, and Dr. Lanza and Dr. McConnell, of the Metropolitan Life Insurance Co., with reference to the Asbestosis situation in the Asbestos industry.

As you no doubt know, Johns-Manville and ourselves have been doing considerable work, in conjunction with the Metropolitan Life Insurance Co., in the way of eliminating Asbestos Dust in our factories, and we have made a very satisfactory job of it.

We have now reached the point where we can eliminate a large part of the Dust, but as yet have no definite information as to what Asbestosis will lead into. They claim it leads to Tuberculosis, but we do not find this to be the case. Still, we cannot go into court and state definitely and specifically that it will not do so. We do know that Asbestos Fibres can, and do, get into the lungs, and may set up a Fibrosis condition, which, for want of a better name, some doctors have called Asbestosis.

Dr. Gardner has a well equipped Laboratory, and a number of separate Dust Chambers in his Laboratory at Saranac, and he and his associates have been studying various types of Dust for a number of years, in connection with Tuberculosis, but practically nothing has been done with Asbestos.

In order to carry on a systematic Dust investigation, it takes from two to three years, and these investigations are generally paid for by industry, mostly working as a unit.

Dr. Gardner's Laboratory charge is $5,000.00 per year, and any study should be based on a three year period, in order to get results that will stand up and be accepted by the medical fraternity, and, I believe, by the courts.

I think the Compensation Laws in the various states will become more rigid in the next few years and, no doubt, Asbestos, on account of the advertising it has had lately, will become one of the Compensation cases, and we should have all the information we can possibly get to submit to the Compensation Commissions of the various states when the question of Asbestosis comes up.

work on experimenting with Asbestos at once, and has suggested to us that the Asbestos industry take over this Dust Chamber and employ him to carry on the experiments with guinea pigs and rabbits.

The idea of Mr. Brown and myself would be to have four or five (or even more if we could get them) Asbestos manufacturers take over this study by subscribing an equal amount per year, for three years, and then we could determine from time to time after the findings are made, whether we wish any publication or not. My own idea is that it would be a good thing to distribute the information among the medical fraternity, providing it is of the right type and would not injure our companies.

This would mean, if four of us went in to carry on this work, it would be $1,250.00 a year for each one of us for a period of three years.

If you are interested in this subject, I should like to have a meeting in New York, on Tuesday, November 17, at 12:30 o'clock, at The Biltmore, or if this is not satisfactory, can make it any place you care to have it.

I am asking the following to attend the meeting,

Mr. Vandiver Brown, Johns-Manville, Inc.
Mr. F. H. Schluter, Thermoid Rubber Co.
Mr. A. S. Blagden, Keasbey & Mattison Co.
Mr. H. D. LaMont, Asbestos Manufacturing Co.
Mr. G. M. Williams, Russell Manufacturing Co.
Mr. S. Simpson, Raybestos-Manhattan, Inc.

Is there any one else you would suggest?

Very truly yours,

SS-G.

President

November 20, 1936

LeRoy U. Gardner, M. D., Director,
The Saranac Laboratory,
Saranac Lake, New York.

Dear Dr. Gardner:

At a meeting yesterday attended by certain brake lining manufacturers, Mr. Simpson and I were able to present to a fairly large group of interested corporations the proposal that one of your dusting chambers be engaged for further experimentation with asbestos dust.

The proposal was very well received and it appears that not less than eight, and perhaps ten or more, corporations will participate in financing these further experiments along the lines discussed when we met with Dr. Lanza and Dr. McConnell a few days ago.

Accordingly, you may consider this letter as an authorization to you to commence the contemplated experiments with asbestos dust for the purpose of determining more definitely the causes and effects of asbestosis. It is my understanding that, among other questions which it is anticipated these experiments will answer, are the following:

(1) What concentration of dust is necessary to produce the fibrosis of the lungs which is designated as asbestosis.

(2) Whether exposure to asbestos dust will produce asbestosis without the existence of previous infection and whether the X-ray changes found in advanced human asbestosis can be reproduced in animals without infection.

(3) Whether the fibrosis produced by asbestos is of the progressive type, that is, will the fibrosis increase (once it has started) after exposure to the dust has ceased.

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(4) Whether the fibrosis resulting from exposure to asbestos dust is occasioned by the silicon content of the asbestos or by its fibrous structure.

(5) Whether the presence of "asbestos bodies" has any diagnostic significance.

It is also our understanding that these experiments will require approximately three years, which will mean that they will not be concluded until about the end of the year 1939; and that they will cost $5,000 annually, or a total of $15,000.

It is our further understanding that the results obtained will be considered the property of those who are advancing the required funds, who will determine whether, to what extent and in what manner they shall be made public. In the event it is deemed desirable that the results be made public, the manuscript of your study will be submitted to us for approval prior to publication.

I shall appreciate your advising me if the foregoing accurately expresses the proposition you had in mind. Also, let me know the manner in which you would like to have the funds advanced to you. Would you, for example, desire to have $1250 paid quarterly in advance, or just what arrangement would suit you best? Any method you suggest will be satisfactory.

Since the experiments are being underwritten by a relatively large group, it has been suggested that, as a matter of convenience, any communications regarding the work be addressed to me and I will, where necessary, communicate the contents thereof to Mr. Simpson and the other parties. You will be provided with funds by either Johns-Manville Corporation or Raybestos-Manhattan, Incorporated and we or they will secure from the other parties their pro rata contribution.

I will advise you later of the names of the other contributing parties.

I shall appreciate your informing me at the earliest possible moment whether the arrangement as outlined herein meets with your approval.

Sincerely yours,

Vandiver Brown

Vandiver Brown
General Attorney

VB:T

THE SARANAC LABORATORY FOR THE STUDY OF TUBERCULOSIS
OF
THE EDWARD L. TRUDEAU FOUNDATION

POST OFFICE BOX 971
7 CHURCH STREET
SARANAC LAKE, N.Y.

RECEIVED
NOV 25 1936
VICE PRESIDENT
SEC. & TREAS. OFFICE

November 23, 1936.

Mr. Vandiver Brown
Johns-Manville Corporation
22 East 40th Street
New York City

Dear Mr. Brown:

Your authorization to proceed with the proposed asbestosis experiments at the Saranac Laboratory is acknowledged with satisfaction.

We believe that such experiments can be expected to furnish asnwers to the questions which you have outlined. The estimated cost of $5,000 annually for a period of three years, making a total of $15,000, is correct.

Your suggestion to make advanced quarterly payments of $1,250 will be entirely satisfactory to the Laboratory. If this is not convenient any other arrangement that you may care to make will be acceptable.

The Saranac Laboratory agrees that the results of these studies shall become the property of the contributors and that the manuscripts of any reports shall be submitted for approval of the contributors before publication.

I would recommend that the experiments be performed with pure Canadian asbestos fibre containing relatively little serpentine rock dust. The "Kings Floats" used in our first experiment was unsatisfactory owing to the fact that it contained such a high concentration of non-fibrous rock dust. If this meets with your approval I would suggest that a sample be submitted to the Laboratory for chemical and petrographic analysis.

Having mutually satisfied ourselves as to the material to be used I would request that the companies agree to supply a sufficient quantity of asbestos, ground to the finest state of subdivision possible. I am not aware whether any of the contributors have apparatus capable of reducing fibres to inhalable dimensions. If this request should not

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prove practical some arrangement for its final reduction will have to be made by the Laboratory. But at least the material received by us should be broken to powder.

It is impossible to estimate the amount of material necessary for the experiments at the present time as its behavior in our dusting apparatus has never been determined. With the "Kings Floats" tests approximately 1200 pounds a year were required. It is conceivable that a pure fibrous dust might be dissipated into the atmosphere more rapidly and hence even a larger quantity would be necessary.

We are ready to start the work at any time and will be pleased to examine samples of dust as soon as they can be procured.

Thanking you for your cooporation in arranging this program, I am

With best regards,

Sincerely yours,

Leroy U. Gardner, M.D.
Director cc

LUG:CC

Naturally, I shall welcome any criticism that you or any of the other contributors would care to offer. Should any of them want to discuss details, I would be pleased to meet with them. May I take this opportunity to thank all the sponsors through you for the support that we have had.

Sincerely yours,

Leroy U. Gardner, M. D.
Director

LUG:=SH

PX 26-54

THE SARANAC LABORATORY
FOR THE STUDY OF TUBERCULOSIS
OF THE EDWARD L. TRUDEAU FOUNDATION
SARANAC LAKE, N.Y.

February 24, 1943

Lanza advises asb. companies on Saranac research and later helps suppress experimental studies showing asbestos could cause lung C (1940's)

Mr. Vandiver Brown
Johns-Manville Corporation
22 East 40th Street
New York, New York

Dear Mr. Brown:

I have at last succeeded in analyzing most of our voluminous experimental data and assessing the results. I realize that this should have been completed before this, but the emergency has left me short-handed in the Laboratory and also necessitated my doing a good deal of extra traveling. I hope that the sponsors of our study of asbestosis will be charitable and realize that the work has far exceeded its original scope.

We have done over 40 different experiments, many of them divided into several parts, which involved exposure of animals for 1 to 3 years to various dusts. The business of preparing microscopic sections and chemically analyzing the tissues on more than 800 animals has been a job in itself. My time for studying sections and analyzing data has been so limited that we are behind our schedule. I have still not had time to write a full report of this work which will of necessity be monographic. However, for the benefit of the contributors, I am submitting a table of contents and an annotated outline to indicate conclusions and the line of argument that will be developed. The latter itself occupies 15 pages, but I hope they will find it sufficiently interesting to read. I shall work on the final manuscript as I have opportunity.

There are a few experiments still in progress which should be completed by the time we are ready for them. The work on methods of dust determination, I consider important enough to include in the study. The question of cancer susceptibility now seems more significant than I had previously imagined. I believe I can obtain support for repeating it from the cancer research group. As it will take two or three years to complete such a study, I believe it would better be omitted from the present report. If it should become possible to make this study, I hope that I may count on some of your members to supply me with enough pure, long fibre asbestos for the purpose.

P X26-61

PLAINTIFF'S EXHIBIT 4

OUTLINE OF PROPOSED MONOGRAPH ON ASBESTOSIS

Saranac Laboratory Study under Grant from Asbestos Association

PART I HUMAN ASBESTOSIS

I Human Pathology - a study of 25 autopsy cases, Illustrated

2 X-ray Patterns in Asbestosis, Illustrated

3 Ash and Mineral Values in Human Asbestosis

4 Complications of Asbestosis

(a) Susceptibility to infection

i Tuberculous
ii Non-Tuberculous
iii Cancer of the lung

5 Disability, causes and comparison with silicosis

6 Diagnosis

(a) History of adequate exposure
(b) X-ray film pattern
(c) Physical examination
(d) Asbestosis bodies in sputum, their significance

PX26-62

PART II Experimental Asbestosis

I Methods

(a) Inhalation exposure to plant dusts.
(b) Injection into lungs through trachea of pure mineral
(c) Injection of pure minerals into other organs.

2 Species Susceptibility

Man, guinea pigs, rabbits, cats, white mice and rats dogs.

3 Peculiar Characteristics of Asbestosis

(a) Unusual localizaion of chrysotile fibre in lungs.
(b) Rate of resultant tissue reaction more rapid than to quartz.
(c) Reaction to chrysotile not progressive after exposure ceases; again the reverse of the situation in silicosi
(d) Asbestosis Bodies

i Composition and methods of formation.
ii Occurence in different species.
iii Formation does not parallel development of fibros
iv Gradual disappearance after exposure ceases.

4 Comparative Effects of Different Asbestiform minerals.

(a) Canadian Chrysotile.
(b) Arizona Chrysotile, low iron.
(c) Crocidolite
i Bolivian specimen, stiff and elastic.
ii South African, soft and flexible.
(d) Anthophyllite
(e) Amosite.
(f) Tremolite.

5 Effects of Control Minerals

(a) Grannular Serpentine, same chemical composition as chrysotile.
(b) Glass Wool, a synthetic silicate fibre.
(c) Brucite, a fibrous magnesium hydroxide almost free of silica

6 Chemical Composition of Asbestiform minerals in Relation to Irritation.

(a) Nothing in composition correlated with relative irritat capacity.
(b) Preliminary acid treatment

i Hydrochloric acid
ii Carbonic acid

(c) Effects of Aluminum

7 Physical Properties in Relation to Irritation

(a) Length of fibre
(b) Effect of Crushing
(c) Heat treatment

8 Nature and Significance of Asbestosis Body

(a) Formation
(b) Protective effect preventing further irritation
(c) Ultimate solubility in tissue

9 Theories of Action of Asbestiform Minerals

(a) Chemical - reasons for considering invalid
(b) Mechanical - experimental demonstration of.

10 Complications

(a) Infection, tuberculosis and other varieties
(b) Cancer of lung - experimental data suggestive but not proven

11 Disability

12 Essential Features of Hazardous Exposure

(a) Nature of dust - fibrous component and size factors
(b) Atmospheric Concentrations - probably lower than for quartz

i Inadequacy of standard impinger sampling method which does not collect the dangerous fibres
ii Electrostatic precipitator sampling preferable but method must be modified

(c) Duration of Exposure

13 Recommendations for a New Standard of Safe Atmospheric Concentrations of Asbestos Dust

(a) The Quasi-official standard of 4 to 5 million particles per cu. ft.
(b) Work upon better method of sampling

(c) Necessity for comparison of results with X-ray findings in employees

14 Prevention

(a) Chemical means not practical

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i Acidosis necessary to dissolve fibre in lungs worse than Asbestosis
ii Aluminum Therapy inapplicable
iii Chief reliance still upon dust prevention with special emphasis upon the fibrous components

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ASBESTOSIS - ANNOTED OUTLINE INDICATING RESULTS

PART I - HUMAN ASBESTOSIS

I Human Pathology and X-ray Patterns - Description

Based upon 23 human autopsies

2 Ash and Mineral Values in Human Lungs.

3 Complication of Asbestosis

(a) Susceptibility to Infection

1 Tuberculous- High incidence in English experience not duplicated in surveys of American Plants. Available autopsy statistics deceiving because of selection of material.

ii Non-Tuberculous- The same reason probably applies should be checked by analysis of absenteeism among asbestos workers.

iii Cancer of Lung — Ditto, but there are now on record 10 cases of lung cancer in asbestos workers. Compared to the total number of autopsies on asbestosis, this incidence is excessive No such frequency has been discovered in silicosis or other forms of pneumoconiosis except the Schneeberg mines of radioactive ores. The evidence is suggestive but not conclusive that asbestosis may precipitate the development of cancer in susceptible individuals.

4 Disability

Clinical experience suggests that truly disabling asbestosis is manifested by less striking X-ray changes than a corresponding degree of silicosis. Such disability in asbestosis is due to disease within the lungs and not to secondary heart disease. As in silicosis, associated pulmonary infection increases the amount of severity of the dust fibrosis with resultant accentuation of disability. There is urgent need for a careful physiological study of pulmonary function in asbestosis of varying severity. Undoubtedly, there are many diagnosable cases with no significant disability.

5 Diagnosis depends upon three factors.

(a) History of adequate exposure, usually 6 to 8 years, sometimes longer, at work where both the concentration and character of the "asbestos" dust are hazardous.

(b) Evidence of disease in a characteristic X-ray pattern.

(c) A physical examination which reveals certain characteristi signs and may reveal evidences of disability if present.

(d) Asbestosis bodies in the sputum are confirmatory when the previous factors are all positive. However, the bodies may be absent, particularly in the absence of bronchitis infection.
Asbestosis bodies unsupported by other evidence do not make a diagnosis. Occasional ones have been found in about 15 autopsy specimens of persons with no known exposure and no fibrosis, probably of non-occupational origin.

••

PART II Experimental Asbestosis

I Methods

(a) Inhalation Exposures to Plant Dust - Specific fibrosis in lungs, but no changes elsewhere.

(b) Injections of Suspensions of Pure Minerals into Trachea Similar results.

(c) Injection of Suspensions of Pure Minerals into other organs Fibres dissolved; no asbestosis bodies; tissue reaction confined to phygocytosis and encapsulation. Compare the asbestos cores of human subjects

II Species Susceptibility

Unlike free silica, asbestos does not produce its specific effec in any organ of any species of animal. It causes fibrosis only the lungs of man and those of a few of the species tested.

Species	Fibrosis	Asbestos Bodies	Species	Fibrosis	Asbestos Bo
Man	4+	4+	Cat	+	±
Guinea Pig	2+	3+	White Mouse	0	±
Rabbit	+	±*	White Rat	0	0
			Dog	0	0

(* ± = very small atypical asbestos bodies)

III Peculiar Characteristics of Asbestosis

(a) Localization of fibrous minerals in lungs differs from that of granular dust particles.

1 Fibres like chrysotile having a certain degree of flexibility and elasticity accumulate within the finest air tubes; granular dust is carried further on and is widely scattered through the terminal air spaces.

(b) Rate of tissue reaction to asbestos is much more rapid than to an active dust like quartz. Evidences of formation appear as soon as sufficient concentration of fibres has localized in specific areas; with quartz, there is a latent period of months.

(c) Reaction to asbestos does not progress on cessation of exposure. Young scar tissue that may have formed, contracts and becomes more dense but the area of involvement decreases in size. In silicosis, the young nodules become larger after exposure ceases.

(d) Asbestosis Bodies are a specific concommitant of this form of pneumoconiosis. They are due to a deposit of protein and iron upon the surface of inhaled fibres. In guinea pigs they form after about 60 days of contact with the tissue. They are abundant in man and guinea pigs, (See paragraph 2 above) but much larger in the former probably because the larger sized air tubes admit larger fibres. In cats, rabbits and mice, there is an atypical coating of a few of the fibres after much longer residence in the lungs; in rats and dogs no bodies could be discovered. From paragraph 2 it is apparent that their occurence does not parallel development of fibrosis. In lung injection experiments, the bodies have not developed until after fibrosis is well advanced. The number of bodies seems to decrease several years after exposure ceases.

V Comparative Effects of Different Asbestosis Minerals

(a) Canadian Chrysotile - highly irritating.

(b) Arizona Chrysotile (low in iron) equally irritating and produces just as many asbestosis bodies as the Canadian product with over 11 times as much iron.

(c) Crocidolite - The South African blue asbestos is known to cause asbestosis. Only a limited supply of this material in pure form was available, most of it was used earlier in the work in non-productive experiments. For the later critical injection tests into the lungs, a Bolivian variety was substituted because of its high purity. Its fibres were much straighter, stiffer and more elastic than the cottony South African variety. Perhaps because of these peculiarities, it has not given reactions comparable to chrysotile. It produced asbestosis bodies but did not localize in the terminal air tubes nor cause any fibrosis. Tests now being repeated with a typical South African crocidolite with physical characteristics simulating chrysotile.

