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PLAINTIFF'S EXHIBIT

MET-338

OUTLINE OF PROPOSED MONOGRAPH ON ASBESTOSIS

Saranac Laboratory Study under Grant from Asbestos Association

PART I HUMAN ASBESTOSIS

I Human Pathology - a study of 26 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

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PX26-62

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 Compoaition 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

(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 precipitatar 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

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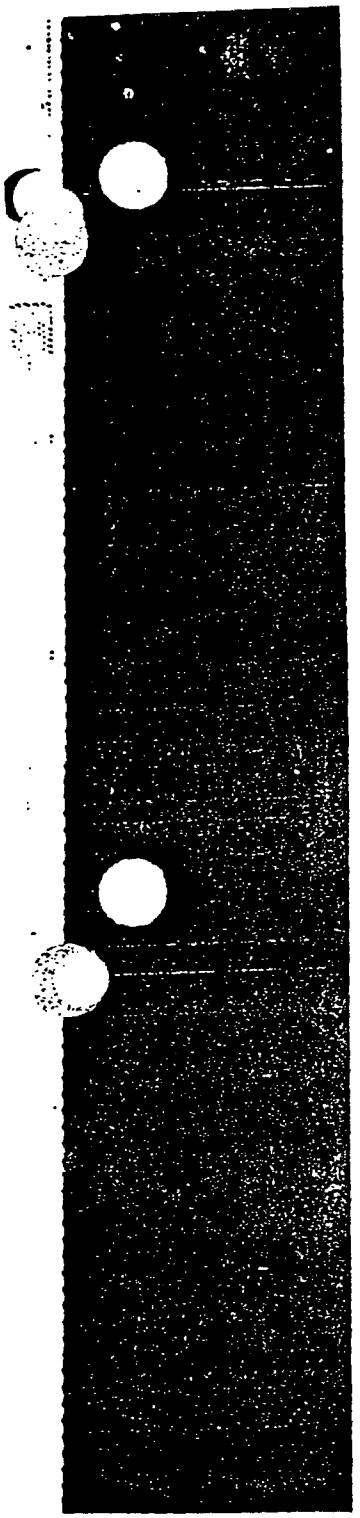
i Acidosis necessary to dissolve fibre in lungs worse than Asbestosis
ii Aluminum Therapy inapplicable
iii Chief reliance still upon dust prevention with special emphasis upon the fibrous components



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 excessiv 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.

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(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.

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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 effect in any organ of any species of animal. It causes fibrosis only in the lungs of man and those of a few of the species tested.

Species	Fibrosis	Asbestos Bodies	Species	Fibrosis	Asbestos Bodies
Man	4+	4+	Cat	+	±
Guinea Pig	2+	3+	White House	0	±
Rabbit	+	±	White Rat	0	0
(* ± = very small atypical asbestos bodies)			Dog	0	0

III Peculiar Characteristics of Asbestosis

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

i 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 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)

26-66 (4)

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	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%	0,51%	4,06%	3,06%	7,21%	6,78%
FeO	0	4,29%	0 ?	33,85%	0	0	9,36%
Al_2O_3	0,36%	1,[illegible]	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%
Na_2O	0,29	6,92	0,52	0,33	0,40	6,78	0,91
K_2O	0,08	0,57	0,15	0,10	0,12	0,99	0,16
H_2O <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 tfibres 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.

X26-66(5)

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(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.

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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 characteristics 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.

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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 18.8%: 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.

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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.

26-66(9)

(c) Duration of Exposure

i Fibrosis visible to the naked eye after 12 months exposure increases in extent in subsequent 12 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 samplin 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 ~~(crocci...)~~ creating an acidosis which would be worse than the effects of the fibrosis.

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Table 7

ANALYSES OF LUNGS OF GUINEA PIGS

AFTER PROLONGED INHALATION OF

SHORT-FIBER ASBESTOS (CHRYSOTILE)

		Time from beginnin		
		months 12	months 15	months 20
Dust Exposure Continuous During Life	Exposure to dust	12	15	20
	Period in normal air	0	0	0
	Amount of ash (per cent of dried lung)	per cent 5.02 4.58 5.16	per cent 5.00 4.76 4.95	per cent 5.86 6.43
	Total SiO_2 (per cent of dried lung)	0.51 0.46 0.54	0.49 0.43 0.53	0.85 0.90
	Total SiO_2 (per cent of ash)	10.23 10.08 10.54	9.96 9.00 10.60	14.46 14.07
	Tissue Reaction*	±	±	2+
Dust Exposure Followed by Prolonged Residence in Normal Air	Exposure to dust	months -	months -	month -
	Period in normal air	-	-	-
	Amount of ash (per cent of dried lung)	per cent -	per cent -	per ce -
	Total SiO_2 (per cent of dried lung)	-	-	-
	Total SiO_2 (per cent of ash)	-	-	-
	Tissue Reaction*	-	-	-

*The symbols merely represent the relative degree of reaction, ranging from ± (questionable) to 4 + (the maximum for this experiment). The relationships apply only within this table and cannot be compared with symbols in other tables.

