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

February 24, 1943 Res

o Admitted in W.V.
o High Jackson office

LEGAL DEPT.

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 amy count on some of your members to supply me with enough pure, long fibre asbestos for the purpose.

PLAINTIFF'S EXHIBIT
MET-1024

PX26-61

060 06 00091

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 fo the support that we have had.

Sincerely yours,

Leroy U. Gardner, M. D.
Director

LUG:EBH

PX26-59

060 06 00092

Ress

OUTLINE OF PROPOSED MONOGRAPH ON ASBESTOSIS

Saranac Laboratory Study under Grant from Asbestos Association

PART I HUMAN ASBESTOSIS

I Human Pathology - a study of 28 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 Disablilty, 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

40

3

PX26-62

060 06 00093

PART II Experimental Asbestosis

I Methods

(a) Inhalation exposure to plant dusts.
(b) Injection into lungs through trachea of pure minerals
(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) Granular 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

7826-63

060 06 00094

(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 particle per cu. ft.
(b) Work upon better method of sampling

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

14 Prevention

(a) Chemical means not practical

PX2C-64

060 06 00095

To p7

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

9X26-65

ASBESTOSIS - ANNOTED OUTLINE INDICATING RESULTS

PART I - HUMAN ASBESTOSIS

I Human Pathology and X-ray Patterns - Description

Based upon 28 human autopsies

2 Ash and Mineral Values in Human Lungs.

3 Complication of Asbestosis

(a) Susceptibility to Infection

i 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.

?X26-66(1)

060 06 00097

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

(c) A physical examination which reveals certain characteristic 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.
Asbestos 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 cases of human subjects

II Species Susceptibility

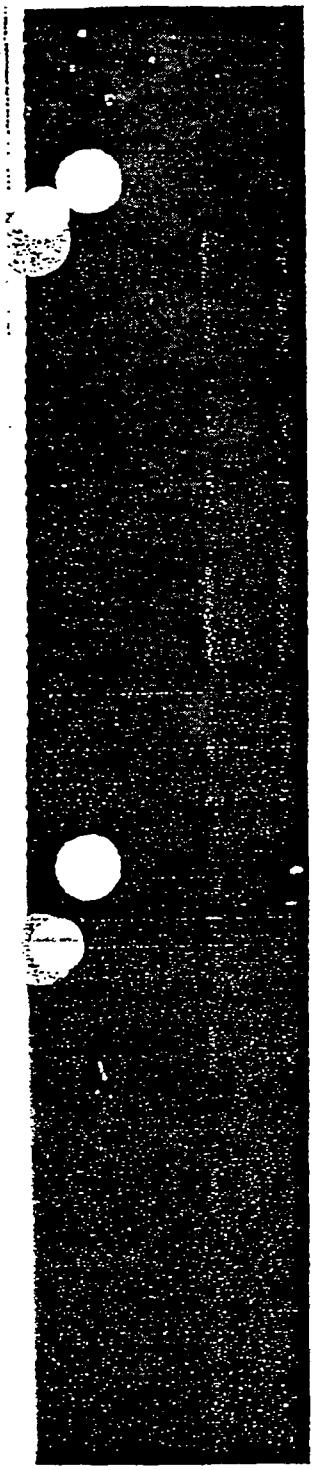
Unlike free silica, asbestos does not produce its specific effec in any organ of any species of animal. It causes fibrosis only the lungs of man and those of a few of the species tested.

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.

5 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 chrysotile is inert causing no fibrosis in lungs or other organs. It attracts iron from the lungs but of course, no 'bodies' develop

(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)

060 06 00100

	Chrys-otile	Crocid-olite	Antho-phyllite	Amosite	Amphi-bole	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%	0,51%	4,06%	3,08%	7,21%	6,78%
FeO	0	4,29%	0 ?	33,83%	0	0	9,36%
Al_2O_3	0.36%	1,02%	0,25%	1,09%	1,69%	0.56%	0,46%
CaO	0.05%	0.79%	0.44%	2,01%	12,22%	4,45%	0,40%
MgO	38,77%	12,25%	29,54%	6,29%	23,29%	20,52%	53,99%
H_2O	0,29	6,92	0,52	0,33	0,40	6,78	0,91
CO_2	0,08	0,57	0.15	0,10	0,12	0,99	0,16
H2O <105°	4.30	0,02	0,62	0,66	0,32	0,34	0,53
>105°	14.92	2,56	2,42	1,51	3,59	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 asbestas 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 ti fibres become coated with a layer of aluminum monohydrate as has been proved in the case of quartz. If they have, the co. 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.

X26-6665

060 06 00101

(c) Heat - At ignition temperatures water is driven off but the fibre structure is preserved. Fibres become extremely brittle. The physical change alters typical localization within the lungs, no fibrosis develops, reaction limited to phyagocytosis. 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 concomitant 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 the 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 completely surrounded by phagocytic cells which would prevent contact of these round, broken ends with the delicate cells supporting the air tubes Observation has demonstrated that these conditions are realized in guinea pigs treated with long fibre chrysotile and fibrosis results With the other asbestiform minerals that have been tested, some or all of the prerequisits were lacking and no fibrosis developed.