(d) Anthophyllite - stiff, straight fibres - atypical asbestosis bodies forms slowly but no localization or fibrosis in lungs.

(e) Amosite - Ditto.

(f) Amphibole - Ditto.

(g) Tremolite - Ditto but very few asbestosis bodies - Observation being continued.

V Control Mineral

(a) Granular Serpentine of same chemical composition as chrysotil is inert causing no fibrosis in lungs or other organs. It attracts iron from the lungs but of course, no "bodies" develo

(b) Glass Wool(a synthetic silicate) fibres are not inhalable from air-borne suspensions, apparently because of their stiffness (the diameter is not responsible as some used were less than 1 micron thick) On injection into the lungs, they do not localize in the air tubes but are widely scattered. They cause no fibrosis. After 3 or 4 months in contact with lung fluid, a few glass fibres take up iron but remain smooth. They never show the swollen ends and lateral projections of the true asbestosis bodies.

(c) Brucite of interest because it is a fibrous mineral practically free of silica (0.9%). Crystallographically the arrangement of its Mg and OH groups in each unit cell is similar to that in chrysotile. The sample used also contained about 16% iron, probably from contaminating magnetite. The fibres are stiff and needle like. Observations not yet completed but after 2 months in the lungs, typical asbestosis bodies develop but there is as yet no fibrosis. The fibre are scattered through the lung instead of being localized inside the terminal air tubes and tissue reaction occurs around, instead of within the tubes.

VI Chemical Composition in Relation to Irritation

(a) Nothing in the following chemical compositions can be correlated with variations in capacity to provoke tissue reaction.

(See Table Next Page)

	Chrysotile	Crocidolite	Anthophyllite	Amosite	Amphibole	Tremolite	Brucite
SiO_2	37,43%	54,99%	57,43%	46,23%	55,04%	56,20%	0,90%
Fe_2O_3	2,35%	16,27%	0,61%	4,06%	3,06%	7,21%	6,72%
FeO	0	4,29%	0 ?	33,85%	0	0	9,36%
Al_2O_3	0.36%	1,02%	0,25%	1,09%	1,69%	0,56%	0,16%
CaO	0,05%	0,79%	0,14%	2,01%	12,22%	1,45%	0,40%
MgO	38,77%	12,25%	29,64%	6,29%	23,29%	20,52%	53,68%
Na_2O	0,29	6,92	0,52	0,33	0,10	6,78	0,91
K_2O	0,08	0,57	0,13	0,10	0,12	0,99	0,15
Loss <105°	4,30	0,02	0,82	0,66	0,32	0,34	0,53
>105°	14.92	2,56	2,42	1,51	3,69	2,78	26,66

(b) Acid treatment of chrysotile fibres

i One hour in dilute or concentrated HCL does not alter appearance of fibre but after such treatment it rapidly dissolves and disappears on injecting into living tissues.

ii Treatment with CO_2 bubbled through water or lung juice suspensions of chrysotile fibres causes partial solution with liberation of silica and magnesia.

(c) Colloidal allumina does not neutralize the effects of asbestc as it does quartz. On injecting chrysotile suspended in aluminum hydrate solution, fibrosis and asbestos bodies develop at the usual rate. It remains to demonstrate whether th fibres become coated with a layer of aluminum monohydrate as has been proved in the case of quartz. If they have, the coa does not affect their capacity to irritate tissue.

VII Physical Properties in Relation to Irritation of Lung Tissue

(a) Length of Fibre

Short chrysotile fibres under 3 microns are practically inert. 20 to 50 micron fibres cause typical fibrosis.
The effects of longer ones could not be tested for technical reasons.

(b) Crushing completely destroys the fibrous structure of chrysotile. With loss of structure, all capacity to irritate disappears.

(c) Heat At ignition temperatures, water is driven off but the fibrewstructure is preserved. Fibres become extremely brittle. The physical change alters typical localization within the lungs, no fibroses develops, reaction limited to phyegocytosis No asbestosis bodies formed.

VIII Nature and Significance of Asbestosis Bodies

(a) Bodies probably result from deposition of iron and organic matter on a slowly dissolving fibre of asbestos. The source of the iron is more likely to be the lung tissue than the mineral itself as the coating is just as heavy on fibrous minerals of low iron content as upon those high in iron.

(b) The effect of asbestosis body formation is assumed to be protective although it has not been possible to isolate a large enough quantity of these structures in unaltered form for purposes of test. The smooth rounded ends presented by the bodies would not be mechanically irritating.

(c) If they were capable of causing irritation, the fibrosis in the lungs should progress after exposure ceases which it does not.

(d) The gradual disappearance of bodies (and fibres) long after exposure points to ultimate solubility in tissue fluids.

(e) The bodies are probably a fortuitous concommitant rather than a cause of fibrosis.

IX Theories of Irritant Action of Asbestiform Minerals

(a) Chemical These experiments do not confirm the theory that asbestosis is merely a form of silicosis resulting from free silica liberated in the solution of a silicate molecule. If this were true asbestos, like quartz, should cause fibrosis in any organ of any species for the experiments have shown that injected asbestos dissolves in these locations. However, it does not cause such reaction in any location but the lungs of a few species.

(b) Mechanical Irritation

We are proposing the theory of mechanical irritation which is manifested only in the lungs because this organ is the only one whose normal physiological functions involve a high degree of mobility. Experiments designed to prove the necessity for motion in this tissue have failed for technical reasons.
For this theory to be applicable, it is necessary that the fibres be concentrated in the fine terminal air tubes. It has been shown that only chrysotile of the asbestiform minerals thus far has the proper physical characteristics to insure such localization. It is also essential that the fibre shall persist long enough before it dissolves in the lungs of species like mice, rats, dogs. It apparently dissolves so rapidly that it exerts no irritation. Similarly rapid solution may explain in part, the lack of fibrosis in organs other than the lungs.

The fibres must be long enough so that they cannot be compl
surrounded by phagocytic cells which would prevent contact c
round, broken ends with the delicate cells supporting the al
Observation has demonstrated that these conditions are reali
guinea pigs treated with long fibre chrysotile and fibrosis
With the other asbestiform minerals that have been tested, a
all of the prerequisits were lacking and no fibrosis develop

(c) If the irritation were chemical, fine serpentine which h
same chemical composition as chrysotile should have also
fibrosis. The crushed chrysotile should have been more
than intact fibres, because of the greater surface area
posed to body fluids. On the assumption that chrysotile
quartz, becomes coated with a very thin layer of alumina
treatment with colloidal aluminum hydroxide, capacity to
fibrosis should be destroyed if the action were chemical
such is not the case.

(d) The heavy coating resulting from asbestosis body formatio
parently does stop tissue reaction but here the effects a
probably mechanical for reasons cited.

(e) Heat sufficient to alter chemical structure d estroys powe
to irritate but it also alters essential physical characte
that affect localization of the fibres in the lungs.

X Complications

(a) Susceptibility to Infection

1 Tuberculous - Asbestos behaves like most other mineral dusts in
this respect and not like quartz which specifically increases
native susceptibility to the tubercle bacillus. This in-
fection may spread for a time but then heals. The result
fibrosis accentuates that caused by the mineral fibre.

ii Non-Tuberculous - of no greater frequency than in animals
inhaling dusts of other kinds. Occasional epidemics of
pneumonia occur in our dust rooms, but these are due to
methods of housing rather than to dust; they ~~can~~ also occu
in unexposed animals.

iii Cancer of Lungs

No experiments were particularly designed to elucidate this point but
certain evidence suggests that asbestosis may actually
favor development of tumors in susceptible species.

1 In guinea pigs, rabbits, rats, cats and dogs lung tumors
are rare.

2 When these species were subjected to 2 to 3 years in-
halation of asbestos dust, the incidence of lung tumor
was not increased.

(26 - 66 (7)

3 Some strains of white mice do develop tumors without apparent cause.

4 Such a strain of white mice was unintentionally used in three inhalation experiments with asbestos.

5 Of 11 mice inhaling long fibre asbestos for 15 to 24 month 8 developed malignant tumors in their lungs and 6 of them had tumors in other organs. The incidence rate 81.8% is excessive.

6 Of 22 mice inhaling short fibre asbestos for not longer th 12 months only 3 developed lung tumors. Rate 13.6%

7 As controls, we have only the experience with mice in othe dust experiments.
For short periods, there were 51 mice exposed to 4 other kinds of dust for 10 to 12 months. Incidence of lung tumo 1.9%.
For long periods, there were 143 mice exposed to 4 differe kinds of dust, including pure quartz, 23 to 31 months. Fo all this group of mice the average incidence of lung tumor was 13.8%: the highest rate (25%) was in a subgroup exposed to flint dust.

Thus the incidence of lung cancer in the long fibre asbestos mice was over 16 times the average for mice inhaling other dusts for comparable periods and over 3 times the maximum for any other group Mice exposed to the practically inert short fibre asbestos showed fewer lung tumors although 7 times more than those in short exposur to other dusts.

These observations are suggestive but not conclusive evidence of a cancer stimulating action by asbestos dust. They are open to several criticisms. The strain of mice was not the same in the asbestos experiment as in many of the others cited; apparently the former were unusually susceptible. Not enough animals survived in the dust for longer than the 15 months apparently necessary to produce many tumors. There were no unexposed controls of the same strain and age and no similar controls exposed to other dusts. It is hoped that this experiment can be repeated under properly controlled conditions to determine whether asbestos actually favors cancer of the lung.

XI Disability

Cannot be determined in animals. The accidental deaths were from the same causes met with in all our dust inhalation experiments.

XII Essential Factors of Hazardous Exposure

(a) Nature of Dust

i The hazrds increases with the proportion of intact fibres in the dust. Granular material and crushed fibre are inert diluents.

ii The long fibres must be thin enough (1-3 Microns) and short enough (under 50 Microns?) to be inhaled.

iii Very short fibres (under 3 Microns) are practically inert.

(b) Atmospheric Concentration Still under study.

Apparently this factor is lower than in the case of dusts composed of granular minerals but methods of estimation are misleading.

i The average standard Public Health Service impinger count in the long fibre asbestos dust room was 40 million particles per cu. ft. of air. This concentration caused fibrosis visible to the naked eye in 20 to 24 months. For comparison the average impinger counts in an experiment with pure quartz was 120 million particles per cu. ft. and fibrosis developed at about the same rate.

ii However, impinger counts are deceptive because by this method of sampling very few fibres, which are the significant elements in the dust are collected.

iii Sampling with an electrostatic precipitator is a much more efficient means of collecting fibres from air-borne suspensions. Samples from our long fibre asbestos room showed that the dust in the air contained 32.5% of fibres few of which had been collected or counted in the impinger sample. The latter sampled largely the inert granular particles.

iv As ordinarily employed precipitator samples are weighed and the results expressed in mg. per cubic foot of air. There is no means of converting such values into numbers of particles particularly when these vary in size, shape and specific gravity.

v Simultaneous sampling with precipitator and standard impinger yielded the respective values of 0.65 mg and 60 million particles per cubic foot of air.

vi Theoretically the best index of hazard would be either the number or weight of fibrous elements in the dust.

(c) Duration of Exposure

i Fibrosis visible to the naked eye after 18 months exposure increases in extent in subsequent 18 months.

ii The span of life of our most susceptible laboratory animal the guinea pig has prevented continuing exposure longer th three years. In this period only the comparatively early stages of asbestosis have been produced. With the knowledge that we have gained, it is probable that more extens disease could have been produced with a purer long fibre chrysotile. The long lived species, like cats, dogs are u fortunately not susceptible.

iii For these reasons X-ray changes have been minimal and we were not able to fulfill one of the objectives of this program.

XIII Recommendation for a New Standard of Safe Atmospheric Concentratio of Asbestos Dust.

(a) While there is no official standard, the tentative one of 4 or 5 million particles per cubic foot of air is frequently quoted.

(b) This is probably unreliable because it is based upon sampling with a standard impinger which we have shown does not collect most of the fibres that are the source of hazard.

(c) We now think that a standard should be based upon samples collected with an electrostatic precipitator if it is feasible to determine readily the relative proportion of fibres in such material.

(d) Work is still in progress upon the latter point.

(e) To be of value the new standard would have to be correlated with the X-ray findings upon employees exposed to different concentrations of dust.

XIV Prevention of Asbestosis

The experiments have failed to develop any practical chemical means of neutralizing the action of fibrous asbestos.

(a) To alter the human lung so that it would dissolve asbestos fibres rapidly like a rat would necessitate ~~(procedure)~~ creating an acidosis which would be worse than the effects of the fibrosis.

6-66(10)

(b) Apparently aluminum, which is so effective against
has little influence upon fibrous chrysotile.

(c) However, it would be of great theoretical interest to
few cases with real dyspnoea from asbestosis by alumi
halation. We are by no means certain whether the fav
results upon advanced silicotics are due to a chemica
zation of quartz in the lungs. Aluminum might have s
general pharmacological effect which influences dyspn

(d) Chief reliance must still be based upon control of dus
air and, in view of these experiments, particularly up
fibrous components of such dust.

Leroy U. Gardner

126-66(11)



November 20, 1936

LeRoy U. Gardner, M. D., Director,
The Saranac Laboratory,
Saranac Lake, New York.

Dear Dr. Gardner:

At a meeting yesterday attended by certain brake lining manufacturers, Mr. Simpson and I were able to present to a fairly large group of interested corporations the proposal that one of your dusting chambers be engaged for further experimentation with asbestos dust.

The proposal was very well received and it appears that not less than eight, and perhaps ten or more, corporations will participate in financing these further experiments along the lines discussed when we met with Dr. Lanza and Dr. McConnell a few days ago.

Accordingly, you may consider this letter as an authorization to you to commence the contemplated experiments with asbestos dust for the purpose of determining more definitely the causes and effects of asbestosis. It is my understanding that, among other questions which it is anticipated these experiments will answer, are the following:

(1) What concentration of dust is necessary to produce the fibrosis of the lungs which is designated as asbestosis.

(2) Whether exposure to asbestos dust will produce asbestosis without the existence of previous infection and whether the X-ray changes found in advanced human asbestosis can be reproduced in animals without infection.

(3) Whether the fibrosis produced by asbestos is of the progressive type, that is, will the fibrosis increase (once it has started) after exposure to the dust has ceased.

PLAINTIFF'S EXHIBIT 1905.0 2 of 2

(4) Whether the fibrosis resulting from exposure to asbestos dust is occasioned by the silicon content of the asbestos or by its fibrous structure.

(5) Whether the presence of "asbestos bodies" has any diagnostic significance.

It is also our understanding that these experiments will require approximately three years, which will mean that they will not be concluded until about the end of the year 1939; and that they will cost $5,000 annually, or a total of $15,000.

It is our further understanding that the results obtained will be considered the property of those who are advancing the required funds, who will determine whether, to what extent and in what manner they shall be made public. In the event it is deemed desirable that the results be made public, the manuscript of your study will be submitted to us for approval prior to publication.

I shall appreciate your advising me if the foregoing accurately expresses the proposition you had in mind. Also, let me know the manner in which you would like to have the funds advanced to you. Would you, for example, desire to have $1250 paid quarterly in advance, or just what arrangement would suit you best? Any method you suggest will be satisfactory.

Since the experiments are being underwritten by a relatively large group, it has been suggested that, as a matter of convenience, any communications regarding the work be addressed to me and I will, where necessary, communicate the contents thereof to Mr. Simpson and the other parties. You will be provided with funds by either Johns-Manville Corporation or Raybestos-Manhattan, Incorporated and we or they will secure from the other parties their pro rata contribution.

I will advise you later of the names of the other contributing parties.

I shall appreciate your informing me at the earliest possible moment whether the arrangement as outlined herein meets with your approval.

Sincerely yours,

Vandiver Brown

Vandiver Brown
General Attorney

VB:T

THE SARANAC LABORATORY FOR THE STUDY OF TUBERCULOSIS
OF
THE EDWARD L. TRUDEAU FOUNDATION

PLAINTIFF'S EXHIBIT 1906

RECEIVED
POST OFFICE BUILDING
7 CHURCH STREET
SARANAC LAKE, N.Y.

November 23, 1936

Mr. Vandiver Brown
Johns-Manville Corporation
22 East 40th Street
New York City

Dear Mr. Brown:

Your authorization to proceed with the proposed asbestosis experiments at the Saranac Laboratory is acknowledged with satisfaction.

We believe that such experiments can be expected to furnish answers to the questions which you have outlined. The estimated cost of $5,000 annually for a period of three years, making a total of $15,000, is correct.

Your suggestion to make advanced quarterly payments of $1,250 will be entirely satisfactory to the Laboratory. If this is not convenient any other arrangement that you may care to make will be acceptable.

The Saranac Laboratory agrees that the results of these studies shall become the property of the contributors and that the manuscripts of any reports shall be submitted for approval of the contributors before publication.

I would recommend that the experiments be performed with pure Canadian asbestos fibre containing relatively little serpentine rock dust. The "Kings Floats" used in our first experiment was unsatisfactory owing to the fact that it contained such a high concentration of non-fibrous rock dust. If this meets with your approval I would suggest that a sample be submitted to the Laboratory for chemical and petrographic analysis.

Having mutually satisfied ourselves as to the material to be used I would request that the companies agree to supply a sufficient quantity of asbestos, ground to the finest state of subdivision possible. I am not aware whether any of the contributors have apparatus capable of reducing fibres to inhalable dimensions. If this request should not

prove practical some arrangement for its final reduction will have to be made by the Laboratory. But at least the material received by us should be broken to powder.

It is impossible to estimate the amount of material necessary for the experiments at the present time as its behavior in our dusting apparatus has never been determined. With the "Kings Floats" tests approximately 1200 pounds a year were required. It is conceivable that a pure fibrous dust might be dissipated into the atmosphere more rapidly and hence even a larger quantity would be necessary.

We are ready to start the work at any time and will be pleased to examine samples of dust as soon as they can be procured.

Thanking you for your cooperation in arranging this program, I am

With best regards,

Sincerely yours,

Leroy U. Gardner, M.D.
Director

LUG:CC

PLAINTIFF'S EXHIBIT 1906(2)

Confidential

MINUTES OF MEETING HELD JANUARY 22, 1947 AT GENERAL HEADQUARTERS TO RECEIVE AND DISCUSS REPORT OF DR. A. J. LANZA RE. THE STATUS OF DIATOMACEOUS EARTH DUST EXPERIMENTS, AS DETERMINED ON HIS RECENT TRIP TO THE SARANAC LABORATORY

Present were: A. J. Lanza
R. V. Lee
A. R. Fisher
A. P. Bloembaat
V. Brown
S. V. Hite
F. H. Armstrong
H. H. Jackson
J. E. Hamilton
J. P. Woodard

Mr. Woodard served as chairman of the meeting.