Table 7

LUNGS OF GUINEA PIGS

ONGED INHALATION OF

ASBESTOS (CHRYSOTILE)

	Time from beginning of dust exposure					
	months 12	months 15	months 20	months 24	months 30	months 33-3/4
to dust n normal air	12 0	15 0	20 0	24 0	30 0	33-3/4 0
	per cent	per cent	per cent	per cent	per cent	per cent
f ash nt of dried lung)	5.02 4.58 5.16	5,00 4,76 4,95	5.86 6,43	5.42 5.50	5,35 6.55	6.06 6,35
O_2 nt of dried lung)	0.51 0.46 0.54	0.49 0.43 0.53	0.85 0.90	0,78 0,78	0.96 1.27	0.75 0.96
O_2 nt of ash)	10.23 10.08 10.54	9.96 9.00 10,60	14.46 14.07	14,48 14,20	17.89 19.46	12.37 15.11
Reaction*	±	±	2+	3+	4+	4+
	months	months	months	months	months	months
to dust n normal air	- -	- -	- -	20 4	20 10	20 13-3/4
	per cent	per cent	per cent	per cent	per cent	per cent
f ash nt of dried lung)	-	-	-	5.16 5.11	6.11 3.98	4.77 5.18 4.77
O_2 nt of dried lung)	-	-	-	0.48 0.36	0.62 0.34	0.25 0.26 0.22
O_2 nt of ash)	-	-	-	9.30 7.16	10.21 8.51	5.31 5.00 4.60
Reaction*	-	-	-	2+	3+	2+

rely represent the reletive degree of reaction,
(questionable) to 4 + (the maximum for this
The relationships apply only within this table
compared with symbols in other tables.

Table 8

ANALYSES OF LUNGS OF WHITE RATS

THAT HAD INHALED

SHORT-FIBER ASBESTOS (CHRYSOTILE)

	Duration of Exposure					
	0 months*	2 months	4 months	6 months	8 months	10 months
	per cent	per cent	per cent	per cent	per cent	per cent
Amount of ash (per cent of dried lung)	3.9 4.3 2.9 3.6 3.3 3.9 3.4	3.5 3.6 2.9 3.2	3.3 3.6 3.4	3.3 3.4 3.7	3.9 3.6 3.5 4.4 3.7	4.9 4.6 5.3 4.7
Total SiO_2 (per cent of dried lung)	0.00 0.00 0.00 0.00 0.00 0.00 0.00	0.08 0.13 0.09 0.05	0.08 0.11 0.07	0.07 0.05 0.04	0.08 0.18 0.15 0.17 0.16	0.18 0.15 0.15 0.13
Total SiO_2 (per cent of ash)	0.0 0.0 0.0 0.0 0.0 0.0 0.0	2.1 3.5 3.2 1.5	2.3 3.0 2.2	2.1 1.5 1.1	2.2 5.5 3.4 4.0 4.2	3.8 3.3 2.8 2.8

* Normal controls (no dust exposure)

[illegible]

[illegible]

(Lungs only without included [illegible] nodes)

		Duration of Exposure				
		2 months	4 months	6 months	8 months	10 months
		per cent	per cent	per cent	per cent	per cent
Amount of Ash (per cent of dried lung)	Short-fiber asbestos	3.6	3.4	3.8	5.0	4.9
	Quartz	4.3	4.9	7.1	4.8	7.6
	Chert	5.0	8.0	8.0	8.0	14.1
	Gypsum-quartz	2.8	3.0	3.4	3.6	4.1
Total SiO_2 (per cent of dried lung)	Short-fiber asbestos	0.08	0.09	0.05	0.15	0.15
	Quartz	0.51	0.51	2.94	1.44	4.40
	Chert	0.25	0.32	3.45	2.40	6.08
	Gypsum-quartz	0.08	0.07	0.11	0.08	0.28
Total SiO_2 (per cent of ash)	Short-fiber asbestos	2.6	2.5	1.6	3.0	3.2
	Quartz	11.7	11.4	41.5	28.4	58.0
	Chert	3.9	3.6	34.4	26.6	43.2
	Gypsum-quartz	2.6	2.0	3.4	3.1	6.7

Table 10

COMPOSITION OF

100 PER CENT BALL-MILLED ASBESTOS DUST

	Short-fiber Asbestos Used in Dusting Machines per cent	Atmospheric Dust Collected with Precipitator per cent
Chrysotile	17	15
Serpentine	55	60
Magnetite	10	10
Quartz	2	2
Brucite	5	3
Hematite	0	0
Other Minerals	11	10
	100	100

Table 11

SIZE-FREQUENCY OF ATMOSPHERIC DUST

COLLECTED INSIDE CAGES

FOR

INHALATION EXPERIMENT WITH 100 PER CENT BALL-MILLED ASBESTOS DUST

		Sample taken before wire brushes installed	Sample taken after wire brushes installed
		per cent	per cent
Distribution of Particles, Clumps and Fibers	Particles and clumps	98.7	98.6
	Fibers	1.3	1.4
		100.0	100.0
Size-frequency of Particles	< 3 microns	86.1	95.0
	3-10	11.9	5.0
	> 10	2.0	0.0
		100.0	100.0
Size-frequency of Fibers	< 3 microns	22	0
	3-10	44	58
	> 10	34	42
		100	100

Table 12

SUMMARY OF INHALATION EXPERIMENTS

WITH

100 PER CENT BALL-MILLED ASBESTOS DUST

Nature of Experiment	Number of Animals	Maximum Dust Exposure	Maximum Survival After Dust Exposure	Results
Dust exposure continuous throughout life	84 g. pigs	24 months	0 months	No appreciable pulmonary reaction.
	40 rats	20	0	No suggestion of asbestosis.
	24 mice	12	0	No suggestion of asbestosis.
Dust exposure followed by a prolonged residence in normal air	16 g. pigs	28 months	12 months	Fibrosis typical of asbestosis was present 12 months after exposure ceased in an amount sufficient to be visible grossly; smaller foci could be seen microscopically at 2 months and 8 months.