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

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

(e) Heat sufficient to alter chemical structure destroys power to irritate but it also alters essential physical characteristi that affect localization of the fibres in the lungs.

X. Complications

(a) Susceptibility to Infection

i Tuberculous - Asbestos behaves like most other mineral dusts in this respect and not like quartz which specifically increase 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 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 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.

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

2 When these species were subjected to 2 to 3 years inhalation 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. For 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.

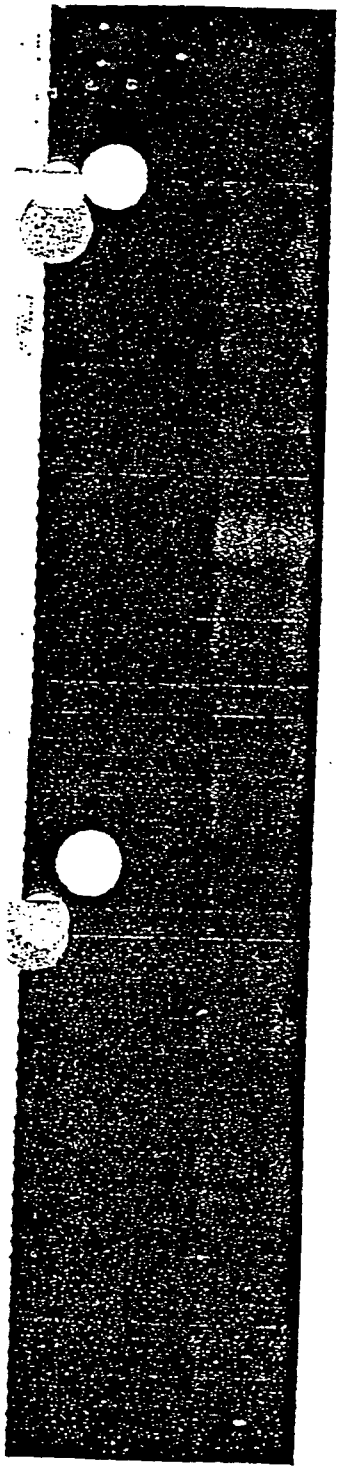
These observations are suggestive but not conclusive evidence of a cancer stimulating action by asbestos dust. They are open to several criticisms. The strain of mice was not the same in the asbestos experiment as in many of the others cited; apparently the former were unusually susceptible. Not enough 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.

[To: 10]

X.26-66 (8)



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 gramular 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.

26-66(9)

(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 Concentrati 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 ~~(probably)~~ creating an acidosis which would be worse than the effects of the fibrosis.

6-66(10)

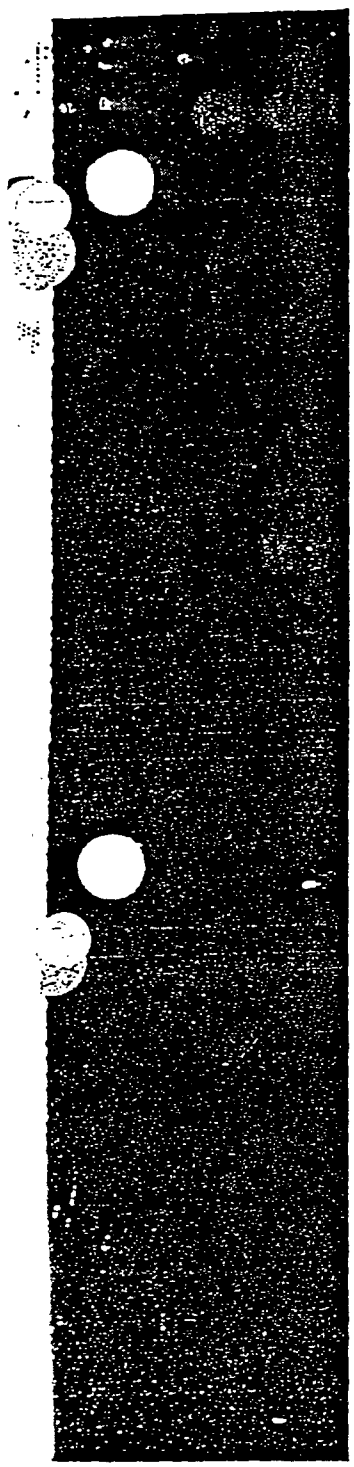
(b) Apparently aluminum, which is so effective against free sili
has little influence upon fibrous chrysotile.

(c) However, it would be of great theoretical interest to trea
few cases with real dyspnoea from asbestosis by aluminum in
halation. We are by no means certain whether the favorable
results upon advanced silicotics are due to a chemical neu
ization of quartz in the lungs. Aluminum might have some no
general pharmacological effect which influences dyspnoea.

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

Leroy U. Gardner

(26-66(11)



060 06 00108