Opening

The meeting was called to order shortly after 2 P.M. in A.R. Fisher's office. No agenda had been prepared, the meeting primarily having been called for the purpose of hearing a report by Dr. A. J. Lanza, of the Metropolitan Life Insurance Company, summarizing the present status of the experiments with diatomaceous earth at the Saranac Laboratory.

The chairman dispensed with a review of the industrial hygiene problems at Lompoc which had been covered in a previous meeting, and invited Dr. Lanza to give a report of the information which he had gathered on his recent trip to the Saranac Laboratory.

Report by Dr. Lanza

Dr. Lanza reported that during his recent visit at Saranac he had had access to all the memoranda and notes left by the late Dr. Gardner, and he had talked with practically everybody there who was concerned with the work. Fortunately, Dr. Gardner had had a very capable secretary, but, unfortunately, she had worked for him only approximately one year before he died. While her own knowledge of the experiments did not go back beyond that year, she did have at her finger tips everything that had happened during the year and she was also able to provide from the files substantial information in connection with earlier experiments with asbestos.

Evidently, Dr. Gardner had planned to issue a comprehensive article on Asbestos: its effect on animals, its effect on human beings; as well as related research problems, production problems, the control of dust in different kinds of industrial plants, etc. He had practically finished the part of his report dealing with the effect of asbestos dust on human beings, and had annotated the rest of it, making rough notes and comments.

Dr. Lanza wrote to Dr. Kenneth Lynch at the Medical School in Charleston, S.C., who had been associated with the late Dr. Gardner and himself on a lot of the early work on asbestos cases, informed him of the situation as he had found it at Saranac, and, as far as being able to provide "smooth copies" was concerned, told him it had been arranged to have the late Dr. Gardner's secretary make the necessary copies and forward them. (Incidentally, the Trustees of the Trudeau Sanatorium and Foundation authorized Dr. Lanza to offer Dr. Lynch a fee of $200 to get the material in order.)

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Dr. Lanza has informed Dr. Lynch that the material will be forwarded to him as soon as it is in shape so that he will not have to try to decipher the late Mr. Gardner's handwriting; and he has received a reply to the effect that, after Dr. Lynch has had an opportunity to examine the material, he will determine whether it is possible to put it together in publishable form.

Dr. Lanza plans to leave on a trip to the West Coast about the first of February and has advised Dr. Lynch that he will arrange if possible to have the material sent to him before that time, but, should it not be ready then, it will be transmitted nevertheless during Dr. Lanza's absence.

Dr. Lanza said he would keep in touch with J-M about this, and also about what Dr. Lynch concludes he can do with the material. He stated that there was quite a lot of material and at least the basic part—that dealing with the effect of asbestos dust on human beings—seemed to be fairly complete and he believed it would make a satisfactory report.

Mr. V. Brown inquired as to whether Dr. Lanza thought Dr. Lynch would attempt to produce the entire work covering 'asbestos' which Dr. Gardner had had in mind, or whether he would concentrate only on the part dealing with the effect of asbestos dust on human beings; to which Dr. Lanza replied he did not know, since Dr. Lynch would not decide about it until after he had received the notes — but he was hoping that all of it could be put into some sort of shape.

Mr. Brown referred to the tests with asbestos which Mr. Fahnal, of the Metropolitan Life Insurance Co., had conducted at the Mines some time ago, and suggested that Dr. Lynch might make use of the information obtained from those tests, in connection with the work which he is about to undertake. Dr. Lanza agreed that this might be done.

Mr. Fisher remarked that the company has a definite job to do in Canada to offset the effects of a lot of propagandizing that has been done in relation to the harmful effects of asbestos dust, and he expressed the opinion that a report, if prepared by Dr. Lynch along the lines outlined, would be of material help to the company.

Referring to Dr. Lynch's statement to Dr. Lanza that he would see if the material sent him could be put into 'publishable' form, Mr. V. Brown called attention to a stipulation in our arrangement with the Saranac Laboratory which provided that there would be no publication of the results of experiments without our consent. He said, if it does turn out to be the sort of report we would be glad to have published, he hoped Dr. Lynch would not include any objectionable material from our point of view, as, for example, any relation between asbestos dust and cancer, such as the reference which Dr. Gardner had made to this in his monograph. He added, that even though the report contained some material that wasn't too favorable, from our point of view, we still would probably be willing to have it published because of the benefit to be gained from the balance of the report.

Dr. Lanza assured Mr. Brown that the intent of the statement in question was that any report prepared by Dr. Lynch would first be submitted to Johns-Manville before being published elsewhere.

Mr. Fisher commented that he wouldn't want to see any report on asbestos 'one thousand percent perfect'. He mentioned the eight dust cases which had been filed against the company at Asbestos during the past two or three years, all of which had been summarily thrown out, and commented upon the fact that this quick action with respect to all eight of the cases had had an adverse effect where community opinion was concerned, as the reaction had been none too good.

Mr. Woodard remarked that the ninth case, however, had turned out quite differently, since it developed that the individual involved was reported to have had lung changes and pathological changes, which had not been found in the other eight.

Dr. Lanza made the observation that very, very few deaths ever have resulted from Asbestosis as such. He referred to the large number of cases which he had followed through, years ago, and which allegedly had been caused by the inhalation of asbestos dust, but in all of which he had found the individuals had been affected by other diseases, such as cancer, Bright's disease, tuberculosis, etc., and none had died from Asbestosis uncomplicated by something else.

Getting back to the progress of the experiments at the Saranac Laboratory, he said the work is going along in good shape on everybody's projects, so far as the ground work is concerned. The technician who has charge of the dusting of animals is extremely capable and probably the equal of anybody to be found in the United States. There has been no let-up in the dusting of the animals, and after the experiments have been run for the required length of time, the animals are killed and their remains sectioned for tests. However, the services of an expert pathologist are necessary to interpret the findings, and that takes time.

Dr. Lanza paid a glowing tribute to Dr. E. E. Packard, who is now Acting Director of the Foundation, when he described as "a very sane, solid individual who 'never rocks the boat'". They had had a very competent pathologist at Saranac by the name of Berwald. During the war he had gone into the service and had finally emerged as head of research for the Navy. Dr. Lanza understood that he was going to become a permanent member of the National Research Council. Dr. Berwald had gone up to Saranac on January 17th, and was still there. Dr. Packard hoped to persuade him to resume his duties there with a title of director in charge of the laboratory. If he does, one of his jobs will be to tackle the tremendous backlog of pathological material and interpret it.

Another new man had arrived to work in the Laboratory, at the same time that Dr. Lanza visited there, and he, too, is engaged on the material. Although they have a crew of good, expert men in the Laboratory at this time—men who thoroughly know how to do the job—nevertheless, when they are through, their part of the job is finished and they can go no further. The co-ordinating head is what is missing. If Dr. Berwald consents to resume his work, it will save a lot of time and trouble that would be involved in orienting a new man. Primarily, the problem now is one of getting caught up on the huge backlog of work, and that is going to take considerable time.

Mr. Brown inquired of Dr. Lanza whether, when speaking about the dusting of animals, he referred to dusting with asbestos, or with diatomaceous earth. Dr. Lanza answered that he meant diatomaceous earth.

In connection with the experiments at Saranac with diatomaceous earth, Dr. Lanza said he had found the notes in Dr. Gardner's handwriting, apparently intended for a report to Johns-Manville. Dr. Lanza copied this material and brought it along with him. He read the copy, as follows:

> "On looking through the notes and records of Dr. Gardner, I find that there were 11 different series of experiments on experimental animals using diatomaceous earth; these included experiments with crude or raw earth, calcined earth, and fluxed calcine. Heating diatomaceous earth to 1710 degrees F. forms free silica with inversion to crystobalite. If quartz is present, there is inversion to tridimite and crystobalite.
>
> "Experiments with the calcined earth started on February 7, 1945 with 100 guinea pigs with 50 more projected with a view to supplement the information on raw earth. After visiting Lompoc, Dr. Gardner realized that the investigations would need to be more extensive than originally contemplated.

"The persistent trouble in connection with the dusting of animals with calcined diatomaceous earth was that it apparently caused them an unusual susceptibility to pneumonia and 38 guinea pigs died in the first month, and up to August, 1946, 67 guinea pigs had died from this cause. There were still surviving 11 with 14 months exposure, 14 with 7 months exposure; these to be kept as long as practicable for a study of malignant effects.

"After 10 months exposure the maximum effects of the calcined earth were no definite fibrosis in the lungs, but an unusual foreign body reaction with chronic inflammation and unlike that obtained from the raw. The changes noted in the lymphatics suggested that a fibrosis of the silicotic type would later appear.

"In January, 1946, the dust concentrations were increased without any notable change. This was done for it was thought that the danger of pneumonia was over. One hundred and fifteen more guinea pigs were added.

"Injection experiments into animals, that is, intravenous, intramuscular, intratracheal, and into the heart, were all completed some considerable time ago. In general, they show that the raw and natural earth has what Dr. Gardner called a Plus 4 Rating on his scale which goes to about 8 points (tryidimite). Also completed were the inhalation experiments with raw Celite, using guinea pigs injected also with a mild type of tubercle. No marked changes were shown from this experiment and no tendency to cause spread of disease.

"Now underway are experiments using calcined earth with intratracheal injection in guinea pigs using Hyflo. By the x-ray refraction method, this shows 24% crystobalite. This was the earth calcined with soda ash. Inhalation experiments were carried on with guinea pigs previous to exposure to tubercle infection, along with tubercle infection, and after exposure to tubercle infection. These experiments will continue for at least one more year; also inhalation experiments with Hyflo without any added infection.

"The indications are so far that Hyflo stimulates tubercle infection."

It was felt that the conclusion reached at the end, to the effect that the indications are that Hyflo stimulates tubercle infection, was rather disturbing and was the part of the report that might give us some concern. Dr. Lanza was asked for his opinion as to how much time would be required before a definite conclusion could be reached about this, and he stated that it probably would take until the end of the year; he thought the technician who has charge of the dusting of animals would have to carry on his experiments for the rest of the year, and, by the time he gets through, the pathologist will have been able to catch up with his interpretations of the slides. He added, that when he gets back from his trip to the West Coast, about the first of June, he would like to go back to Saranac, as soon as possible after that, to find out just what progress has been made.

To an inquiry from Mr. Kleinhans as to whether 'the indications are that Hyflo stimulates tubercle infection' was the late Dr. Gardner's opinion, Dr. Lanza replied that it was not, but that it was Mr. Kleinhans's impression, and that he is considered a very experienced man. Mr. Kleinhans inquired further whether there was any evidence that Dr. Gardner had reached any such conclusion himself; and Dr. Lanza answered in the negative.

Mr. Eisenbud also referred to a previous request he had made, that Mr. Lemon check, if possible, at Sarnamo on the dusting experiments with a sample of diatomaceous earth which had come from the Gerhart Refractories, which was found to contain chrysotobilite, and which had produced the results that had influenced Mr. Gardner's thinking. Lompoc has shipped natural powders to Gerhart, but has never shipped flamed calcined material to them, and inasmuch as we had never seen the particular sample of material in which Mr. Gardner first detected chrysotobilite, Mr. Eisenbud felt it was of interest to determine the source and origin of that sample. This prompted his inquiry as to whether Mr. Lemon had found any reference to it in the late Mr. Gardner's notes.

Mr. Lemon stated that while he had not been able to make a check on this sample, he thought it would not be difficult for anyone to obtain the desired information by writing to Sarnamo, as they probably could provide it from the record they keep there of numbers covering the different samples used in experiments.

Mr. Brown expressed doubt that Mr. Gardner had carried on any dusting experiment with the sample in question. The "Gerhart" sample had given him the clue and, in following up that clue, he had analyzed some Lompoc flamed calcined material and found a substantial percentage of chrysotobilite in it. He knew, then he found material with this percentage of chrysotobilite, that he had a "bad actor".

Mr. Eisenbud contended, however, that the Gerhart material—to which a man's death had been attributed, could have been a product of different properties from Hyflo, or the percentage of chrysotobilite it contained might have been greater than in Hyflo, and for this reason he believed it important to try to establish the source and origin of the Gerhart sample.

So far as Lompoc material was concerned, Mr. Eisenbud thought it should be established whether or not the physiological effect is caused by the particle size of the dust inhaled, or by the chemical make-up of the material.

Mr. Lemon observed that the asbestos product produces the effect mechanically. With materials that are chemically active, however, he said the finer they are, the more active they are. His impression was that the technician at Sarnamo takes the Hyflo powder just as he receives it from Lompoc (which is the regular commercial grade), and that it has many particle sizes in it. He promised, however, to write to Sarnamo and inquire whether it was used just as it was received, or whether any effort had been made to separate it and use different particle sizes in the dusting experiments. He added, that he believed the technician would routinely determine what the average particle sizes were.

Belief was expressed, however, that the determination of such facts would have no effect in changing the industrial hygiene problem at Lompoc or the experiments being made at Sarnamo. Both fine and coarse materials are involved in the problem affecting Lompoc, and it was felt that no further time need be lost in coming to a decision as to what must be done to control the dust situation at that plant.

Closing

Before leaving the meeting, Mr. Lemon offered his services in any capacity while on the West Coast during the next four months. He was informed of the company's desire to engage a competent Ventilation Engineer at Lompoc. He said he would keep this in mind and let Mr. Eisenbud know if he comes across an applicant whom he could recommend.

When mention was made of the text book which will deal with 'Silicosis', and on which Dr. Johnson, of Los Angeles, is presently engaged in writing, Dr. Lemon stated that he knew Dr. Johnson well and doubtless would discuss with him, at Los Angeles, his recent request that we provide for the book any material on diatomaceous earth which we know to be extant.

Dr. Brown suggested to Dr. Lemon that, should he have occasion to talk with Dr. Smart in Los Angeles, he might want to discuss with him a recent report he had made of a case where he believed diatomaceous earth had had the effect of retarding, or scaling off, the progress of tuberculosis in a certain individual who, if he had been an ordinary case, would have died at a much earlier date than he did.

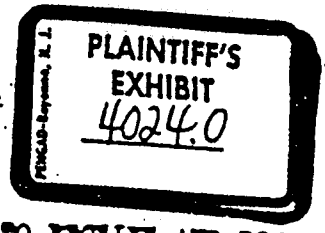
Dr. Lee said he hoped Dr. Lemon would visit Lompoc during his visit to the West Coast. Dr. Lemon assured him that he expected to; and Mr. Fisher suggested that, when he visits the plant, he sit down and talk over industrial hygiene matters personally with Mr. Vestmont, rather than with a group of five or six people. Mr. Vestmont, he said, had a more intimate and thorough knowledge and understanding of the whole problem which he could better impart in a conversation alone with Dr. Lemon than he could if a larger group were called in.

Dr. Lemon asked Mr. Hiscobest to inform Mr. Vestmont that he probably would visit Lompoc sometime during the latter part of February.

Mr. Vestmont assured Dr. Lemon that all those present felt quite relieved over the notes he had been able to obtain from Dr. Gardner's files, as well as the report he had made on the experiments in progress at Lompoc, for it now seemed apparent that the company would get practically all that it would have got had Dr. Gardner not died, except, of course, his own expert interpretation of the experiments.

J. E. Hamilton

Confidential



MINUTES OF MEETING HELD JANUARY 21, 1947 AT GENERAL HEADQUARTERS TO RECEIVE AND DISCUSS REPORT OF DR. A. J. LANZA RE. THE STATUS OF DIATOMACEOUS EARTH DUST EXPERIMENTS, AS DETERMINED ON HIS RECENT TRIP TO THE SARANAC LABORATORY



Present were:

A. J. Lanza
R. V. Lee
A. R. Fisher
A. S. Eisenbast
V. Brown
C. W. Kite
F. M. Armstrong
H. M. Jackson
J. R. Hamilton
J. P. Woodard

Mr. Woodard served as chairman of the meeting.

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The meeting was called to order shortly after 2 P.M. in A.R. Fisher's office. No agenda had been prepared, the meeting primarily having been called for the purpose of hearing a report by Dr. A. J. Lanza, of the Metropolitan Life Insurance Company, summarizing the present status of the experiments with diatomaceous earth at the Saranac Laboratory.

The chairman dispensed with a review of the industrial hygiene problems at Lompoc which had been covered in a previous meeting, and invited Dr. Lanza to give a report of the information which he had gathered on his recent trip to the Saranac Laboratory.

Report by Dr. Lanza

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Dr. Lanza reported that during his recent visit at Saranac he had had access to all the memoranda and notes left by the late Dr. Gardner, and he had talked with practically everybody there who was concerned with the work. Fortunately, Dr. Gardner had had a very capable secretary, but, unfortunately, she had worked for him only approximately one year before he died. While her own knowledge of the experiments did not go back beyond that year, she did have at her finger tips everything that had happened during the year and she was also able to provide from the files substantial information in connection with earlier experiments with asbestos.

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Mr. Woodard remarked that the ninth case, however, had turned out quite differently, since it developed that the individual involved was reported to have had lung ch

Exhibit

"One persistent trouble in connection with the dusting of animals with calcined diatomaceous earth was that it apparently caused them an unusual susceptibility to pneumonia and 38 guinea pigs died in the first month, and up to August, 1946, 67 guinea pigs had died from this cause. There were still surviving 11 with 14 months exposure, 14 with 7 months exposure; these to be kept as long as practicable for a study of maximum effects.

"After 10 months exposure the maximum effects of the calcined earth were no definite fibrosis in the lungs, but an unusual foreign body reaction with chronic inflammation and unlike that obtained from the raw. The changes noted in the lymphatics suggested that a fibrosis of the silicotic type would later appear.

"In January, 1946, the dust concentrations were increased without any notable change. This was done for it was thought that the danger of pneumonia was over. One hundred and fifteen more guinea pigs were added.

"Injection experiments into animals, that is, intravenous, intramuscular, intratracheal, and into the heart, were all completed some considerable time ago. In general, they show that the raw and natural earth has what Dr. Gardner called a Plus 4 Rating on his scale which goes to about 8 points (tridimite). Also completed were the inhalation experiments with raw Celite, using guinea pigs injected also with a mild type of tubercle. No marked changes were shown from this experiment and no tendency to cause spread of disease.