Table 13

ANALYSES OF LUNGS OF GUINEA PIGS

EXPOSED TO DUST IN

INHALATION EXPERIMENT WITH 100 PER CENT BALL-MILLED ASBESTOS DUST

		Time from beginning of dust exposure		
		months 1	months 2	mo 3
Dust Exposure Continuous During Life	Exposure to dust	1	2	3
	Period in normal air	0	0	0
	Amount of ash (per cent of dried lung)	per cent 4.35 4.30 4.35	per cent 4.66 4.60 5.05	per c 5.6 5.0 5.7
	Total SiO_2 (per cent of dried lung)	0.21 0.30 0.24	0.23 0.34 0.61	0.7 0.3 0.5
	Total SiO_2 (per cent of ash)	4.28 7.05 5.60	4.90 7.40 12.01	12.4 6.8 9.7
	Tissue Reaction*	0	0	0
		Time from beginning of dust exposure		
		months 30	months 36	mon 4C
Dust Exposure Followed by Prolonged Residence in Normal Air	Exposure to dust	28	28	28
	Period in normal air	2	8	12
	Amount of ash (per cent of dried lung)	per cent 7.25 8.67	per cent 5.25 5.96	per 6.3 5.3
	Total SiO_2 (per cent of dried lung)	1.57 2.19	0.68 0.87	0.8 0.6
	Total SiO_2 (per cent of ash)	21.63 25.24	12.99 14.55	13. 12.9
	Tissue Reaction*	+	+	2+

*The symbols merely represent the relative degree of reaction, ranging from 0 to ± (questionable) to 2+ (the maximum observed in this experiment. The relationships apply only within this table and cannot be compared with symbols in other tables.



:TOS DUST

Time from beginning of dust exposure								
months 1	months 2	months 3	months 5	months 8	months 12	months 16	months 20	months 24
1	2	3	5	8	12	16	20	24
0	0	0	0	0	0	0	0	0
per cent	per cent	per cent	per cent	per cent	per cent	per cent	per cent	per cent
4.85	4.66	5.60	5.10	4.35	5.65	5.40	5.65	6.30
4.30	4.60	5.07	5.08		6.24	5.01	5.20	5.56
4.35	5.05	5.74	5.02					
0.21	0.23	0.70	0.38	0.52	1.25	1.02	1.28	1.85
0.30	0.34	0.32	0.38		1.45	1.11	1.28	1.21
0.24	0.61	0.56	0.39					
4.28	4.90	12.47	7.51	11.86	22.16	18.96	22.60	29.05
7.05	7.40	6.38	7.47		23.28	21.95	24.61	21.70
5.60	12.01	9.77	7.72					
0	0	0	0	0	0	±	±	±

Time from beginning of dust exposure		
months 30	months 36	months 40
28	28	28
2	8	12
per cent	per cent	per cent
7.25	8.25	6.38
3.67	5.96	5.17
1.57	0.68	0.84
2.19	0.87	0.64
21.63	12.89	13.08
25.24	14.55	12.41
+	+	2+

of reaction, ranging
served in these experi-
able and cannot be

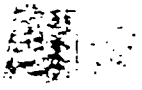


Table 14

ANALYSES OF LONG-FIBER ASBESTOS DUST

(as received)

Chemical	
SiO_2	38.40%
Fe_2O_3	5.52
Al_2O_3	0.78
MnO	0.00
CaO	0.31
MgO	40.18
Na_2O	0.06
K_2O	0.06
CO_2	0.57
H_2O	14.00
	99.76

Petrographic

The material contains about 75 per cent of fibrous asbestos, probably chrysotile, with some serpentine and small amounts of calcite, magnetite and chloritic or micaceous minerals. Only a trace of quartz was seen. There were shreds of non-separated fibers 10 to 50 microns long and 5 to 15 microns wide.

COMPARISON OF APPROXIMATE ANALYSES OF

LONG-FIBER AND SHORT-FIBER ASBESTOS DUST

	Long-Fiber		Short-Fiber	
	Original Material	Atmospheric Dust	Original Material	Atmospheric Dust**
	per cent	per cent	per cent	per cent
Chrysotile	75	60	17	15
Serpentine	15	20	55	60
Magnetite	5	3	10	10
Quartz	tr	3*	2	2
Brucite	2	4	5	3
Hematite	0	10*	0	0
Other	3	-	11	10
	100	100	100	100

* Contamination from other dusts.

** Atmospheric sample was 100 per cent ball-milled dust.

Table 16

COMPARISON OF SIZE-FREQUENCY OF ATMOSPHERIC LONG-FIBER AND 100 PER CENT BALL-MILLED ASBESTOS DUST COLLECTED INSIDE CAGES

		Long-Fiber	Ball-Milled
		per cent	per cent
Grains	< 3 microns	66.4	90.6
	3-10	1.1	4.6
	> 10	0.0	0.0
Fibers	< 10	25.8	0.8
	> 10	6.7	0.6
Clumps		1.0	3.2
		100.0	100.0

TABLE 17

SUMMARY OF INHALATION EXPERIMENTS

WITH

LONG-FIBER ASBESTOS

Nature of Experiment	Number of Animals	Maximum Dust Exposure	Maximum Survival After Dust Exposure	Results
Dust exposure continuous throughout life	117 g. pigs	36 months	0 months	Definite fibrosis in 16 months.
	4 cats	42	0	Slowly developing fibrosis first seen at 24 months.
	20 rats	25	0	Marked peribronchiolar fibrosis first seen at 24 months.
	20 mice	25	0	Limited reaction; no fibrosis.
Dust exposure followed by a prolonged residence in normal air	12 g. pigs	20 months	14 months	Clearing of inflammatory reaction and definite contraction of fibrosis.
	9 g. pigs	27 months	9	Clearing of inflammatory reaction and slight contraction of fibrosis.
	2 cats	18	24	Similar to continuous exposure group; suggestion of progression in one of the two animals.

Table 18

ANALYSES OF LUNGS OF GUINEA PIGS

EXPOSED TO DUST IN

INHALATION EXPERIMENT WITH LONG-FIBER ASBESTOS

		months 1	months 2	months 3	months 5	s
	Exposure to dust Period in normal air	1 0	2 0	3 0	5 0	
Dust Exposure Continuous During Life		per cent	per cent	per cent	per cent	pe
	Amount of ash (per cent of dried lung)	4.35 4.33 4.37	4.45 4.48 4.35	4.38 4.38 4.51	4.77 4.63 5.08	
	Total SiO_2 (per cent of dried lung)	0.04 0.09 0.04	0.05 0.05 0.06	0.05 0.05 0.06	0.08 0.12 0.09	
	Total SiO_2 (per cent of ash)	1.10 2.11 0.93	1.23 1.18 1.46	1.20 1.13 1.48	1.75 2.67 1.77	
	Tissue Reaction*	0	±	±	±	
		months	months	months	months	
	Exposure to dust Period in normal air	20 0	20 4	20 10	20 14	
Dust Exposure Followed by Prolonged Residence in Normal Air		per cent	per cent	per cent	per cent	pe
	Amount of ash (per cent of dried lung)	3.54 3.60 3.58	2.92 2.81	4.18 4.30	5.01 5.04	
	Total SiO_2 (per cent of dried lung)	0.43 0.49 0.52	0.21 0.27	0.24 0.22	0.21 0.18	
	Total SiO_2 (per cent of ash)	12.22 13.63 14.59	7.23 9.50	5.75 5.07	4.19 3.58	1
	Tissue Reaction*	2+	2+	2+	+	

*The symbols merely represent the relative degree of reaction, ranging from
The relationships apply only within this table and cannot be c[illegible] with

hs	months 5	months 8	months 12	months 16	months 20	months 24	months 27	months 30	months 34	mo
	5 0	8 0	12 0	16 0	20 0	24 0	27 0	30 0	34 0	
ent	per cent	per cent	per cent	per cent	per cent	per cent	per cent	per cent	per cent	per
3	4.77	4.72	4.87	2.98	3.54	3.42	3.40	3.53	3.85	4
3	4.63	4.92	5.02	2.83	3.60	3.52	3.74	3.03	6.70	2
1	5.08	4.34	5.16	3.16	3.53			3.88		
5	0.08	0.10	0.25	0.38	0.43	0.36	0.39	0.37	0.50	0
5	0.12	0.09	0.20	0.35	0.49	0.29	0.48	0.34	0.84	0
3	0.09	0.07	0.31	0.34	0.52			0.24		
)	1.75	2.21	5.20	12.70	12.22	10.18	11.61	10.55	8.60	8
5	2.67	1.90	4.09	12.26	15.65	8.29	13.15	11.22	12.47	12
3	1.77	1.58	5.99	10.91	14.59			6.10		
	±	+	+	2+	2+	3+	3+	4+	4+	1

[redacted]nning of dust exposures

ns	months 20 14	months 27 0	months 27 3	months 27 7	months 27 9
nt	per cent	per cent	per cent	per cent	per cent
3	5.01	3.40	3.56	3.19	3.21
)	5.04	3.74	2.64	3.18	2.75
4	0.21	0.39	0.31	0.25	0.29
2	0.18	0.49	0.18	0.28	0.23
5	4.19	11.51	8.59	7.99	8.96
7	3.58	13.15	5.94	8.72	8.31
	+	3+	2+	2+	2+

ranging from 0 to ± (questionable) to 4 + (the maximum for this experiment).

[redacted]red with symbols in other tables.

Table 19

COMPARISON OF REACTION TO CHRYSOTILE AND SERPENTINE

INJECTED INTRATRACHEALLY

Dosage

Each animal was injected intratracheally with 0.5 cc of a 5 per cent suspension of the dust. Two weeks later another similar injection was given. Total amount of dust injected = 50 mg.

Animals Used

Six groups of 9 guinea pigs each (one group for each type of dust).

Sacrificing Periods

One or two animals in each group at 1, 2, 3, 8-1/2 and 12 months after injection.

Preparation of Dust

Chrysotile (ball-milled) unheated: Ball-milled for 1176 hours, dried and reground in agate mortar.

Chrysotile (ball-milled) ignited: Ball-milled chrysotile heated for 2 hours at about 700° C., then ground in agate mortar 2 or 3 minutes.

Chrysotile (fibrous) unheated: Ground in agate mortar to pass 200 mesh.

Chrysotile (fibrous) ignited: 200-mesh material heated for 2 hours at about 700° C. No further grinding.

Serpentine (ball-milled) unheated: Ball-milled for 1488 hours, dried and reground in agate mortar.

Serpentine (ball-milled) ignited: Ball-milled serpentine heated for 2 hours at about 700° C., then ground in agate morter 2 or 3 minutes.

Mineral	Size of Dust Particles	Results
Chrysotile (ball-milled) unheated	3 microns and less	Grinding destroyed capacity to cause fibrosis. At 1 month considerable inflammatory edema and cellular proliferation and localization of dust particles about bronchioles; at 2 months, only a very slight proliferative reaction; at 6, 8-1/2 and 12 months, widely-scattered small mononuclear phagocytes. At 12 months, a few microscopic patches of thin alveolar wall thickening with some adenomatoid change in portion of air spaces abutting on thickened bronchi. No asbestosis bodies seen.
Chrysotile (ball-milled) ignited	3 microns and less	Reaction limited to large foreign-body giant cells without production of fibrous tissue.

(continued on page 62)

Table 19 continued from page 61.