"Now underway are experiments using calcined earth with intratracheal injection in guinea pigs using Hyflo. By the x-ray refraction method, this shows 24% crystobalite. This was the earth calcined with soda ash. Inhalation experiments were carried on with guinea pigs previous to exposure to tubercle infection, along with tubercle infection, and after exposure to tubercle infection. These experiments will continue for at least one more year; also inhalation experiments with Hyflo without any added infection.

"The indications are so far that Hyflo stimulates tubercle infection."

It was felt that the conclusion reached at the end, to the effect that the indications are that Hyflo stimulates tubercle infection, was rather disturbing and was the part of the report that might give us some concern. Dr. Lanza was asked for his opinion as to how much time would be required before a definite conclusion could be reached about this, and he stated that it probably would take until the end of the year; he thought the technician who has charge of the dusting of animals would have to carry on his experiments for the rest of the year, and, by the time he gets through, the pathologist will have been able to catch up with his interpretations of the slides. He added, that when he gets back from his trip to the West Coast, about the first of June, he would like to go back to Saranac, as soon as possible after that, to find out just what progress has been made.

To an inquiry from Mr. Eisenbast as to whether 'the indications are that Hyflo stimulates tubercle infection' was the late Dr. Gardner's opinion, Dr. Lanza replied that it was not, but that it was Mr. Delehan's impression, and that he is considered a very experienced man. Mr. Eisenbast inquired further whether there was any evidence that Dr. Gardner had reached any such conclusion himself; and Dr. Lanza answered in the negative.

Mr. Elsenbast also referred to a previous request he had made, that Dr. Lanza check, if possible, at Saranac on the dusting experiments with a sample of diatomaceous earth which had come from the Corhart Refractories, which was found to contain chrystobilite, and which had produced the results that had influenced Dr. Gardner's thinking. Lompoc has shipped natural powders to Corhart, but has never shipped fluxed calcined material to them, and inasmuch as we had never seen the particular sample of material in which Dr. Gardner first detected chrystobilite, Mr. Elsenbast felt it was of interest to determine the source and origin of that sample. This prompted his inquiry as to whether Dr. Lanza had found any reference to it in the late Dr. Gardner's notes.

Dr. Lanza stated that while he had not been able to make a check on this sample, he thought it would not be difficult for anyone to obtain the desired information by writing to Saranac, as they probably could provide it from the record they keep there of numbers covering the different samples used in experiments.

Mr. Brown expressed doubt that Dr. Gardner had carried on any dusting experiment with the sample in question. The "Corhart" sample had given him the clue and, in following up that clue, he had analyzed some Lompoc fluxed calcined material and found a substantial percentage of chrystobilite in it. He knew, when he found material with this percentage of chrystobilite, that he had a "bad actor".

Mr. Elsenbast contended, however, that the Corhart material--to which a man's death had been attributed, could have been a product of different properties from Kyfle, or the percentage of chrystobilite it contained might have been greater than in Kyfle, and for this reason he believed it important to try to establish the source and origin of the Corhart sample.

So far as Lompoc material was concerned, Mr. Elsenbast thought it should be established whether or not the physiological effect is caused by the particle size of the dust inhaled, or by the chemical make-up of the material.

Dr. Lanza observed that the asbestos product produces the effect mechanically. With materials that are chemically active, however, he said the finer they are, the more active they are. His impression was that the technician at Saranac takes the Kyfle powder just as he receives it from Lompoc (which is the regular commercial grade), and that it has many particle sizes in it. He promised, however, to write to Saranac and inquire whether it was used just as it was received, or whether any effort had been made to separate it and use different particle sizes in the dusting experiments. He added, that he believed the technician would routinely determine what the average particle sizes were.

Belief was expressed, however, that the determination of such facts would have no effect in changing the industrial hygiene problem at Lompoc or the experiments being made at Saranac. Both fine and coarse materials are involved in the problem affecting Lompoc, and it was felt that no further time need be lost in coming to a decision as to what must be done to control the dust situation at that plant.

Closing

Before leaving the meeting, Dr. Lanza offered his services in any capacity while on the West Coast during the next four months. He was informed of the company's desire to engage a competent Ventilation Engineer at Lompoc. He said he would keep this in mind and let Mr. Elsenbast know if he comes across an applicant whom he could recommend.

PLAINTIFF'S EXHIBIT

00012000

When mention was made of the text book which will deal with 'Silicosis', and on which Dr. Johnson, of Los Angeles, is presently engaged in writing, Dr. Lanza stated that he knew Dr. Johnson well and doubtless would discuss with him, at Los Angeles, his recent request that we provide for the book any material on diatomaceous earth which we knew to be sound.

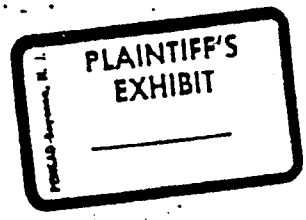
Mr. Brown suggested to Dr. Lanza that, should he have occasion to talk with Dr. Smart in Los Angeles, he might want to discuss with him a recent report he had made of a case where he believed diatomaceous earth had had the effect of retarding, or scaling off, the progress of tuberculosis in a certain individual who, if he had been an ordinary case, would have died at a much earlier date than he did.

Mr. Lee said he hoped Dr. Lanza would visit Lompoc during his visit to the West Coast. Dr. Lanza assured him that he expected to; and Mr. Fisher suggested that, when he visits the plant, he sit down and talk over industrial hygiene matters personally with Mr. Westcott, rather than with a group of five or six people. Mr. Westcott, he said, had a more intimate and thorough knowledge and understanding of the whole problem which he could better impart in a conversation alone with Dr. Lanza than he could if a larger group were called in.

Dr. Lanza asked Mr. Eisenhart to inform Mr. Westcott that he probably would visit Lompoc sometime during the latter part of February.

Mr. Woodard assured Dr. Lanza that all those present felt quite relieved over the notes he had been able to obtain from Dr. Gardner's files, as well as the report he had made on the experiments in progress at Saranac, for it now seemed apparent that the company would get practically all that it would have got had Dr. Gardner not died, except, of course, his own expert interpretation of the experiments.

J. R. Hamilton



THE SARANAC LABORATORY
OF THE EDWARD L. TRUDEAU FOUNDATION
SARANAC LAKE, N.Y.

LEROY U. GARDNER, M.D.
DIRECTOR

February 27, 1947

Kenneth M. Lynch, M.D., Dean
Medical College of State of South Carolina
Charleston, South Carolina

Dear Dr. Lynch:

Dr. Lanza has asked me to get together and send to you all pertinent material in connection with the report Dr. Gardner was preparing for Johns-Manville, and this I have attempted to do.

In one folder you will find progress reports that have been made from May 5, 1937, through February, 1943, when Dr. Gardner submitted to Johns-Manville an outline of a proposed monograph on ASBESTOSIS. Attached to the monograph are various data identified with it. I have copied from Dr. Gardner's notes his comments on papers on the subject by Dr. Gloyne and Dr. Merewether, also two outlines which may be of interest to you. There is also enclosed a draft of a paper by Dr. Gardner and Mr. Donald E. Cummings; apparently this was to follow the 1931 preliminary report referred to which was published in The Journal of Industrial Hygiene, Vol. XIII, No. 2, February, 1931 (reprint enclosed).

I have included considerable data on the susceptibility of animals to lung tumor, since this has a bearing on the ASBESTOSIS problem. Dr. Gardner intended to carry on further investigation in this connection, and undoubtedly his successor will wish to do so.

In a second folder are a number of reprints, and in a third folder, the illustrations Dr. Lanza used in his book "Silicosis and Asbestosis."

All of this material, of course, we would eventually like to have returned to us.

There are many gaps, I know, and if you will call on me from time to time as the need arises, I will try to provide any additional data which you may require.

Sincerely yours,

Lillian R. Blinn

(Mrs.) Lillian R. Blinn
Secretary to the late Dr. Gardner

CC: A. J. Lanza, M.D.

P.S. The above is being sent to you by Railway Express. Please acknowledge receipt.

KL12

Progress Reports - May 5, 1937
April 18, 1938
December 9, 1938
December 14, 1939
November 30, 1940
December 4, 1940

Proposed Monograph - February, 1943 (accompanying data)

Dr. Gardner's comments on papers by Dr. Gloyne and Dr. Marewether

Two outlines

Draft of a paper by Dr. Gardner and Mr. Donald E. Cummings.

Experimental data

February 26, 1947

Enclosures to Dr. Lynch

KL35

Public Health Bulletin No. 241 - A STUDY OF ASBESTOSIS IN THE ASBESTOS TEXTILE INDUSTRY

Special Bulletin No. 37, Commonwealth of Pennsylvania, Department of Labor and Industry, Harrisburg, Penna., October 1, 1934 - ASBESTOSIS - Part I

Special Bulletin No. 42, Commonwealth of Pennsylvania, Department of Labor and Industry, Harrisburg, Penna., September 20, 1935 - ASBESTOSIS - Part II and Part III

Reprint No. 1665 from the Public Health Reports, Vol. 50, No. 1, January 4, 1935, pp. 1 to 12 - EFFECTS OF THE INHALATION OF ASBESTOS DUST ON THE LUNGS OF ASBESTOS WORKERS

Reprint - THE FORMATION OF THE ASBESTOSIS BODY IN THE LUNG by S. Roodhouse Gloyne, M.D. (reprinted from Tubercle, June, 1931)

Reprint - THE MORBID ANATOMY AND HISTOLOGY OF ASBESTOSIS by S. Roodhouse Gloyne, M.D. (reprinted from Tubercle, July, August and September, 1933)

Reprint - A MEMORANDUM ON ASBESTOSIS by E. R. A. Merewether, M.D. (reprinted from Tubercle, November-December, 1933, January, 1934)

Booklet - THE PRODUCTION AND GRADING OF ASBESTOS by Johnson's Company, Thetford Mines, Quebec, Canada

Reprint - WARTIME OPERATIONS EMPHASIZE INDUSTRIAL HYGIENE PROBLEMS OF ASBESTOS INDUSTRY (reprinted from The Illinois Labor Bulletin, February 28, 1943 issue)

Paper - AIR SAMPLING OF ASBESTOS DUST, COMPARISON OF IMPINGER AND ELECTROSTATIC PRECIPITATOR METHODS by J. Wm. Fehnel (given before the Twenty-fourth Annual Meeting of the American Association of Industrial Physicians and Surgeons with American Conference on Occupational Diseases and Industrial Hygiene, Cleveland, Ohio, June 5-8, 1939)

Illustrations used in book "Silicosis and Asbestosis" by A. J. Lanza, M.D.

February 26, 1947

Enclosures to Dr. Lynch

KL 30

Asbestosis

March 10, 1947.

Dr. A. J. Lanza,
c/o Metropolitan Life Insurance Company,
600 Stockton Street,
San Francisco 20, Calif.

Dear Doctor Lanza:

I have received the material from Saranac but have not yet had time to even review it. I shall do that as soon as possible, in relation to the present very pressing season, and shall then let you know my thoughts on the whole proposition.

With best personal regards, I am

Sincerely yours,

Kenneth M. Lynch, M. D.,
Dean.

KML:kbp.
CC: Mrs. Lillian R. Blinn
Saranac Laboratory,
Saranac, N. Y.

KL 34

THE SARANAC LABORATORY
OF THE EDWARD L. TRUDEAU FOUNDATION
SARANAC LAKE, N.Y.

LEROY U. GARDNER, M.D.
DIRECTOR

March 18, 1947

Kenneth M. Lynch, M. D., Dean
Medical College of the State of South Carolina
Charleston 16, South Carolina

Dear Dr. Lynch:

Enclosed are copies of an exchange of letters with Mr. Vandiver Brown of the Johns-Manville Corporation, which I believe you will find entirely self-explanatory.

You have no idea how grateful we are to you for acceding to Dr. Lanza's request that you undertake to bring Dr. Gardner's notes on asbestosis into transmittible shape.

Sincerely yours,

Manfred Bowditch
Field Director

MB:AD
enc..

KL 30

THE SARANAC LABORATORY
OF THE EDWARD L. TRUDEAU FOUNDATION
SARANAC LAKE, N.Y.

LEROY U. GARDNER, M.D.
DIRECTOR

March 18, 1947

Mr. Vandiver Brown, Secretary
Johns-Manville Corporation
22 East 40th Street
New York 16, N. Y.

Dear Mr. Brown:

Thank you for your letter of March 12. I am very glad to comply with your suggestion and am doing so by sending to Dr. Lynch copies of your letter and enclosure, and of this reply.

The distinction which Dr. Gardner used to discuss with me was mainly that between fibrous and particulate asbestos dust, whereas Dr. King and his colleagues refer to long and short fibres. Just what they mean by these designations is not clear from the abstract and I find that we do not have the original paper. King was here last summer for an extended stay and I am sure that this was one of the many subjects on which he and Dr. Gardner exchanged notes, though the paper was probably submitted for publication before King left England. I am taking steps to secure a copy of the paper.

Dr. Gardner, in the notes which have been transcribed and sent to Dr. Lynch, makes the following points:

1. The English experience with regard to tuberculosis among workers exposed to asbestos dusts has not been duplicated in our American plants.

2. Fibres under 3 μ are practically inert, those between 20 and 50 μ caused typical fibrosis, while material crushed to destroy the fibrous structure is wholly inert.

3. To cause damage, the fibres must be long enough so that they cannot be completely surrounded by phagocytic cells.

4. 81.8% of mice inhaling long fibre asbestos develop lung cancer, a figure sixteen times that of the average for other dusts. 13.6% of mice inhaling short fibre asbestos develop lung cancer, a figure seven times the average for other dusts. These results are suggestive, rather than conclusive.

The above quotations from Dr. Gardner's notes are given merely for the purposes of this correspondence and should not be regarded as anything more. To what extent they may be modified, in the light of other findings, in the final report remains to be seen.

Sincerely yours,

MB:AD

Manfred Bowditch
Field Director

KL 11

METROPOLITAN LIFE INSURANCE COMPANY

ONE MADISON AVENUE, NEW YORK 10, N.Y.

ANTHONY J. LANZA, M.D.
ASSOCIATE MEDICAL DIRECTOR
HEALTH AND WELFARE

June 25, 1947

Dr. Kenneth M. Lynch
Dean, Medical College of the
State of South Carolina
Charleston 16, S. C.

Dear Dr. Lynch:

I have finally returned from my stay on the West Coast.

I am planning to go up to Saranac on July 8th for a couple of days as I am anxious to confer with Dr. Vorwald. Before I go up, I would appreciate it if you would let me know what the going is with respect to the Gardner material. Is it workable and if so, when do you think a report will be available?

With best regards.

Sincerely yours,

A. J. Lanza, M.D.
Associate Medical Director

XL 24

June 30, 1947

Dr. A. J. Lanza,
Associate Medical Director,
Metropolitan Life Insurance Co.,
1 Madison Avenue,
New York 10, New York.

Dear Mr. Lanza:

Followingour previous correspondence I received Gardner's material and as well as I could, during the extreme pressure of working on a large legislative program here, I examined it in relation to the expressed desire that some publication should be made of it, possibly even a monograph.

I came to the tentative conclusion that the more ambitious type of publication as a real monograph is questionable, but that the partially completed manuscript which Gardner left could properly be published as a final report upon the experimental program which so far as the immediate problem was concerned, had been completed.

Then I got involved in finishing up the year's effort and decided to delay my decision until I could review the question. Your letter came just as I was turning the matter over in mind again.

It appears to me that to use Gardner's material in a monograph in which the writer would have to set forth his own views and add material of his own would be neither fish nor flesh and might be foul, to use a bad paraphrase. Although Gardner's material would be used, the view point would not be his and the writer might not be able to accurately represent him, try as he might. Also the additional material necessary would not be Gardner's. In other words, to collaborate with anyone, posthumously, without that one having even contemplated it, perhaps would not be proper.

On the other hand to submit his manuscript for publication practically as he has it written, with an explanation, would be to properly represent him. He undoubtedly meant to add to the manuscript, but it is worthy as it stands.

KL 23

Dr. A. J. Lanza June 30, 1947

My present idea is that it should be sent to the same publication as Gardner's first report on this study and entitled as a final report.

Please discuss this with the people in Saranac and let me know what you think and if any decision is reached.

Sincerely yours,

Kenneth M. Lynch, M. D.,
Dean.

KML:rj.

KL 23a

-/ Ile

A. J. LANZA, M. D.
ONE MADISON AVENUE
NEW YORK

July 2, 1947

Dr. Kenneth M. Lynch
Dean, Medical College
State of South Carolina
Charleston 16, South Carolina

Dear Dr. Lynch:

I am very much obliged to you for your thoughtful letter of June 30th and quite in agreement with what you say.

I am going up to Saranac on July 8th and will spend a couple of days there during which I will have the opportunity of discussing this subject with Dr. Packard and Dr. Vorwald who has taken over as Dr. Gardner's successor. I then hope your suggestion that Dr. Gardner's manuscript be published can be accomplished within the next few months.

There is a situation here which has given me and others who are interested in the successful continuance of the Saranac Laboratory, considerable concern. It is almost ten years since various industries began making annual appropriations to the Saranac Laboatory for research in the effects of asbestos upon human beings who inhaled it. In that time, those of us who have been following what was done at Saranac and who have had the opportunity of first-hand clinical information, have learned quite a bit, but there has been no authoritative pronouncement embodying the results of the Saranac research. This state of affairs is nobody's fault, but it is quite unfortunate. During the war period, as you know, Dr. Gardner lost, through death, three of his chief assistants and could find no replacements for them. His efforts to carry on with all the added responsibilities due to these deaths, I think, were largely responsible for his own death. In the meantime, there has been quite a stirring up of activity on the part of State Industrial Commissions and similar bodies in the United States and Canada, with the result that there has been threatened legislative actions or procedures based upon assumptions as to the effects of asbestos which may or may not be correct.

All concerned are looking to Saranac for a reply to their questions and it would be an immense help to both industry and constituted authorities if they could believe that some of the fruits of Dr. Gardner's activities will soon be available.

I will write you again as soon as I return from Saranac which will be about July 11th.

With best regards, I am,

Sincerely yours,

KL 22

A. J. Lanza, M. D.

METROPOLITAN LIFE INSURANCE COMPANY
ONE MADISON AVENUE, NEW YORK 10, N.Y.

ANTHONY J. LANZA, M.D.
ASSOCIATE MEDICAL DIRECTOR
HEALTH AND WELFARE

July 14, 1947

Dr. Kenneth M. Lynch
Dean, Medical College
State of South Carolina
Charleston, 16, South Carolina

Dear Dr. Lynch:

With further reference to my letter of last week, I have just returned from a trip to Saranac where I discussed your letter of June 30th with Dr. Vorwald.

I think we are all agreed that it is desirable that as much of Dr. Gardner's material as is workable be presented at an early date. It would be best if you could give us such excerpts of material as can be presented in one article dealing with asbestos. Please let me know if this idea meets with your approval.

With best regards, I am

Sincerely yours,

A. J. Lanza, M. D.
Associate Medical Director

2 wks - 7/21

KL21

July 23, 1947.

Dr. A. J. Lanza,
Associate Medical Director,
Metropolitan Life Insurance Company,
New York, 10, N. Y.

Dear Doctor Lanza:

I am sending herewith Gardner's manuscripts as I have arranged, joined and titled them in a proposed single publication.

The experimental report is left as it was, except for the heading. Please pass judgment on the title and footnote.

His monograph outline of human asbestosis contains little if any significant material. No one else can write what he intended without it becoming the writer's instead of Gardner's.

On the other hand, the outline on experimental asbestosis is more than that. It is really a summary of Gardner's observations and is valuable and publishable as it stands. I have put a heading on that part, deleted section 1, on "Methods", and renumbered the other sections.

The whole makes somewhat of a bulky publication, but I believe that you can induce the Journal of Industrial Hygiene to take it in this form. If not, let's split it into two.

I am sending the detached Part I of the Outline also, in order that you may see what I mean.

Please consult with such others at Saranac as you should and with the Absestos people, if that is in order. Feel free to reject any idea of mine which does not seem best and criticize freely.

With best personal regards, I am

Sincerely yours,

Kenneth M. Lynch, M. D.

KML:kbp.

KL20

July 23, 1947.

P. S. I am retaining for the present the other material sent me. Can someone at Saranac reddily supply the references in the manuscript? I am a bit short on time. Should Cummings be in this?

KML.

KL20a.

C O P Y.

(From Dr. Leroy U. Gardner's OUTLINE SUMMARY OF ASBESTOSIS)

9. Complications

A. Susceptibility to Infection.

i. Tuberculous. Asbestos behaves like most other minersls in this respect not like quartz, which specifically increases native susceptibility to the tubercle bacillus. This infection may spread for a time, but then heals. The resultant fibrosis accentuates that caused by the mineral fiber.

ii. Non-tuberculous. Of no greater frequency than animals inhaling dusts of other kinds. Occasional epidemics of pneumonia occur in our dust rooms, but these are due to methods of housing rather than to dust; they also occur in unexposed animals.

iii. Cancer of Lungs. No experiments were particularly designed to elucidate this point, but certain evidence suggests that asbestosis may actually favor development of tumors in susceptible species.

a. In guinea pigs, rabbits, rats, cats and dogs, lung tumors are rare.

b. When these species were subjected to 2 to 3 years inhalation of asbestos dust, the incidence of lung tumor was not increased.

c. Some strains of white mice to develop tumors without apparent cause.

d. Such a strain of white mice was unintentionally used in three inhalation experiments with asbestos.

e. Of 11 mice inhaling long fibre asbestos for 15 to 24 months, 8 developed malignant tumors in their lungs, and 6 of them had tumors in other organs. The incidence rate, 81.8% is excessive.

KL 15a

f. Of 22 mice inhaling short fiber asbestos for not longer than 12 months, only 3 developed lung tumors. Rate 13.6%.

g. As controls, we have only the experience with mice in other dust experiments. For short periods, there were 51 mice exposed to 4 other kinds of dust for 10 to 12 months. Incidence of lung tumor 1.9%.
For long periods, there were 143 mice exposed to 4 different kinds of dust, including pure quartz, 23 to 31 months. For all this troup of mice the average incidence of lung tumor was 18.8% the highest rate (25%) was in a subgroup exposed to flint dust.

Thus the incidence of lung cancer in the long fiber asbestos mice was over 16 times the average for mice inhaling other dusts for comparable periods, and over 3 times the maximum for any other group. Mice exposed to the practically inert short fiber asbestos showed fewer lung tumors, although 7 times more than those in short exposures to other dusts.

These observations are suggestive but not conclusive evidence of a cancer stimulating action by asbestos dust. They are open to several criticisms. The strain of mice was not the same in the asbestos experiment as in many of the others cited; apparently the former were unusually susceptible. Not enough animals survived in the dust for longer than the 15 months apparently necessary to produce many tumors. There were no unexposed controls of the same strain and age and no similar controls exposed to other dusts. It is hoped that this experiment can be repeated under properly controlled conditions to determine whether asbestos actually favors cancer of the lung.

KL15 b

THE SARANAC LABORATORY
OF THE EDWARD L. TRUDEAU FOUNDATION
SARANAC LAKE, N.Y.

LEROY U. GARDNER, M.D.
DIRECTOR

August 1, 1947

Kenneth M. Lynch, M.D., Dean
Medical College of State of South Carolina
Charleston, South Carolina

Dear Doctor Lynch:

As you perhaps know, I have been released to inactive duty after five years and six months with the Navy. During the past two years of that duty I served as Director of the Medical Sciences Division of the Office of Naval Research. In that capacity my office enjoyed some correspondence with you.

Now, I have returned to Saranac Lake as Director of Research of the Trudeau Foundation and Director of The Saranac Laboratory in an attempt to discharge many of Dr. Gardner's obligations and commitments and to accomplish much of what he planned and envisioned. That task is indeed a tremendous one, yet my prewar years of association with him afford at least some background for the solution of the problems and issues confronting the Laboratory at this time.

One of the problems relates to the collation of clinical and experimental studies of asbestosis accomplished by The Saranac Laboratory. In reviewing these studies and related correspondence, I learn of your kind efforts in editing Dr. Gardner's manuscripts and recorded writings for purposes of a report and publication. This matter has been discussed with our mutual friend Dr. Lanza, who has kept the Laboratory informed by copies of correspondence pertinent to such publication. In consequence, a copy of your letter of June 30 to Dr. Lanza and his reply thereto have been forwarded to me.

I recognize your concern and appreciate the difficulty in presenting adequately the interpretations and views which Dr. Gardner recorded before his death. The manuscript which he was preparing constitutes a significant contribution. Its publication alarms me, however, lest other evidence accumulated in the past several months might have caused Dr. Gardner to revise some of the statements which he recorded at that time. In his interests and also because of the Laboratory, which must continue as a lasting memory in his honor, I know you will agree with my alarm. I am sure that Dr. Lanza would concur. Therefore, Dr. Lynch, I would appreciate your comments and views so that our action concerning the host of studies, reports and publications which we contemplate might be prepared accordingly.

KL19

We at the Laboratory would welcome you at any time should you find the opportunity to visit us.

Sincerely yours,

Arthur J. Vorwald, M.D.
Director of Research
The Edward L. Trudeau Foundation

AJV:LB

CC: Dr. Anthony J. Lanza

KL 19a

METROPOLITAN LIFE INSURANCE COMPANY
FREDERICK H. ECKER, *Chairman of the Board*
LEROY A. LINCOLN, *President*
ONE MADISON AVENUE, NEW YORK 10, N.Y.

ANTHONY J. LANZA, M.D.
ASSOCIATE MEDICAL DIRECTOR
HEALTH AND WELFARE

August 4, 1947

K. M. L.
AUG 6 194
MCL

Dr. Kenneth M. Lynch
Dean, Medical College of the
State of South Carolina
Charleston 16, South Carolina

Dear Dr. Lynch:

I am in receipt today of a copy of the letter Dr. Vorwald wrote you on August 1st. I am not too clear about the concern that Dr. Vorwald expressed. However, I note that at the end of his letter, he hopes that you might be able to pay him a visit.

I am going up to Saranac myself on August 16th. Would you consider making a trip to Saranac at any time soon, possibly we could meet there on the 15th. You can fly from New York to Saranac in about an hour and a half, which certainly takes the curse off that part of the trip. If you could find it possible to come, we would be glad to take care of all your expenses and make reservations for you.

Please do not think that I am trying to urge you to do anything for which you have no inclination and if you feel that you do not have the time to make such a trip, or that it is unnecessary, do not hesitate to say so.

I have to go to Washington on Thursday so will telephone your office Wednesday afternoon to get your reaction to this letter.

With best regards, I am,

Sincerely yours,

A. J. Lanza, M. D.
Associate Medical Director

KL16

Charleston, S. C.,
Aug. 7, 1947.

TELEGRAM - straight message.

Dr. A. J. Lanza,
Metropolitan Life Ins. Co.,
New York 10, N. Y.
(1 Madison Avenue)

ACCOUNT SCHEDULE IMPORTANT MATTERS HERE UNABLE TO LEAVE AT TIME REQUESTED. LETTER FOLLOWS.

(signed) K. M. Lynch.

KML:kbp.
10:55 A. M.

KL 10

August 7, 1947

Dr. A. J. Lanza,
Associate Medical Director,
Metropolitan Life Ins. Company,
New York 10, N. Y.

Dear Doctor Lanza:

Following your telephone call Wednesday morning, I received your letter of August 1 and I assume that you also received a letter from me which was then mailed.

Because of very pressing business here during that time, I do not feel that I can make the trip to Saranac on or about August 15. If there should remain a reason for a conference there, it is possible that I might make it sometime in September, or I might at least get to New York City for a conference there, if that may be desirable.

Like you, I am not clear as to the reasons for the concern expressed by Dr. Vorwald. However, from the copy of my letter to him which I sent to you, you may see that I think that the course to be followed should be decided by those on the ground. Without any knowledge of what is in Dr. Vorwald's mind, I still believe Gardner's material is publishable as it stands and that perhaps revision by anyone else might not truly represent him. On the other hand, if Dr. Vorwald is to carry on the work, it should be decided whether Dr. Gardner's efforts may be merged, with full credit to him.

I offer these suggestions out of a cooperative interest, and I feel that the decisions should be made by you and him and your colleagues without regard to any other consideration of my participation than that.

Incidentally, I wish to offer my congratulations and best wishes on your new connections which I have seen announced.

Sincerely yours,

KL9

Kenneth M. Lynch, M. D.,

THE SARANAC LABORATORY
OF THE EDWARD L. TRUDEAU FOUNDATION
SARANAC LAKE, N.Y.

LEROY U. GARDNER, M.D.
DIRECTOR

August 8, 1947

Kenneth M. Lynch, M.D., Dean
Medical College of the
State of South Carolina
Charleston 16, S.C.

Dear Doctor Lynch:

I appreciate the expression of your opinion as recorded in your letter of August 4 apropos the work accomplished by Dr. Gardner during his many years of research in the interest of asbestosis.

All of us recognize the high degree of relative urgency regarding the correlation of our experimental and clinical studies for the purpose of a report for the sponsoring industries and for publication. Every effort will be made toward an early accomplishment in that regard. I will appreciate your continued counsel and advice concerning it, so that in final analysis the contribution will be a creditable and lasting record in the memory of Dr. Gardner.

Your letter of July 30 and the manuscript which you enclosed have been forwarded to me by Dr. Lanza. He will be in Saranac Lake on Saturday, August 16, and I will discuss the matter with him at that time. Please know, Dr. Lynch, that the Laboratory would be honored should you collaborate in the final publication. This point will certainly be considered at the time of discussion with Dr. Lanza.

With sincere good wishes,

Cordially yours,

Arthur J. Vorwald, M.D.
Director of Research
The Edward L. Trudeau Foundation

AJV:LB
CC: Anthony J. Lanza, M.D.

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ABSTRACT

Asbestosis is a pulmonary disease caused by the inhalation of asbestos dust. In animals it is characterized by a peribronchiolar fibrosis which seems to be the result of mechanical, rather than chemical, irritation of the tissue by asbestos fibers. Only the long fibers produce a typical reaction; short fibers are relatively inert. The filamented structure of the fibers is an essential factor in the mechanism of irritation; a characteristic tissue response can be produced by non-siliceous as well as siliceous fibrous minerals. Inhalation of asbestos dust apparently does not alter significantly the course of experimental tuberculosis in guinea pigs. The asbestosis body, which is a specific concomitant of asbestosis and forms soon after the entrance of the asbestos fiber into the lung, is believed to prevent further damage to the tissue by the fiber and thus to limit progression of the reaction when exposure ceases. Aluminum does not exert a protective action against the tissue irritation of asbestos fibers as it does against that of quartz particles.

EXPERIMENTAL STUDIES OF ASBESTOSIS

2. Introduction

Asbestosis is a form of pneumoconicsis resulting from prolonged inhalation of asbestos dust. The name asbestos, literally "unburnable," is not that of a particular mineral but is a term applied to a number of different minerals whose characteristic feature is a structure composed of long, parallel, flexible fibers. This structure is unique because the fibers are capable of repeated longitudinal subdivision to units of molecular proportions. In length the fibers vary from a few microns to six or more inches. Some varieties are stiffer than others but many are sufficiently flexible to be spun into yarn and woven on modified textile machinery.

3. Asbestos Minerals

The asbestos minerals are silicates of variable composition and belong to the serpentine and the amphibole groups. Listed below are the more common varieties.

Amphibole Group	
Anthophyllite	(Mg, Fe) silicate
Amosite	(Mg, Fe, Al) silicate
Amphibole	(Ca, Mg, Fe, Al, Na, K) silicate
Tremolite	(Ca, Mg) silicate
Actinolite	(Ca, Mg, Fe) silicate
Crocidolite	(Na, Fe) silicate + Fe silicate
Serpentine Group	
Chrysotile	Mg silicate (hydrous)

The bulk of the asbestos of commerce is chrysotile, $3MgO.2SiO_2.2H_2O$, which is mined in the Thetford region of the Province of Quebec. Crocidolite and amosite are also used commercially but in much smaller amounts. Chrysotile occurs as veins in serpentine, a mineral similar in chemical composition to chrysotile but which exists in massive form and is made up of microscopic fibers without the parallel orientation characteristic of chrysotile. The massive blue black serpentine, which is smooth and soapy to the touch, is traversed by veins of fibrous chrysotile varying in width from a barely perceptible line to six or more inches. The fibers run across the vein and not lengthwise with the formation.

Attention is directed to the mineral brucite, $MgO.H_2O$, which is often found in the same formations with serpentine and chrysotile and may be fibrous in structure. It has no commercial value at present because its fibers are not sufficiently flexible to be used in textiles but they are capable of repeated longitudinal subdivision. Unlike other asbestiform minerals, brucite is not a silicate and for this reason it has been a valuable tool in an experimental evaluation of the action of fibrous minerals upon lung tissue.

IV. EXPERIMENTAL ASBESTOSIS

For many years studies have been carried on by the Saranac Laboratory in an investigation of the cause, nature and development of asbestosis. The present report is devoted to Experimental Asbestosis. In it are described the animal experiments with various kinds of asbestos dust. Another report, to be prepared and issued later, will be concerned with human Asbestosis and will cover the health aspects of workers who have been exposed to asbestos dust in an industrial environment.

Although asbestosis in man is a chronic disease which requires years to develop, it is possible to reproduce in one or more species of animal characteristic tissue changes which are similar to the lesions of human asbestosis. Since the life-span of the experimental animal is relatively short, it is not possible to develop the characteristic lesions in animals under the usual ~~industrial~~ conditions. Consequently, to obtain a complete evaluation of the tissue response to inhaled particulate and fibrous material, it is necessary to accelerate the reaction by employing higher concentrations of dust than would ordinarily be encountered in industry. While conditions of exposure are thus different, the information yielded by experiments with animals is invaluable in furnishing a better understanding of the reaction of the human organism to inhaled asbestos dust.

5. Experimental Methods

For investigating the biological reaction of the experimental animal to the various asbestos minerals, two types of technique have been employed, namely, the inhalation method and the injection method. In inhalation experiments, groups of animals - up to 100 or more guinea pigs and sometimes smaller numbers of rabbits, cats, dogs, rats or mice - are kept for eight hours a day in a cubical dust room, eight feet in dimension, in which a cloud of asbestos dust is maintained. At intervals during the experiment, a few animals are sacrificed and the tissue examined to determine the nature and extent of the dust reaction. Some animals are exposed for periods up to three years. The injection experiments, in which the dust, either dry or suspended in fluid, is introduced into the animal by the intravenous, intraperitoneal or intratracheal procedure, are used to determine whether or not a particular dust has a potential capacity to produce tissue reaction.

Long-term inhalation experiments furnish information upon which great reliance is placed when estimating the degree to which a dust might be hazardous to industrial workers. Whether or not atmospheric dust, even though potentially dangerous, can be inhaled, pass the natural defense barriers and reach the pulmonary tissue in quantities sufficient to cause damage can be determined only by inhalation procedures. Injection experiments are useful because in them contact between the dust particles and tissues is assured and the potential capacity of the dust to produce reaction can be estimated accurately. When dealing with fibrous minerals like asbestos, the intratracheal method is valuable since it permits observing the effect of the fibers on pulmonary tissue.

6. Species Susceptibility

Unlike free silica, asbestos does not exert its specific effect in all organs of all species of animal (Table 1). Injection of fine quartz into various organs of the guinea pig, rabbit, rat, mouse, cat, dog, chicken and even tadpole will produce silicotic nodules. However, similar injections of long or short fiber asbestos have resulted in a fibrous reaction in the lung and, to a lesser extent, in the peritoneum but not in other organs of the guinea pig, rabbit, cat and white rat. The dog and white mouse failed to respond. This variation in species is yet to be accounted for.

7. Peculiar Characteristics of Asbestos

Experience has demonstrated that most of the particulate matter inhaled into the lungs of man and animal is 10 microns or less in maximum diameter. Larger particles apparently are excluded by the protective mechanism of the upper respiratory tract. In the case of fibrous materials, however, this restriction does not apply and fibers 100 and even 200 microns in length have been found in the terminal air spaces of human lungs. In small laboratory animals exposed to asbestos dust the maximum length of fiber found in the lung rarely exceeds 60 microns. Not every kind of fibrous material is inhaled with equal readiness; for example,

the synthetic fibers of glass wool apparently are too inflexible to pass easily through the nose, pharynx, trachea and bronchi and seldom reach the terminal bronchioles and alveoli.

Inhaled particulate matter comes to rest throughout the terminal air spaces (alveolar duct, atria, alveoli) in all parts of the lungs; inhaled asbestos fibers are first retained in the respiratory bronchioles. These very small tubes are immediately distal to bronchioles lined by ciliated epithelium. Their own essential lining is a low cuboidal type of epithelium but, as their name implies, they actually function in respiration through lateral alveoli given off as pouches along their walls. Either these pouches, or the abrupt change in the character of the lining epithelium, or the decrease in diameter of the tube, or perhaps the combination of all three factors is responsible for local retention of the inhaled fiber. Only after asbestosis is well established are appreciable numbers of fibers carried into the more peripheral air spaces.