Mineral	Size of Dust Particles	Results
Chrysotile (fibrous) unheated	20-50 microns approx.	A distinct fibrosis. Reaction localized to connective tissue about terminal bronchioles; little within those tubes. Contraction caused adenomatoid appearance of air spaces given off directly from terminal bronchioles. Reaction area became smaller with progress of time; no new regions involved. No chronic pleurisy even at points abutting intrapulmonary change. At 1 month considerable inflammatory edema and foci of cellular proliferation; at 2 months well-marked cellular proliferation and fibrosis occurring focally about respiratory bronchioles. This reaction developed before asbestosis bodies had formed and was as advanced as that produced by 2 years inhalation of asbestos dust. At 6 months, reaction less extensive than at 2 months, apparently due to contraction of fibrous tissue; asbestosis bodies were abundant. At 8-1/2 months, reaction still less extensive, confined to the immediate vicinity of the small terminal bronchioles, where the scar tissue was quite dense and was becoming hyaline in character. Sometimes it even obliterated the bronchiole. Asbestosis bodies had become scarce. At 12 months, the well-developed peri- and intrabronchial adenomatoid areas of fibrosis had produced considerable distortion. More peripherally were patches of pneumonitis with eosinophilic infiltration, some of which was being transferred into fibrous tissue. These seemed to be precursors of the localized, diffuse patches of thin alveolar wall fibrosis seen elsewhere.
Chrysotile (fibrous) ignited	20-50 microns approx.	Reaction limited to large foreign-body giant cells without proliferation. Heating the fibers, which made them brittle, destroyed their capacity to produce significant reaction.
Serpentine (ball-milled) unheated	3 microns and less	Dust relatively inactive. At 1 and 2 months, simple phagocytosis without proliferation; at 6 months, no change except possibly lymphoid cell infiltration; at 8-1/2 months, a slight chronic pneumonitis; at 12 months, only a little pneumonitis without suggestion of fibrosis.
Serpentine (ball-milled) ignited	3 microns and less	Dust relatively inactive. Reaction essentially the same as for unheated serpentine. With ignited serpentine, less tendency for dust to be carried to bronchial nodes.

Table 20

[illegible] DUSTS

INJECTED INTRATRACHEALLY

Dosage
See Table 19

Animals Used

From 6 to 9 guinea pigs for each dust.

Sacrificing Periods
Usually at 1, 4, 8 and 12 months after injection.

Size of Dust Particles
Separated so that most fibers are from 20 to 50 microns long.

Mineral	Results
Chrysotile (Thetford)	A distinct fibrosis. Additional information given opposite Chrysotile (fibrous) unheated, in Table 19.
Chrysotile (Arizona; low iron content; 0.2% Fe_2O_3)	Reaction virtually identical with that to Thetford Chrysotile. Both fibrosis and asbestosis bodies produced with an asbestos containing very little iron. Fibrosis occurred as plugs within terminal bronchioles and as finer deposits at periphery. Fibrosis developed before asbestosis bodies seen and was in cellular state well-formed at one month. With age, fibrous tissue contracted and occupied smaller area but was more dense. Adenomatoid changes similar to those with Thetford Chrysotile. Pleurisy limited to immediate vicinity of early reaction about areas of massive localization. Asbestosis bodies formed but were few in number. At 1 month after injection, minute foci of mononuclear proliferation about bronchioles and in areas of atelectasis; at 1-1/2 months, heavy peribronchiolar patches of fibrosis often with papillary projections partially closing lumen of bronchiole; adenomatoid appearance marked; connective tissue reaction showed heavy collagen but no hyalinization; at 2 months, minute foci of well-matured fibrosis about bronchioles; at 6 months, mature asbestosis fibrosis with evidence of contraction; considerable chronic pneumonitis with infiltration of lymphocytes and eosinophiles. At 9 months, small intrabronchiolar fibrous plugs with foci of more delicate fibrosis at periphery.
Amosite	Typical fibrous endo- and peribronchiolitis with formation of atypical asbestosis bodies. Haustration of bodies began before 4th month after injection, well-developed by 8th month. Bodies persist after 12th month. Reaction at 1 month heavy endo- and peribronchiolitis already showing

(Continued on Page 64)

Table 10 continued from Page 64.

Mineral	Results
Amosite (cont'd)	fibrous changes; atelectasis and fibrosis with some necrosis at site of massive localization of dust. At 4 months, heavy, widely-scattered endo- and peribronchiolitis, now fibrous, with marked deformity of bronchioles and with an adenomatoid appearance. At 8 and 10-1/2 months, reaction in lung essentially the same as at 4 months. At 12 months, foci of fibrous endo- and peribronchiolitis still large with more dense scar tissue and more deformity of bronchial tubes but no extension into, or atelectasis of, peripheral parenchyma.
Crocidolite (Bolivia)	Advanced fibrous endo- and peribronchiolitis. Beaded asbestosis bodies noted at 8 months. At 1 month, early fibrous endo- and peribronchiolitis; many giant cells and some lymphocytic reaction. At 4 months, small areas of endobronchiolitis scattered throughout the lung; cellular fibrosis. At 8 and 12 months, areas of bronchiolitis smaller because of contraction of dense scar tissue; at 12 months, marked lymphocytic infiltration and adenomatoid appearance.
Crocidolite (S. Africa)	Typical advanced fibrous endo- and peribronchiolitis produced by 0.5% suspension (1 cc total dose); most animals would not tolerate usual 5% suspension. Fibrosis well-developed before asbestosis bodies seen. At 4 months, well-developed fibrous bronchiolitis with lymphocytes and giant cells and adenomatoid change. At 8 months, typical bronchiolitis not quite as extensive or as heavily fibrous as with a 5% suspension, otherwise the same. Many deeply-stained fibers with a good proportion of haustrated asbestosis bodies. At 12 months, heavy fibrous bronchiolitis, more peri- than endobronchiolitis, with lymphocytes and giant cells; very marked adenomatoid appearance.
Anthophyllite	Lymphocytic infiltration and giant cells but no fibrosis. A very few atypical asbestosis bodies. At 1 month, many scattered foci of intrabronchiolar dust without massive localization; lymphocytic infiltration of walls and a few giant cells. At 8 and 12 months, little evidence of dust; a few bronchioles and bronchi with giant cells in adjacent alveoli and with lymphocytic infiltration of walls.
Tremolite	Fibrosis about bronchioles. At 1 month, area of dust localization with collapse of alveoli and infiltration with acute inflammatory cells, macrophages and giant cells. Within the area were a few foci of fibrous tissue and numerous areas of hypertrophy of alveolar epithelium. Many bronchioles packed with fibers. At 4 months, general appearance of lesion unchanged; pleura slightly thickened over heavy localizations of dust. An occasional segmented asbestosis body seen. At 8 months, many foci of fibers in bronchioles and alveolar ducts with cellular reaction as before; also,

(Continued on Page 65)

Table 20 continued from Page 64.