8. Rate of Tissue Reaction to Asbestos Fibers

The rate of tissue reaction to asbestos is much more rapid than to an active dust like quartz. Evidences of tissue response appear as soon as fibers have localized in sufficient concentration in specific areas. In rats receiving asbestos fibers by intratracheal injection this evidence is visible as early as two weeks after injection; for quartz dust the latent period might be two months or more.

The behavior of the tissue reaction to inhaled dust after the termination of exposure is not the same in silicosis as in asbestosis. In silicosis, the young nodules become larger; in asbestosis, young scar tissue, that may have formed, contracts and becomes more dense but the area of involvement decreases in size. If exposure to asbestos dust is terminated after a brief period, the recently-inhaled

fibers in the lung may cause the fibrous tissue response to continue for a short time, until the fibers have been coated. This progression is of only a slight degree and of little significance.

9. Asbestosis Bodies

The peculiar structure known as the asbestosis body or curious body is a specific concomitant of asbestosis. The typical body is a golden-yellow, beaded or haustrated rod which may be either straight or curved. Often one or both ends are bulbous like a dumb-bell. The bodies vary considerably in length, and dimensions up to 250 microns have been recorded.

It is believed that asbestosis bodies are due to a deposit of protein and iron pigment upon the surface of inhaled fibers. In guinea pigs they form after about 60 days of contact with the tissue. They are abundant in man and the guinea pig (see Table 1) but are much larger in the former, probably because the larger-sized air tubes admit fibers of greater dimension. In cats, rabbits and mice there is an atypical coating of a few of the fibers after much longer residence in the lungs. In rats and dogs no bodies could be discovered. Although the evidence is incomplete, it appears that the formation of the asbestosis body prevents damage to the tissue by the fiber.

X. INHALATION EXPERIMENTS

Four comprehensive inhalation experiments have been conducted at the Saranac Laboratory with various forms of asbestos dust. In each of these investigations more than 160 animals were used and the experiments were carried on for periods ranging from 2 to more than 5 years. The four kinds of asbestos dust employed are identified as King's floats, short fiber, 100 per cent ball-milled, and long-fiber asbestos dust.

XI INHALATION EXPERIMENTS

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12. Inhalation Experiment with "King's Floats" Asbestos Dust

The first inhalation experiment conducted at the Saranac Laboratory with asbestos dust was begun in 1928. Animals inhaled the dust for periods up to nearly three years and some guinea pigs lived for about four years after their first exposure to dust. A preliminary report giving observations after 29 months of exposure appeared in the February, 1931 issue of THE JOURNAL OF INDUSTRIAL HYGIENE.* At that time observations covered a period of only 2-1/4 years and the conclusions as to the ultimate effects of inhaled asbestos dust were provisional. Results of the completed study show that most of the conclusions drawn in the preliminary report were substantiated. A complete review of this experiment follows.

12. The dusting material was a commercial variety of asbestos dust known as King's floats and was composed of short fibers and particles of variable size. It was obtained from the Thetford, Quebec plant of the Asbestos Corporation of America.

13. The dust composition (Table 2) reveals that the amount of fibrous chrysotile was only 14 per cent, a rather low value. However, there was sufficient fibrous material to produce a characteristic fibrosis.

14. The dust concentration at first was quite low and for impinger samples taken soon after the experiment was started, the average light field count by the standard technique was only 6.0 million particles per cubic foot of air. An appreciable number of large particles (or fibers) also were present, as

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*STUDIES ON EXPERIMENTAL PNEUMOCONIOSIS. VI. Inhalation of Asbestos Dust., Gardner, L.U., and Cummings, D.E. J. Ind. Hyg., 13: 65-81, 97-114, 1931.

shown by an average count of 0.6 million for particles greater than 10 microns. After the inhalation experiment had been under way for about two years, the speed of the rotating paddle in the dusting machine was increased and for the remaining 9 or 10 months of the experiment considerably more dust was dispersed into the atmosphere. Average dust counts for impinger samples collected after this change were 53.7 million for the usual light-field method, and 1.6 million for particles larger than 10 microns.

15. Reaction in Animals to Inhaled "King's Floats" Asbestos Dust. Results of the investigation, briefly summarized in Table 3, show that inhalation of King's floats asbestos dust produced a typical peribronchiolar fibrosis in guinea pigs but not in rabbits or rats.

16. Guinea Pigs. Seven groups of guinea pigs were used. In three groups the effect of a continuous and of an interrupted dust exposure was studied; in two other groups the relationship between infection and dust exposure was investigated. The remaining two groups were infection controls.

17. Rate and Type of Reaction. Guinea pigs inhaling this dust for periods up to 33 months developed a characteristic fibrosis occurring in conical patches about the respiratory bronchioles. During this exposure the peripheral alveoli were not involved. The particulate elements in the dust were transported to the lymphatic system where they caused no significant reaction; the fibrous elements remained fixed at the site of original localization and were seldom detected in the lymphoid tissue. Pleurisy and fibrosis in the septa were observed only when infection complicated the process.

After exposure of approximately a year, a small amount of cellular reaction had been produced about many respiratory bronchioles. As more dust was inhaled, it continued to accumulate in the same location and later stages of the disease

consisted of extensions of the original lesions. New areas were not involved.

Apparently, the inhaled fibers were caught in the pocket-like alveoli that are given off from the lateral walls of the respiratory bronchioles. There they were phagocytized and many of them were carried into the wall by migratory cells. Mononuclear leucocytes attracted to the area caused an appreciable thickening of the bronchial wall. After 16 months a delicate fibrosis made its appearance. The process evolved so gradually that mitotic division of fibroblasts could rarely be discovered; nevertheless, the number of fine intercellular collagenous fibers (fibrosis) steadily increased. As this fibrosis contracted, it partially closed the alveoli, and with this atelectasis the lining epithelium assumed its embryonic cuboidal form. The result was the adenoma-like appearance that Willis described in guinea pigs inhaling silicon carbide. The longer exposures resulted only in more thickening of the walls of the air spaces, largely due to an increase in the amount of fibrosis. The fibrous tissue always remained cellular and never showed the hyalinization characteristic of silicosis.

18. Progression. The reaction produced in exposed guinea pigs did not progress significantly during a subsequent period of 37 months when the animals lived in a normal atmosphere. Between 8 and 11 months after exposure ceased, the cellular reaction had been completely replaced by thin strands of fibrous tissue. Observed still longer, the scar tissue decreased in amount but in the last animal sacrificed, 37 months after discontinuing dust exposure, some fibrosis was still visible.

19. Infection Coincident with Dust Inhalation. Of the group of 40 guinea pigs infected with attenuated tubercle bacilli (R_1 strain) 31 died or were sacrificed before two years of dust exposure and were reported in the paper by Gardner and Cummings mentioned

above. Seventeen of these died from intercurrent pneumonia. Briefly, the results were as follows: 10 revealed some evidence of spread of the tuberculous process; in 6 of these it was confined to the lungs and in the other 4 the abdominal viscera also were involved. Usually a slight local extension of the tuberculous infection had occurred but subsequent healing had resulted in fibrosis of both the pulmonary lesions and the secondary lesions in other organs. The healed pulmonary lesions showed more fibrosis than is characteristic of either tuberculosis or asbestosis alone.

The 9 animals which were still alive after two years of dust exposure were sacrificed at intervals during the following year. In 4 of them the primary foci of infection had healed with fibrosis and even calcification and there was no evidence of progression. In the other 5 the tuberculous foci showed evidence of having previously spread locally: in 4 of them it had healed, by the time of autopsy, with excessive fibrosis; in the other animal there was a generalized chronic tuberculous pneumonia in one lobe and isolated primary tubercles, which were still active but had not spread in the other lobes.

Evidence of extension of the infection was first seen after 7 months of dust inhalation; during the next 20 months more than half of the animals showed an actively spreading tuberculosis and in 3 of them small cavities had developed. During the last 8 months no animals exhibited any evidence of active infection although in half of them the healed fibrous scars of previous extensions were obvious. Sixty per cent of the guinea pigs with spreading pulmonary tuberculosis showed tuberculosis of the spleen and liver.

20. Infection Superimposed Upon an Established Asbestosis. Twelve guinea pigs, after inhaling asbestos dust for nearly 26 months, were infected with tubercle bacilli and then removed to normal air. The subpleural tubercles in the dusted animals were

no more numerous than in non-dusted controls, but a considerable number were found in the depths of the lung about foci of asbestosis. The reaction to infection showed only slight local extension about the original sites in the lungs and tracheobronchial lymph nodes. The abdominal viscera were involved in only one animal. Caseation was found in tubercles 1-1/2 months old but by 5-1/2 months it had completely disappeared, leaving only scar tissue. The latter still persisted in the last animal, which was killed 14 months after infection.

21. Asbestosis Bodies. Moderate numbers of asbestosis bodies occurred in the lungs of the guinea pigs, becoming more numerous and more distinctly segmented in later months.

22. Rabbits. Rabbits exposed to the asbestos dust for periods up to 19 months developed a low-grade foreign-body type of reaction but no fibrosis. Although their lungs contained particulate elements of the dust, fibers were not present, indicating that the upper respiratory mechanism of the rabbit is adequate to exclude fibrous foreign bodies. Two rabbits, after inhaling dust for 6 and 18 months, lived in normal air for more than two years. At autopsy neither animal showed any evidence of cellular reaction or fibrosis in the terminal bronchioles nor were there any asbestosis bodies.

23. Rats. All the white rats had acquired an infection, resulting in the formation of pulmonary abscesses, before they came to autopsy. Apparently, so much heavy mucus obstructed their bronchi that very few fibers could have entered their lungs. In a few of the rats, an occasional asbestosis body was discovered but there was no fibrosis.

2b. Summary and Interpretation of Inhalation Experiment with King's Floats Dust.

The findings in the experiment with King's floats dust can be summarized under three headings.

A. Effect of the inhaled dust on normal animals. The King's floats dust caused a characteristic peribronchiolar fibrosis in guinea pigs but not in rabbits or rats. The fibrosis did not progress after the dust exposure was discontinued and the guinea pigs transferred to normal air.

B. Effect of the inhaled dust on tuberculosis in guinea pigs. In guinea pigs infected with attenuated tubercle bacilli and then placed in the dust room, the results were more variable than is usual in an experiment of this type. A few animals showed no sign of progression; in most of them there was evidence of temporary progression with subsequent healing; in one animal there was continuous progression to death. In contrast, when guinea pigs, after being infected, are exposed to quartz instead of asbestos dust, the infectious process continues to progress and eventually causes the death of the animals. On the other hand, exposure of infected animals to a harmless dust like calcite or gypsum does not lead to any progression of the infection. Guinea pigs infected with attenuated tubercle bacilli following the termination of about two years' exposure to asbestos dust did not develop progressive disease. The only modification of the infection was in its localization, a few bacilli being retained in the fibrous terminal bronchioles and forming tubercles there in addition to the usual foci beneath the pleura.

In view of this variability, the unusual nature of the response and the high proportion of deaths from intercurrent pneumonia it is felt that definite conclusions as to the influence of ~~this dust~~ asbestos on the course of tuberculous infection are not justified.

C. Effect of tuberculous infection on the reaction to inhaled dust.

Infection complicating asbestosis accentuated the tendency of the dust to produce fibrous tissue. This change occurred whether or not the bacterial lesion was in contact with the area of dust reaction.

XXV INHALATION etc

25. Inhalation Experiment with Short-fiber Asbestos Dust.

Since hazardous dusts like quartz are most effective in producing fibrosis when the particles are 3 microns and less in size, an inhalation experiment was carried on to determine whether this condition is true also for asbestos dust. It was thought that by using a short-fiber asbestos dust consisting almost entirely of fibers and particles smaller than 3 microns an accelerated tissue response might be initiated and an advanced reaction obtained in a short time. The previous inhalation experiment with King's floats asbestos, which contained fibers from 1 mm. to 1 micron or less in length as well as a great deal of particulate matter and which produced a typical peribronchiolar fibrosis in exposed guinea pigs, served as a basis of comparison.

26. The dusting material for this experiment was forwarded from the Manville plant of the Johns-Manville Corporation. It was the remains of fibers collected in dust bins after a carding operation and screened to pass 200 mesh. Since the material as received contained many long fibers, it was ground in a steel ball mill to reduce practically all the particles to 3 microns or less in size. When used alone in a standard dusting machine, this finely-ground asbestos tended to pack in the hopper and it became necessary to mix one volume of the unground material with three volumes of the ground to generate a satisfactory dust cloud. The addition of the small quantity of unground asbestos was unfortunate because it confused the interpretation of results. Probably the minor amount of reaction that developed was due to the long fibers in the mixture although the

data of this experiment do not prove the point.

27. The composition of the short-fiber asbestos as received is disclosed by the chemical and petrographic analyses given in Table 4. Samples taken before and after grinding yielded about the same values on analyses, indicating that there was no contamination from the mill or loss of water content.

28. The dust concentration varied somewhat during the experiment and light field counts for atmospheric samples collected inside the animal cages with the impinger apparatus ranged from 83 million to 182 million. The average of counts was 130 million for the first year of the experiment, 134 million for the second year and 140 million for the third year.

29. Size-frequency measurements of air-floated dust from inside the cages at a magnification of 1300X revealed a great preponderance of fine particles (Table 5). Nearly 90 per cent of the particles seen were smaller than 3 microns.

30. Reaction in Animals to Inhaled Short-Fiber Asbestos Dust. Four species of animals - guinea pigs, white rats, cats and rabbits - were used in this experiment. The results of the dust exposure, which are summarized in Table 6, will be considered more in detail below.

31. Guinea Pigs. Eighty guinea pigs were originally placed in the dust room but 21 of them were later eliminated from the experiment and killed because of enlarged lymph nodes. Of the other 59 animals, 46 remained in the dust room until they were sacrificed or died from natural causes and 13, after being exposed to dust for 20 months, were transferred to a normal atmosphere.

32. Rate and Type of Reaction. The type of tissue reaction to the inhaled

short-fiber asbestos was essentially the same as that already observed in the experiment with King's floats asbestos. The rate of reaction also was approximately the same but the extent of involvement with the short-fiber dust was very much less and after 16 to 24 months of exposure only a very few small foci of reaction, which generally required microscopic examination for detection, were produced in the guinea pigs.

Until exposures had continued for approximately one year, there was little tendency for dust-containing phagocytes to collect into clumps. By 16 months phagocytes had begun to collect about the walls of a few of the respiratory bronchioles with a little proliferation or infiltration of mononuclear cells in these walls. There were also some multinucleated cells but they were always of the inert foreign-body type. At 20 to 24 months the cellular clumps were sometimes quite marked and sometimes changes in the epithelium resulted in the adenoma-like or "adenomatoid" appearance previously described in Section 17. In most of the subsequent members of the series, the reaction remained cellular in type. In a few, however, fibrous elements dominated the picture. In the latter case, the collagen was pale in color and tenuous with no heavy swollen hyalinization. As in the rats described below, the alveolar walls might be made up of a band of collagen supporting a layer of epithelium, but with no contained capillaries. In the tracheobronchial lymph nodes the reaction was more pronounced in this experiment than in the previous one with King's floats asbestos, probably because of the transportation of an excess of fine particles to the nodes in animals inhaling short-fiber asbestos. The reaction was essentially an increase in reticulum, rather than a fibrosis, with preservation of the original cells between the thickened reticular fibers. Diffuse chronic pleurisy without evidence of pulmonary infection was present in a few animals.

33. Progression. In the 13-3/4 months following the cessation of 20 months' exposure to dust, progression of disease was not definitely demonstrated but neither could it be absolutely disproved, owing to the variability of the response in different animals. At the end of the dust exposure of 20 months two pigs were read as + and one as 2+. Among the 13 removed from dust the findings were variable: in 2 the reaction was ±; in 4 it was +; in 3 it was 3+; in 3 it was 4+; and in one animal it was 5+. It is quite possible that those with the most marked changes had already developed more reaction than the remainder by the time exposure ceased. Since the more severe reactions occurred sporadically and bore no relationship to the length of time after cessation of exposure the differences were attributed to variation in individual susceptibility. This view received support from the chemical analyses (Table 7), which often revealed comparable amounts of ash and silica in lungs with widely different amounts of tissue change. For example, the ash and silica values were quite similar for three animals in dust 20 months and then in normal air 13-3/4 months, yet the tissue reaction for one animal was 4+; for another, +; and for the third, only ±.

34. Asbestosis Bodies. The formation of asbestosis bodies was at first extremely limited. After 5 months' exposure only a very rare short body could be found, usually inside of cells. Around the finest intracellular particles there were yellow deposits having the same color as the asbestosis body. Exposure of one year had permitted an accumulation of many longer fibers about which the asbestosis-body coating developed. Most of these were still short enough to be partially or entirely within phagocytic cells. By the 20th month and thereafter, they were comparatively numerous although still rare in comparison with the findings in the King's floats experiment.

35. White Rats. Seventy-three white rats were exposed to atmospheric short-fiber asbestos dust for periods up to 32 months. Sacrificings during the first 10 months were made bimonthly and for the remainder of the experiment at less frequent intervals.

36. Rate and Type of Reaction. The dust cells until 8 months were widely scattered and existed in foci only sporadically. Reaction was limited to occasional slight thickenings of the septa about small accumulations of dust cells. In a few rats at 10 months, there was a suggestion of early fibrosis but the change was so slight that it would probably be overlooked without the clump of dust cells to attract attention to the area. Only 10 animals were exposed from 12 to 32 months. In each of them the lungs showed minute patches of well-defined fibrosis distributed like that of asbestosis but without asbestosis bodies. The lesions, visible only at a magnification of 150 diameters or more, consisted of patches along alveolar ducts in which the walls of the air spaces were very thick, due to swollen collagen framework. Connective tissue and Foot-Bielschowski silver preparations revealed complete loss of capillary bed locally. Outside the collagen was a thin layer of epithelial cells. This did not resemble the "adenomatoid" change characteristic of guinea pig asbestosis. No pleurisy was present. Near the lesions the air spaces were filled with phagocytes containing gray to yellow particulate dust and a rare long naked asbestos fiber. Careful search failed to reveal even a suggestion of an asbestosis body. The tracheobronchial nodes showed compact focal collections of monocytic cells at 12 months and, at 20 months, some diffuse thickening of the reticulum. In a few rats there was definite fibrosis along the margins of the node and extending into the mediastinal areolar tissue. Compared with the response to active dusts like quartz and chert the reaction to short-fiber asbestos was negligible.

Results of chemical analyses made on the white rats are given in Table 8 and the average values have been tabulated in Table 9 for comparison with similar values for rats inhaling other dusts. The concentration of atmospheric particles to which the animals were exposed was approximately the same for asbestos and quartz; for the gypsum-quartz mixture, it was about twice as high and for chert five times as high. It will be noted that the percentages for asbestos are lower than those for quartz or chert but are similar to those for the gypsum-quartz mixture, in which atmospheric agglutination tended to reduce the amount of dust inhaled. It might be inferred that the total quantity of asbestos dust inhaled was low or that it had been eliminated from or dissolved within the lungs. In the present state of our knowledge evaluation of these hypotheses is not possible.

37. Cats. Twenty cats were used in this inhalation experiment with the short-fiber asbestos. Eighteen were kept in the dust room until death, the exposure period ranging from one month to nearly 4-1/2 years, and two, after a dust exposure of 31-1/2 months, were removed to normal air. One of these was sacrificed 5 months, and the other 24 months, later.

38. Rate and Type of Reaction. The reaction was essentially that to an inert dust, even after more than 4 years of exposure. The tissue response in this species was confined to microscopic foci of fibrosis in the walls of groups of subpleural alveoli, rather than in the peribronchiolar areas. In one animal the change was extensive enough to be visualized on gross inspection of the section.

39. X-Ray Changes. Only in the animal with the longest exposure did the X-ray reveal definitely abnormal shadows. After 29-3/4 months the picture was negative; after 45 months a faint mottling could be detected throughout both lungs. At autopsy, 3 months later, there was only microscopic

fibrosis in the subpleural zone plus heavy lymphocytic infiltration about small bronchioles.

40. Asbestosis Bodies. On prolonged search a few yellow atypical asbestosis bodies, smooth and without haustrations, were found in two animals exposed for more than a year.

41. Rabbits. Eight rabbits were exposed to dust for periods extending from one to more than five years. The last animal was removed from the dust room and left in normal air 6 months before being sacrificed.

42. Rate and Type of Reaction. There was never enough fibrosis to be detected grossly and there was no chronic adhesive pleurisy. Microscopic evidence of alveolar wall thickening was first detected after about 3 years of exposure and was seen in all five animals examined thereafter. In one animal that died of paralysis after nearly four years of exposure the reaction was extensive enough to be visible on gross inspection of tissue sections. The possibility of pulmonary infection in this animal could not be excluded. However, in another animal dying two years later the focal fibrosis was not nearly as obvious or as advanced. Areas of involvement, which were largely visualized because of phagocytic reaction within the air spaces, tended microscopically to become more fibrous with the passage of time but there was never much encroachment upon the lumen of air spaces and the architecture of the lung was preserved.

43. Asbestosis Bodies. Asbestos bodies were not detected in rabbits that died early in the experiment but were seen in all animals that had been exposed to the dust for more than three years.

44. Summary and Interpretation.

The original purpose of the experiment was to evaluate the chemical theory of the pathogenesis of asbestosis. It was felt that if the tissue reaction to asbestos were chemical in origin an accelerated or accentuated response would result from exposure to finely-divided asbestos, as is the case with quartz. This experiment, in which the reaction was slower and less extensive than with King's floats, indicates that the reaction ~~probably~~ is not primarily chemical in nature.

Of the four species exposed in this experiment only the guinea pig and rat reacted with characteristic peribronchiolar fibrosis. The cat reacted with atypical sub-pleural fibrosis and in the rabbit the fibrosis which occurred could not be positively attributed to the dust because of a strong possibility of pulmonary infection.

XLV INHALATION. etc

~~45.~~ Inhalation Experiment with 100 Per Cent Ball-Milled Asbestos Dust.

In the inhalation experiment with short-fiber asbestos dust a small quantity of unground asbestos was mixed with ground material in order to produce a suitable dust cloud. When evidence of a dust reaction appeared in the guinea pigs during the experiment, it was not clear whether this was a tissue response to the small number of long fibers in the unground asbestos or was a delayed effect of the more abundant fine dust. Consequently, another inhalation experiment was started in which no unground material was used.

46. The dusting material was the ground short-fiber asbestos used in the previous inhalation experiment but no unground material was mixed with it. To obtain a sufficient amount of atmospheric dust, the design of the dusting apparatus was changed to an open type of hopper and fresh dust was added daily.

Owing to the tendency of the material to form small spherules which prevented much of the fibrous portion from floating out of the hopper, the dispersal of the dust was not entirely satisfactory and after 7 months of operation, the dusting machine was reconverted to its original design. To prevent "pilling" or the formation of spherules of asbestos, steel wire brushes were attached to the inside surface of the hopper and to the rotating paddle. This arrangement gave satisfactory results and was used for the remaining 21 months of the experiment.

47. The composition of the raw material (short-fiber asbestos) and of atmospheric dust liberated from the ball-milled product in the dusting machine is given in Table 10. These values are based upon petrographic study and X-ray diffraction analysis. The atmospheric sample was collected with an electrostatic precipitator after wire brushes had been installed in the dusting machine. Previous to this, the chrysotile content of the air-suspended material was undoubtedly less than the 15 per cent value given in Table 10. In an interim report, it was stated that the air-borne dust contained about 5 per cent of chrysotile before the wire brushes were used and up to 8 per cent afterwards, but these values were probably low. Quantitative estimates on ball-milled asbestos dust may be somewhat inaccurate because it is difficult to determine how much of a dust sample is fibrous chrysotile and how much is non-fibrous serpentine.

48. The dust concentration for the first 7 months of the experiment was about 100 million particles per cubic foot of air. After the wire brushes had been installed, the dust counts were a little higher and the overall average for the first year was 106 million. The average of counts for the second year was 163 million and for the third year 145 million.

49. The size-frequency of the components of atmospheric dust collected inside the animal cages with the electrostatic apparatus is reported in Table 11. Two samples were taken, one before the wire brushes were installed and one after. It will be noted that after the wire brushes were in use a greater proportion of very fine particles and also of longer fibers was released into the air.

50. Reaction in Animals to Inhaled 100 Per Cent Ball-Milled Asbestos Dust. Guinea pigs, rats and mice were used in the inhalation experiment with the 100 per cent ball-milled asbestos dust. The results are summarized in Table 12.

51. Guinea Pigs. The experiment was started with 100 guinea pigs. As the dust exposure proceeded, there were 39 accidental deaths, 32 of pneumonia in an epidemic. After 28 months of dusting the 16 surviving guinea pigs were transferred to normal air.

52. Rate and Type of Reaction. For the first year of exposure practically the only reaction to the dust was the presence of scattered phagocytes and an occasional minute asbestosis body. At 16 and 20 months no gross response was visible on the tissue section but microscopically peribronchiolar foci of inflammatory cells could be seen. At 24 months there was still no change large enough to be seen with a hand lens although microscopic examination revealed cellular accumulations about terminal bronchioles and many more asbestosis bodies, chiefly within cells.

Chemical analyses of the lungs (Table 13) reveal that in spite of the limited tissue reaction considerable dust had been retained in the lung.

53. Progression. The lungs of animals exposed for the full dusting period (28 months) and then living in normal air for 2 months revealed the changes described above and also very slight peribronchiolar fibrosis. After 8 months in normal air the findings were similar but at 12 months 3 of 4 animals showed grossly-visible characteristic peribronchiolar fibrosis with adenomatoid change.

54. Lymph Node Involvement. The tracheobronchial nodes were essentially negative until exposure had been continued for more than a year and a half. Animals sacrificed at 12 months and 16 months revealed a few minute collections of phagocytes containing particles but practically no fibers large enough to be recognized as such. After 20 months of exposure many monocytes filled with yellow granules were present. At 30 months there had been a slight increase in reticulum but no fibrosis. No further changes occurred in the nodes. Asbestosis bodies were not seen in the nodes of any of the guinea pigs.

55. Asbestosis Bodies. Minute asbestosis bodies were observed as early as 3 months after exposure began, but they did not become numerous until 16 months had elapsed. The bodies were short and practically all were intracellular, although at 20 months some were long enough to project beyond the cell borders.

It is important to note that in the later months of exposure there was a distinct increase in the number of long fibers (up to 70 microns in length) in the lungs and that after exposure ceased characteristic long asbestosis bodies were seen.

56. White Rats and Mice. In this experiment 40 rats were exposed for periods up to 20 months and 24 mice for periods up to 12

months. Neither species developed even a suggestion of asbestosis and reaction was limited to phagocytosis of inhaled particles by widely-scattered dust cells which remained free in air spaces or were transported to the tracheobronchial lymph nodes. No asbestosis bodies were found in the rats but in the mice there were a very few small non-haustrated forms within phagocytes.

In 21 mouse lungs sectioned there were 3 instances of pulmonary adenoma (14%).

57. Summary and Interpretation.

The tissue reactions observed in this experiment were much less extensive and slower in development than in the previous investigation with short-fiber asbestos. Since presumably there were fewer fibers longer than 3 microns in the material used in this experiment, the results tend to confirm the interpretation made in Section 44 of the short-fiber experiment that the reaction primarily is not primarily chemical in nature.

The finding of long asbestosis bodies in animals inhaling the ball-milled material is an example of the difficulty of completely eliminating long fibers from an asbestos preparation.

In regard to progression of reaction after removal from dust, which was observed in this experiment but not in the others, the following interpretation is offered: When the reaction is well-developed at the termination of exposure, the contraction of the fibrous tissue would obscure any possible progression. In this experiment, however, since only the earliest stage of reaction was present at the time of removal from dust, its subsequent progress was apparent. It should be noted that the degree of progression was so slight that it can have little, if any, practical significance.

EXHIBIT INHALATION d.

58. Inhalation Experiment with Long-fiber Asbestos Dust.

After animals inhaling short-fiber asbestos dust for more than a year had failed to develop significant reaction, the hypothesis that asbestosis is produced by the mechanical irritation of long fibers was given added support. Since the King's floats asbestos used in the first inhalation experiment had a rather low content of fibrous chrysotile and contained considerable serpentine and other impurities, it was decided to conduct a new inhalation experiment with a purer form of chrysotile which would be richer in long fibers.

59. The dusting material employed in this investigation was obtained from the Manville plant of the Johns-Manville Corporation. Samples of several varieties of asbestos dust were first submitted to the Saranac Laboratory for examination and one kind, identified as Lot D, which was low in magnetite and chromite and had a fibrous content estimated to be about 75 per cent, was selected as most suitable. Steel wire brushes were fastened to the inside surface of the hopper and to the rotating paddle in order to open up the bundles of asbestos and liberate more fibers into the atmosphere.

60. The composition of the long-fiber asbestos used in this experiment is indicated by the chemical and petrographic analyses given in Table 14. It appears that this material was a much purer form of asbestos than the short-fiber dust used in other experiments. This is borne out by comparing the approximate analyses of the long-fiber and short-fiber idust in Table 15.

61. The dust concentration as revealed by impinger samples taken inside the animal cages was much lower than the concentration for the experiments with short-fiber or ball-milled dust. For the first year of the experiment with long-fiber asbestos the average of the light field counts was 32 million; for

the second year, 48 million; for the third year, 39 million; and for the fourth year, 43 million. Examination of the impinger samples with dark field illumination disclosed that many fine particles less than one micron in size accompanied the larger particles and dark field counts were, on the average, about 5 or 6 times larger than the light field counts.

62. The size-frequency of atmospheric samples of the long-fiber asbestos dust and of the ball-milled dust is shown in Table 16. Both samples were collected with the electrostatic precipitator. It will be noted that there was far more fibrous material in the long-fiber dust.

63. Reaction in Animals to Inhaled Long-Fiber Asbestos Dust. Guinea pigs, cats, rats and mice were employed in the inhalation experiment with long-fiber asbestos. Results of the experiment, summarized in Table 17, are described in greater detail below.

64. Guinea Pigs. The experiment was started with 100 guinea pigs. After exposure had been carried on for a year, a severe epidemic of pneumonia arose in the dust room and about one-third of the animals died or were killed. To replace them, 38 more guinea pigs were added to the surviving group in the dust room.

65. Rate and Type of Reaction. Histological examination revealed grossly visible lesions in the lungs after 8 months of exposure to dust, consisting of cellular infiltration about the terminal bronchioles. At 12 months, there were adenomatoid changes in the air spaces and by the 16th month a definite fibrosis was present in these areas in half the animals. The fibrous lesion could be seen macroscopically at 20 months. From this time on the reaction increased in extent and in the amount of collagen and

by the 20th month, it had fanned out into the parenchyma. The lesions were rather sharply localized and the extensions from different bronchioles showed no tendency to fuse, even in animals exposed for the maximum period (3 years). Although the intra-pulmonary reaction sometimes reached the pleura, there was no involvement of that membrane. No emphysema was visible at any point. Some thickening of the larger bronchi with a chronic inflammatory infiltration was revealed, but it probably was no more than would be produced by a similar exposure to any dust. For the first 5 months the phagocytes consisted of monocytes or very small giant cells; later, giant cell formation was more prominent. After 16 months the giant cells were large, filled with yellowish-brown pigment and sometimes vacuolated. An occasional animal showed an admixture of polymorphonuclear leukocytes and, in guinea pigs exposed for a considerable period, eosinophiles. The reaction was at first entirely cellular but by 16 months fibrous tissue formation was definite. However, it never attained a stage of hyalinization suggestive of silicosis.

A moderate individual variation occurred among the exposed animals, both in the rate of developing lesions and in the stage of development attained at the end of exposure.

Analyses of the lungs (Table 18) disclosed that although the tissue response was much greater in these guinea pigs than in those exposed to either short-fiber or ball-milled asbestos, the amount of mineral matter in the lung ash was less.

66. Progression. In guinea pigs exposed to the dust for 20 months and then removed to normal air, there was a marked tendency for cellular inflammatory reaction to clear. This effect, accompanied by contraction of the fibrous tissue, resulted in a diminishing size of the focal lesions. None

of these animals, killed at various periods up to 14 months after exposure, revealed lesions as large as those in the group sacrificed at the end of the 20-month exposure period or those in animals which remained in the dust room for more than 20 months. Fourteen months after dust exposure ceased, the foci in four of the six remaining guinea pigs were so small that they were visible only with a hand lens.

Reaction in the group exposed for 27 months and then transferred to a normal atmosphere was quite similar to the response in the 20-month exposure animals mentioned above. However, small foci were always visible on gross inspection of sections of all guinea pigs of the 27-month series but in no instance was there evidence of extension of the reaction.

67. Lymph Node Involvement. Reaction in the tracheobronchial lymph nodes was first visible at the third month of exposure. At the 8th month patches of cellular connective tissue began to appear in the medulla and by the 14th month most of the node had been replaced by cellular connective tissue. This picture, which resembled that in early silicosis, persisted to the end of the experiment. Some animals, as a variant, showed heavy sheets of diffuse monocytes and large active giant cells but there was never any necrosis or byaline formation. The spindle-shaped new cells were yellowish in color from fine pigment granules that stained for iron. No fibers or asbestosis bodies were seen.

68. Asbestosis Bodies. Although asbestosis bodies were seen in the lung as early as one month after exposure began, they were rare and hard to find. At 5 months more were visible, chiefly coiled inside giant cells, and at 8 months many bodies were free in connective tissue. They became fairly abundant as exposure Continued progressed although in some later animals the asbestosis bodies were only moderately numerous.

69. Cats. Four cats inhaled the long-fiber asbestos dust for periods of 14, 25, 33 and 42 months, respectively, and were immediately sacrificed. Two other cats, after being exposed to dust for 18 months, lived in a normal atmosphere for an additional 24 months.

70. Rate and Type of Reaction. Exposure for 14 months was sufficient to produce cellular accumulations of phagocytes around terminal bronchioles and peripheral arterioles together with compact collections of similar cells in the tracheobronchial lymph nodes. At that time there were no typical asbestosis bodies, but smooth pointed yellow fibers were seen very rarely. With continued exposure, up to 42 months, reaction in the locations noted progressed to the formation of cellular connective tissue which made well-defined sheaths about the respiratory bronchioles and arterioles, marked lymphoid hyperplasia and lymphoid infiltration of bronchiolar walls. The bronchiolar epithelium was low and flattened, giving the tubes a smooth contour. Typical asbestosis bodies were not formed although there was an occasional yellow, smooth, pointed fiber. No pleurisy was present. The reaction was similar in location to that in the guinea pigs, but fibrosis was much slower in development and had not reached the same degree of maturity.

71. X-Ray Changes. Roentgenograms of three cats were made after exposure periods of 25, 33 and 42 months, but tissue changes were not dense enough to be seen on an X-ray film.

72. Rats. Although 20 rats were placed in the dust room, many died from pneumonia and were not suitable for study. Five animals, of which one was exposed for 19 months and four for 25 months, were free from pulmonary infection and offer a basis for conclusions.

73. Rate and Type of Reaction. All four animals sacrificed at 25 months showed a well-marked peribronchiolar fibrosis. In the 19-month animal, reaction was just beginning. Asbestosis bodies were practically absent at both 19 and 25 months although two small smooth bodies were found in the 19-month animal after a long search. Thus, these animals exhibited fibrosis without asbestosis bodies.

74. Mice. Out of 20 white mice used in this experiment, 11 lived a year or more in dust and died or were killed without showing an appreciable degree of pulmonary infection.

75. Rate and Type of Reaction. Reaction was limited to phagocytosis by mononuclear cells. Usually these were widely scattered through the air spaces; a limited number were grouped about the terminal bronchioles producing some thickening of their walls. There was no suggestion of fibrosis. The striking feature of the experiment was that 9 out of the 11 mice (82 per cent) exposed to dust for a year or more showed pulmonary tumors, usually adenomatous in type. These lesions did not contain dust or asbestosis bodies.

Numerous asbestosis bodies were observed in animals killed late in the experiment. Thus, these animals exhibited asbestosis bodies without fibrosis.

76. Summary and Interpretation.

The purpose of this experiment was to evaluate the importance of long fibers in the tissue response to inhaled asbestos. The results indicate strongly that long fibers are chiefly responsible for the reaction. Thus, in guinea pigs reaction developed earlier and became more extensive than in previous experiments in spite of a smaller concentration of atmospheric dust and a lower mineral content in the lungs. Furthermore, a typical peribronchiolar fibrosis was produced

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in cats although in a previous experiment with short-fiber dust it did not develop in this species.

The cause of the cellular fibrosis in the lymph nodes of the guinea pigs is not clear. It did not occur in other inhalation experiments with asbestos.

LXXVII. INJECTION EXPERIMENTS

In order to determine to what extent the various fibrous minerals possess the capacity to produce tissue damage, numerous injection experiments were performed. In these experiments guinea pigs and rabbits were used and the mineral dust was injected by the intratracheal, intraperitoneal and intravenous techniques. For the purpose of simplification the findings in each series of tests have been condensed and reported in tables, to which reference will be made later.