Mineral	Result
Tremolite (cont'd)	some fool showed distinct collagen deposition. At 12 and 18 months, reaction as before with fibrosis about bronchioles more apparent because of contraction and decrease of inflammation. Giant cells prominent. Pleura markedly involved.
Brucite	Typical fibrous endo- and peribronchiolitis like reaction to asbestos minerals. At 1 month, extensive endo- and peribronchiolitis with giant cells; dense fibrous loops within bronchioles and cellular fibrosis about them; adenomatoid change present. At 2 months, heavy intrabronchiolar and peribronchiolar fibrosis producing marked deformity with distortion of tubes and obliteration of surrounding air spaces; fibrosis pale without hyalinization but with few nuclei; no necrosis. Typical asbestosis bodies seen. At 4 and 8 months, little change; fibrous tissue contracting. At 10-1/2 months, dense fibrous bronchiolitis with asbestosis bodies. No pleurisy. No extension to surrounding lung.
Glass Wool	No fibrosis within a year. At 1 month, no reaction inside bronchioles; in peripheral air spaces clumps of giant cells packed with fine spicules of glass with lymphocytic infiltration of adjacent walls; no asbestosis bodies. At 2 months, reaction less intense than at 1 month; fair-sized clumps of elongated giant phagocytes containing spicules and particles of glass; no endobronchitis. At 4 and 8 months, reaction still diminishing. At 12 months, focal areas of pneumonitis with no fibrosis or endobronchitis; moderate number of smooth iron-staining fibers.

Table 21

COMPARISON OF FIBROSIS PRODUCED BY

LONG-FIBER AND SHORT-FIBER DUSTS

INJECTED INTRATRACHEALLY

Dosage
Animals Used — SEE TABLE 19
Sacrificing Periods

Mineral	Size of Dust Particles	Results
Chrysotile (Thetford)	Long-fiber 20-50 microns	A distinct fibrosis. Refer to Chrysotile (fibrous) unheated in Table 19.
	Short-fiber 3 microns and less	No fibrosis. Refer to Chrysotile (ball-milled) unheated in Table 19.
Amosite	Long-fiber 20-50 microns	Typical endo- and peribronchiolitis. Refer to Table 20.
	Short-fiber 20 microns and less	Reaction limited to phagocytosis with lymphocytic infiltration of adjacent walls. Short fibers packed inside swollen phagocytes; longer ones free, some coated to form typical asbestosis bodies. At 1 month after injection, alveoli contained good-sized giant cells; most phagocytes were within air spaces and had not migrated to walls. At 4 months, free extracellular fibers had worked themselves into interstitial tissue where there was extensive proliferation of lymphoid cells and monocytes but no fibrosis. At 8 months, foreign body reaction with some pneumonitis, no bronchiolitis. Typical asbestosis bodies present.
Crocidolite (Bolivia)	Long-fiber 20-50 microns	Advanced fibrous endo- and peribonchiolitis. Refer to Table 20.
	Short-fiber 20 microns and less	No fibrosis. At 1 month, air spaces compressed and largely filled with giant cells packed with dust needles. Walls heavily infiltrated with monocytes and lymphoid cells. At 4 months, a moderate degree of cellular infiltration of walls; small giant cells packed with dust spicules.

(Continued on Page 67)

Table 22

SUMMARY OF INJECTION EXPERIMENTS BY INTRAVENOUS TECHNIQUE

Dosage
Total amount of dust = 1.0 gram, divided into 20 equal doses (each dose was 5 cc of

Mineral	Size of Dust Particles	Animals Used	Maximum Survival After Last Injection	
Chrysotile (Thetford)	3 microns and less (ball-milled 192 hours)	6 rabbits	-	The rabbit the 6 dio after 27 Reaction lungs. No for fatal thrombi.
Amosite	3 microns and less (ground in agate mortar)	5 rabbits	17 months	Advanced shortenin sacrifice the 6 mon focal nec
Crocidolite	3 microns and less (ground in agate mortar)	4 rabbits	12 months	Reaction at 3, 4, no change stroyed t rather th
Anthophyllite	3 microns and less (ball-milled 1400 hours)	4 rabbits	24 months	Reaction Only sugg the liver nuclear a animal. in the li No fibers
Tremolite (soda-iron)	3 microns and less (ball-milled 140 hours)	4 rabbits	19 months	Reaction liferatic No evider
Tremolite (soda)	3 microns and less (ball-milled 48 hours)	4 rabbits	24 months	An inert 12 and 24

was 5 cc of a 1 per cent suspension) which were given twice a week for 10 weeks.

Results
The rabbits did not tolerate intravenous injections of finely-ground chrysotile and 5 of the 6 died after 1 to 5 injections of even diluted suspensions; the other animal died after 27 injections of one-quarter strength suspension (69 days after first injection). Reaction limited to few large giant phagocytes of inactive type in liver, spleen and lungs. No thrombi of dust cells seen in pulmonary capillaries. No definite explanation for fatalities discovered but material may have been retained in heart and caused local thrombi.
Advanced pulmonary infection killed 3 animals at 9, 11 and 17 months after last injection, shortening intended duration of experiment and complicating picture. However, rabbits sacrificed earlier (3 and 6 months) showed only inert phagocytosis with no progression in the 6 months animal. The last two (11 and 17 months) were probably the same although focal necrosis of the liver and amyloid of the spleen made interpretation difficult.
Reaction was that to an inert substance with no change in 12 months. (Other observations at 3, 4, and 6 months). Simple phagocytosis of particles. No tendency to agglomerate and no change in adjacent tissues. Grinding the dust to sizes of 3 microns and under destroyed the fibrous structure of this mineral and injected material resembled plates rather than fibers.
Reaction essentially that of an inert mineral. Observations made at 3, 6, 12 and 24 months. Only suggestion of irritating properties manifested in spleen and lymph nodes, but not the liver, of the 24 month rabbit. In this animal there had been proliferation of mononuclear and giant cells that was not present in either spleen or lymph node of 12 month animal. The absence of associated fibroblastic reaction in these organs and of any change in the liver condition justifies the classification of anthophyllite as an inert silicate. No fibers were retained in lung to demonstrate whether asbestosis bodies would develop.
Reaction essentially that of an inert mineral. Last animal sacrificed showed a little proliferation and lymphocytic infiltration in liver, not seen earlier (at 3, 6 and 12 months). No evidence of any activity in lesions in other organs.
An inert foreign-body reaction with no change in 24 months. Observations made at 3, 6, 12 and 24 months.

Table 21 continued from Page 66.

Mineral	Size of Dust Particles	Results
Crocidolite (Bolivia) cont'd		At 6 and 8-1/2 months, masses of giant cells, containing mineral particles, in small bronchi but not in respiratory bronchioles; smaller ones widely scattered in terminal air spaces. Numerous asbestosis bodies. No reaction in connective tissue. No endobronchial proliferation. At 12 months, many scattered small monocytes packed with dust. No endobronchitis. No peripheral fibrosis. In lymph node, a slight reticulosis; no fibrosis.
Anthophyllite	Long-fiber 20-50 microns	Lymphocytic infiltration and giant cells but no definite fibrosis. Refer to Table 20.
	Short-fiber 3 microns and less	No fibrosis and practically no asbestosis bodies. At 1 month, focal collections of dust-filled monocytes and a few giant cells; at 4 months, some adematoid epithelial reaction; at 8 months, simple pneumonitis with phagocytosis of short-fibers; at 12 months, isolated and sharply localized collections of dust cells inside air spaces about terminal arterioles. Reaction in walls limited to lymphoid cell infiltration. No fibrosis. In lymph node, reaction limited to slight prominence of reticulum.
Tremolite	Long-fiber 20-50 microns	Fibrosis about bronchioles. Refer to Table 20.
	Short-fiber 20 microns and less	Simple foreign-body reaction. No acute inflammation. No accumulation of dust in or about terminal bronchioles. No endobronchitis. At 1 month, scattered small giant cells and considerable infiltration of adjacent small giant cells and considerable infiltration of adjacent walls with monocytes and lymphoid cells. At 4 months, little change except more cellular infiltration of connective tissue. At 8 months, lymphoid infiltration and thickening of walls about some but not all terminal bronchioles.
Brucite	Long-fiber 20-50 microns	Typical fibrous endo- and peribronchiolitis-like reaction to asbestos minerals. Refer to Table 20.
	Short-fiber (made by crushing long fibers with rubber policeman)	Inert type of reaction. At 1 month after injection, small monocytes widely scattered through air spaces; focus of atelectasis with lymphoid infiltration of compressed air-space walls. No endobronchial reaction as with chrysotile. At 2 months, reaction similar to that at 1 month; typical asbestosis bodies seen. At 12 months, [illegible]

Table 23

[redacted]

BY

INTRAPERITONEAL TECHNIQUE

Dosage

Each animal* received a single injection intraperitoneally of 2 cc of a 10 per cc

Mineral	Size of Dust Particles	Animals Used	Maximum Survival After Injection	
Chrysotile (Thetford)	3 microns and less (ball-milled 216 hours)	15 g. pigs	36 months	No fibro nucleate dissolve fat or a made at
Chrysotile (Thetford)	Long fiber (through 100 mesh)	4 g. pigs	2 months	Definite develope tions on
Amosite	3 microns and less (ground in agate mortar)	9 g. pigs	12 months	[redacted] Infection and limi tations
Crocidolite	3 microns and less; also some long spicules (ground in agate mortar)	7 g. pigs	12 months	Dust foci amount of that in g crons, or slightly
Anthophyllite	3 microns and less (ball-milled 1400 hours)	5 g. pigs	25 months	Essential monocytes was also cytes and
Anthophyllite (originally labeled talc)	Mostly 3 microns and less; some fibers 30 microns or more long (ground in agate mortar)	5 g. pigs	12 months	Reaction, ocytes, w experimen connectiv that it o
Tremolite (soda-iron)	3 microns and less (ball-milled 13 hours)	5 g. pigs	12 months	Inert typ tion abou 12 months

*Each animal receiving long-fiber chrysotile was injected with 2 cc of a 0.5 per cent dust suspension.

(Continued on Page 70)

[redacted]

10 per cent dust suspension. Total amount of dust injected = 0.2 gram.