78. Experiments Using Intratracheal Technique.

Since the asbestos minerals do not cause a typical advanced fibrosis in extra-pulmonary tissue, the intratracheal technique is the perferred way of introducing fibrous dust into the experimental animal. In this method the dust suspension is injected by means of a special needle or catheter deep into the trachea, from which it flows into the lungs.

79. Comparison of Fibrous and Non-Fibrous Dusts. To demonstrate that the ability of asbestos to produce fibrosis resides in its fibrous character, the series of injection experiments reported in Table 19 were performed. The tests were made with unheated long-fiber chrysotile and with chrysotile that had been ignited to destroy its

flexible structure or ball-milled to reduce the length of fiber to 3 microns and less. At the same time control tests were made with serpentine, which has the same chemical composition as chrysotile but is non-fibrous. A review of the findings reveals that only the unheated long-fiber chrysotile produced fibrosis. Fibers subjected to ignition or shortened by ball-milling had lost their capacity to cause serious tissue damage. Ignition produced important changes in the chrysotile fibers, among them being loss of water, an alteration from a flexible to a brittle structure and possibly other changes.

80. Comparison of Various Long-Fiber Dusts. Some very interesting findings are disclosed by the results of the experiments included in Table 20. First, all the long-fiber asbestos minerals tested, with the exception of anthophyllite, produced a typical fibrosis. It is not entirely clear why anthophyllite behaved differently from the other asbestos minerals. Unfortunately, 5 of 8 animals died of pneumonia within the first two weeks of the experiment and the remaining animals were sacrificed at 1, 8 and 12 months; thus observations were not made at the optimum periods of 2 and 4 months.

Second, with the mineral brucite, which is not a silicate but is a fibrous form of magnesium hydroxide, a characteristic fibrosis like that of the asbestos minerals was obtained. Since the brucite used contained only 0.90 per cent silica (as an impurity), it is obvious that a siliceous component is not an essential factor in the development of asbestosis.

Third, no fibrosis resulted from the injection of glass wool fibers, even though glass wool resembles asbestos in some ways. There are fundamental differences, however. A glass wool fiber 3 microns in diameter is a solid rod and, in short lengths, is fairly rigid, while an asbestos fiber of the same diameter is a bundle of extremely fine filaments which impart to the fiber a high degree of flexibility. It would seem that this structure and the associated flexibility are

important factors governing the capacity of a mineral to produce peribronchiolar fibrosis.

81. Comparison of Long-Fiber and Short-Fiber Dusts. With quartz dust it has been demonstrated that the smaller the particles, the more intense is the tissue reaction, and that there is little reaction to particles larger than 3 microns in diameter. In the case of asbestos, however, the reverse is true and apparently only long fibers have any specific effect. This is confirmed by the data of Table 21, in which a series of tests with fibrous minerals is reported. When the injected dust consisted of fibers 20 to 50 microns long, all the minerals tested (except anthophyllite, as noted in Section 80) produced a fibrosis; when the material was prepared by first grinding the fibrous dust until the length of fibers was reduced to 20 microns and less (or, in some cases, 3 microns and less), none of the injected mineral dusts caused fibrosis.

82. Experiments Using Intravenous Technique.

The experiments, described in Table 22, in which the intravenous method of injection was employed, show that the asbestos minerals are far different from quartz in their action on tissue. It has been repeatedly demonstrated that intravenous injection of quartz particles 3 microns and less in diameter will cause a typical tissue reaction with the development of hyaline nodules in extrapulmonary sites, such as the liver and spleen. Asbestos minerals, however, on intravenous injection generally produce only an inert type of reaction, as is revealed by the results given in the table. The reason for the early deaths in the experiment with chrysotile particles is not clear; it may have been caused by silicic acid liberated by the finely-ground mineral.

83. Experiments Using Intraperitoneal Technique.

The results of injection experiments with the intraperitoneal technique are given in Table 23. It will be noted that the long-fiber dusts produced a fibrous reaction while dusts composed of particles 3 microns and less in size caused only an inert type of response. These experiments indicate also that the fibrosis initiated by the irritation of asbestos fibers is not restricted to the lungs, as was formerly assumed, but can be produced in the peritoneum as well.

LXXXIV. OTHER EXPERIMENTS WITH ASBESTOS MINERALS

A number of additional experiments were conducted to throw more light on specific phases of the asbestosis problem.

85. Protective Action of Aluminum Compounds.

Intratracheal injection of a suspension of long-fiber chrysotile to which colloidal aluminum hydroxide had been added revealed that the addition of the aluminum compound did not prevent the tissue irritation produced by chrysotile. If anything, the acute inflammatory response to the injected fibrous mineral was accelerated. One month after the last injection of the dust suspension the bronchiolitis was becoming fibrous.

86. Formation of Asbestosis Bodies.

The iron in the coating of the asbestosis body appears to be derived from blood or tissue elements and not, as has been suggested, from the mineral fiber. Following subcutaneous injection of two kinds of chrysotile into the groin of guinea pigs - one kind containing 2 per cent and the other 0.2 per cent Fe_2O_3 - the asbestosis bodies were equally numerous at both sites of injection.

An attempt to produce asbestosis bodies in guinea pigs by implantation of three silk bags containing fibrous chrysotile was unsuccessful. One bag planted subcutaneously in the abdominal wall disappeared; the other two bags, placed in the peritoneal cavity, produced a little foreign body reaction but no asbestosis bodies in a year.

Intratracheal injection into guinea pigs of asbestosis bodies recovered from human lung tissue failed to produce the typical tissue reaction to asbestos fibers. The injected material was obtained by digesting with sodium hypochlorite solution lung tissue removed at autopsy from an asbestos worker. The asbestosis bodies could be seen in the guinea pigs for at least a year after injection. This experiment shows that the asbestosis body has a rather resistant coating which is not destroyed by moderate hypochlorite treatment and may be maintained in vivo for a year or longer.

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LXXXVII. THEORY OF IRRITANT ACTION OF ASBESTOS MINERALS[99]

Two hypotheses have been proposed to explain the tissue irritation and reaction caused by asbestos fibers: the chemical and the mechanical. In the chemical theory, which is based upon experience with quartz, it is assumed that the asbestos minerals dissolve in the body fluids and that in this process their bases are leached away to leave silica in a form capable of irritating tissues. According to this hypothesis, asbestosis would be merely an indirect silicosis. Several facts make the chemical theory untenable: (1) intratracheal injections of brucite fibers, which had a silica content of only 0.90 per cent, caused a typical fibrosis like that produced by the asbestos minerals; (2) free-silica particles increase in potency as the particle size becomes less, but asbestos fibers shorter than about 10 to 20 microns are relatively innocuous; (3) aluminum

hydroxide neutralizes the irritating effect of quartz but not of asbestos; (4) serpentine has the same chemical composition as long-fiber chrysotile but it does not produce the same kind of tissue reaction; (5) there is a wide range in the chemical composition of the minerals which do cause asbestosis (see Table 24). In view of this evidence it seems more likely that asbestosis is caused by an unusual mechanical irritation from long asbestos fibers; Probably this irritation being related to the peculiar filamented structure of the fiber and the associated flexibility, which are possessed by no other foreign body. For example, ignition of chrysotile fibers changed their structure and made them inert while the same fibers, before being heated, would produce fibrosis (see Table 19). Further support for the theory of mechanical irritation is that asbestosis occurs in an organ of high mobility - the lung - and that a fibrous reaction can be produced by injection of asbestos fibers into the peritoneum, where there is also a degree of mobility, but not in other extrapulmonary organs.

LXXXVIII. COMPLICATIONS

The experimental investigation with asbestos minerals was concerned primarily with the effect of the dust on normal tissue but some attention was given to other phases, such as susceptibility to infection and occurrence of malignancy.

89. Infection.

The only experiment in which the effect of inhaled asbestos dust on a pulmonary infection was studied was the first inhalation experiment, carried on with "King's floats" dust. It is, perhaps, unfortunate that infection studies were not made in the other inhalation experiments also.

90. Susceptibility to Tuberculous Infection. The development of a tuberculous process initiated at the beginning of exposure to asbestos dust, and also of an infection superimposed upon an established asbestosis, was described in Sections 19 and 20 of this report. It will be noted that asbestos, when classified according to the effect of a dust on tuberculous infection, would be placed below an active dust like quartz but above inert dusts, such as calcite and gypsum. In animals infected with attenuated tubercle bacilli, quartz will cause the infectious process to progress until the animal dies of tuberculosis. Inert dusts will have no effect on the infection and the lesions will usually heal and the disease disappear. Asbestos dust is in a different category. When the fibrous dust was being inhaled during the evolution of the infection, there was a spreading of the tuberculous process for a time but usually the stimulus for continued proliferation of the tubercle bacilli was not sustained, the progression was arrested and healing followed. In guinea pigs infected with attenuated tubercle bacilli following the completion of nearly three years of exposure to asbestos dust, progressive disease did not develop. The only modification of the infection was one of localization, a few bacilli being retained in the fibrous terminal bronchioles and forming tubercles there in addition to the usual foci beneath the pleura. Such tubercles healed in a few months and there was nothing to suggest any influence on the course of the disease.

91. Susceptibility to Non-Tuberculous Infection. There was no pointed experiment concerning the effect of inhaled asbestos dust on non-tuberculous infection. Intercurrent pneumonia among animals exposed to asbestos dust was rather common, the frequency in guinea pigs exposed in the four inhalation experiments ranging from 16 to 39 per

cent. This incidental evidence suggests the possibility of an effect of asbestos dust on non-tuberculous infection. Nevertheless, since such epidemics are not uncommon in inhalation experiments with other dusts and even in the colony of normal animals, it is felt that the inhalation of asbestos dust does not exert a significant effect on the susceptibility to non-tuberculous pulmonary infection.

92. Neoplasm.

No specific experiment was conducted to determine whether the inhalation of asbestos favors the development of neoplastic disease, but certain observations on this subject were recorded in the outline of the proposed monograph on asbestosis submitted by the late Dr. L. U. Gardner in February 1943. In it he called attention to the high incidence of lung cancer among mice inhaling long-fiber asbestos. In his experimental notes, however, he referred to these lesions as adenomas.

There is an important distinction between adenoma and cancer which should be made clear. A cancer is a tumor, or neoplasm, capable of local invasion and destruction of tissue, which can distribute cells through the lymphatics or blood stream to produce isolated foci, from which new tumors develop. This phenomenon of dissemination is known as metastasis and any tumor which exhibits it is a malignant growth, of which cancer is one type. An adenoma, on the other hand, is a so-called benign or non-malignant tumor (neoplasm) which may or may not be capable of local invasion but which does not metastasize.

In order to clarify the exact nature of these lesions the pathological material is being carefully examined. Since it is felt desirable to have the benefit of Doctor Vorwald's judgment, a review of the data on this subject is being postponed until after his return from Europe. Rather than delay the entire report, further discussion will be reserved for a supplement to be issued later.

XCIII. CONCLUSIONS

Owing to the vast amount of data included in this report it seems most convenient to state the conclusions derived from the investigation and, when necessary, follow each one with a brief resume of the evidence.

A. Various forms of asbestos fibers produce a peribronchiolar fibrosis of the lungs of guinea pigs, rats, cats and rabbits but not of mice and dogs.

Both inhalation and injection experiments provide ample support for this conclusion. Figures 5 and 6 show the reaction to two different kinds of asbestos mineral.

B. The mode of action ~~appears to be primarily mechanical~~ rather than chemical in nature.

The evidence is given in section LXXXVII. Figures 1, 2, 3, 4 and 7 illustrate the important points. The fibrous filamented structure of asbestos ~~appears to~~ play an essential part in the irritating action, since the solid fibers of glass wool do not produce fibrosis (see Figure 8).

C. Short asbestos fibers do not produce fibrosis.

The ~~conclusion~~ is implied in the evidence mentioned in paragraph B above. Experiments which further support this finding are reported in Tables 21 and 23.

D. Typical fibrosis can be produced by an atmospheric suspension of asbestos dust containing only an extremely small proportion of long fibers.

In the inhalation experiment with 100 per cent ball-milled asbestos dust a typical, though delayed, fibrosis was

obtained (see Table 12), although less than 1 per cent of the atmospheric dust consisted of fibers longer than 10 microns, as is shown in Table 11. In contrast, the intratracheal injection experiment with fine asbestos dust containing no long fibers failed to produce fibrosis, (see Table 21).

5. Inhalation of asbestos dust ~~apparently does~~ not alter significantly the course of experimental tuberculosis in guinea pigs ~~studied~~.

This ~~conclusion~~ is tentative since the evidence on which it is based does not conform with our usual experience. Reference to Table 3 will show that when infection was coincident with onset of dust exposure there was temporary progression of the disease with subsequent healing; when infection was initiated after 25 3/4 months of dust exposure the course of the tuberculous disease was not appreciably altered. In contrast, it has been observed in experiments with mixed dusts containing quartz that if there is a slight progression of the tuberculosis when infection and dust exposure are coincident, this effect is more marked (instead of less, as with asbestos) when infection is initiated after a period of dust exposure.

This conclusion concerning the effect of inhaled asbestos dust on tuberculosis seems justified because in the more sensitive test (infection initiated after a period of dust exposure) there was no appreciable increase in susceptibility to the tuberculous infection. However, since the findings in the asbestos [illegible] not conform with previous experience, and

since the dusting material used in the single experiment dealing with infection contained only a relatively small amount of fibrous asbestos, it is recommended that a further investigation of this phase of asbestosis be considered.

F. The formation of asbestosis bodies seems to represent a coating of the fibers and results in loss of the ability of the fiber to produce fibrosis.

Intratracheal injection of asbestosis bodies failed to produce the typical tissue reaction (see section 86). The cessation of progressive reaction to inhaled asbestos dust soon after exposure terminates may be due to the formation of asbestosis bodies.



AFFIDAVIT

WASHINGTON)
) ss.
DISTRICT OF COLUMBIA)

BEFORE ME, the undersigned Notary Public, personally came and appeared MICHAEL RHODE, a person of the full age of majority, being of sound mind and body, who, after being first duly sworn by me, did depose and say:

I, MICHAEL RHODE, am an employee of the Armed Forces Institute of Pathology, Washington, D.C. I am custodian of the original archives of Dr. Arthur J. Vorwald.

Pages 1 through 12 attached hereto are true, correct and authentic copies of documents from Dr. Arthur Vorwald's archives. The pages attached are Revised version of ASBESTOSIS - Experimental Studies by The Saranac Laboratory, Report to the Johns-Manville Corporation, dated January 31, 1949

Dr. Vorwald was the Director of the Saranac Laboratory of the Trudeau Institute. Upon his death, Dr. Vorwald's archives were donated to the Armed Forces Institute of pathology by his widow.

Dr. Vorwald's archives are in such condition as to raise no suspicion concerning their authenticity; they were received by the Armed Forces Institute of Pathology from Dr. Vorwald's widow after

Dr. Vorwald's death; they are presently on file as authorized by law in the National Museum of Health & Medicine, Armed Forces Institute of Pathology, Building 54, Walter Reed Army Medical Center, Washington, D.C. 20306-6000; and the archives ~~have been in~~ existence for 20 (twenty) or more years.

MICHAEL RHODE, AFFIANT

SWORN TO AND SUBSCRIBED before me, the undersigned Notary Public, on this the 27th day of April, 1992.

NOTARY PUBLIC

Printed Name: Bernice Williams

My Commission Expires:
3-14-95

METROPOLITAN LIFE INSURANCE COMPANY

ONE MADISON AVENUE, NEW YORK 10, N.Y.

ANTHONY J. LANZA, M.D.
ASSOCIATE MEDICAL DIRECTOR
HEALTH AND WELFARE

December 16, 1948

Dr. Arthur J. Vorwald
The Trudeau Foundation
The Saranac Laboratory
Saranac Lake, New York

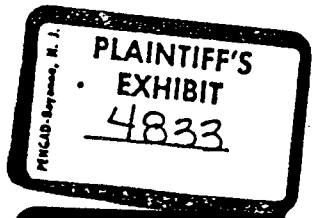
Dear Art:

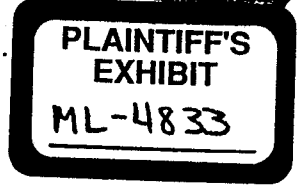
Thanks for your letter of the 14th. I have just been informed by Mr. Woodard that a meeting has been called by the authorities in Montreal for December 20th to discuss the asbestos situation in Quebec and to define the position of the provincial government. It would be extremely helpful if it were possible to have one or two copies of the revised report available to Mr. Woodard and his colleagues for this conference. I realize that this is a difficult demand but the situation is really one of emergency.

With best regards and best wishes for the holiday season.

Sincerely yours,

A. J. Lanza, M.D.
Associate Medical Director





METROPOLITAN LIFE INSURANCE COMPANY

One Madison Avenue, New York 10, N.Y.

ANTHONY J. LANZA, M.D.
Associate Medical Director
Diseases and Welfare

December 20, 1948

Dr. Arthur Vermeil
The Saranac Laboratory
Saranac Lake, New York

Dear Art:

Everything is under control and there will be no necessity for you to go to Montreal on the 28th.

Best regards,

Sincerely yours,

A. J. Lanza, M.D.
Associate Medical Director

March 9, 1949

American BrakeBlok Div. of A.B.S. & F.
Gatke Corporation
Keasbey & Mattison Company
Raybestos-Manhattan, Inc.
The Russell Mfg. Co.
Thermoid Company (Southern Asbestos)
Union Asbestos & Rubber Co.
United States Gypsum Co.

Saranac Laboratory
Asbestos Dust Experiments

We have now received from Saranac Laboratory a revised report (copy of which is enclosed) entitled "ASBESTOS PNEUMOCONIOSIS". I have examined this carefully and I believe it adopts the substance of all of the suggestions that were made by representatives of the underwriting group with respect to the report of September 30, 1948. You will recall that the earlier draft was reviewed at a meeting in New York on November 11, 1948. Minutes of this meeting, including a list of the recommended changes, were sent you by Mr. J. P. Woodard under date of November 30, 1948.

As the findings are generally favorable, we have renewed our request that Saranac Laboratory arrange for the publication of the report as promptly as possible, preferably in the Journal of Industrial Hygiene, and with an appropriate introduction by Dr. A. J. Lanza.

Very truly yours,

Vandiver Brown,
Secretary and General
Attorney.

VBsy

Encl.

cc A. R. Fisher
L. C. Hart
J. P. Woodard