Results
No fibrosis nor asbestosis bodies. Dust particles ingested by phagocytes, chiefly multinucleated variety. Six months after injection fibrous elements of dust appear to have dissolved leaving only the insoluble magnetite, a contaminant. No reaction in surrounding fat or areolar tissue. No transporting of dust to regional lymph nodes. Observations made at intervals from 1 to 36 months after injection.
Definite fibrous reaction produced, delicate and non-hyaline. Atypical asbestosis bodies developed but all were unusually small. No evidence of extra-long fibers seen. Observations only at 2 months.
Infection interfered with interpretation. Dust reaction appeared to be of inert type and limited to phagocytosis with a moderate tendency to lymphocytic infiltration. Observations at 1, 4, 8 and 12 months.
Dust foci consisted only of large mononuclear and giant phagocytes surrounded by a minimum amount of cellular connective tissue. The injected dust contained not only fine material that in grinding had been mashed into irregular plates but also many long spicules 10 microns, or more, in length. No asbestosis bodies seen although the longer spicules appear slightly swollen and greenish. Observations at 1, 4, 8 and 12 months.
Essentially inert foreign body reaction. In early animals (1, 4 and 8 months) focus of monocytes and small giant cells and a little central necrosis. In the 4 month animal there was also slight peripheral fibrosis. At 12 and 25 months, non-progressive mass of monocytes and giant cells; no fibrosis.
Reaction, which consisted of very large giant cells surrounded by a variable number of lymphocytes, was much heavier to these unintentionally long fibers than to the fine dust in the experiment above. There was more or less proliferation of fibroblasts producing cellular connective tissue visible in areas where the quantity of foreign particles was not so great that it obscured the reaction. Observations at 1, 4, 8 and 12 months.
Inert type of response never progressing beyond the stage of very slight lymphocytic reaction about masses of dust-filled phagocytes. No fibrosis. Observations at 1, 4, 8 and 12 months.

Table 23 continued from Page 69

Mineral	Size of Dust Particles	Animals Used	Maximum Survival After Injection	
Tremolite (soda)	3 microns and less (ball-milled 48 hours)	5 g. pigs	18 months	Inert nc 4, 8, 12
Anthophyllite (originally labeled talc) Pyrophyllite (fibrous) Pyrophyllite (crystalline)	100 microns and less	15 g. pigs	12 months	Distinct quent re about lc anthophy 4 months all thre necrosis

Results
Inert non-progressive foreign-body type of reaction. No fibrosis. Observations at 1, 4, 8, 12 and 18 months.
Distinct early fibrosis produced by anthophyllite and fibrous pyrophyllite with subsequent regression; crystalline pyrophyllite inert throughout. At 1 month, giant cells about long thick splinters; at 4 months, definite fibrosis replacing giant cells of anthophyllite and fibrous pyrophyllite reaction; at 8 months, fibrosis which started at 4 months had decreased, especially with fibrous pyrophyllite. At 12 months, reaction to all three dusts consisted of foreign-body giant cells with lymphocytes but without necrosis or fibrosis. No asbestosis bodies.

Table 24

ANALYSES OF FIBROUS MINERALS

	Amosite	Amphibole	Antho-phyllite	Brucite	Chrysotile	Croci-dolite	Tremolite
	per cent	per cent	per cent	per cent	per cent	per cent	per cent
SiO_2	46.23	55.04	59.80	0.90	38.56	54.93	56.20
Fe_2O_3	4.06	3.05	0.57	6.78	2.35	15.27	7.21
FeO	33.83	-	-	9.36	-	4.29	-
Al_2O_3	1.09	1.69	0.32	0.46	0.34	1.01	0.56
CaO	2.01	12.22	0.44	0.04	0.03	0.80	4.44
MgO	6.28	23.29	33.37	53.99	38.95	12.25	20.52
Na_2O	0.33	0.43	0.52	0.91	0.29	6.92	6.78
K_2O	0.20	0.12	0.15	0.16	0.08	0.57	0.99
Ignition Loss (<105°C	0.66	0.32	0.27	0.53	4.30	0.02	0.34
(>105°C	5.28	3.60	4.08	26.66	14.99	2.56	2.78
	99.97	99.77	99.52	99.79	99.89	99.68	99.82



Fig. 1 - King's Floats Inhalation, Guinea Pig, 30 Months.

The lesion is more pronounced than most of those seen in this experiment. The two larger central spaces are bronchioles, and they are surrounded by scar tissue, forming the typical peribronchiolar fibrosis. The so-called "adenomatoid" change is prominent, especially between the two bronchioles. 200X

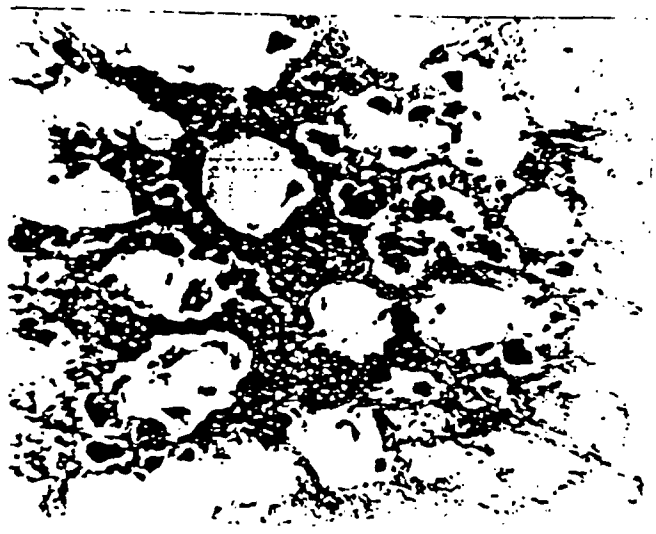


Fig. 2 - Short-Fiber Asbestos Inhalation, Guinea Pig, 30 Months.

A bronchiole is present in the left center of the field. In the central portion, to the right of the bronchiole, is a small zone of cellular fibrosis. The scattered dark structures are phagocytic cells filled with particles of dust. 200X

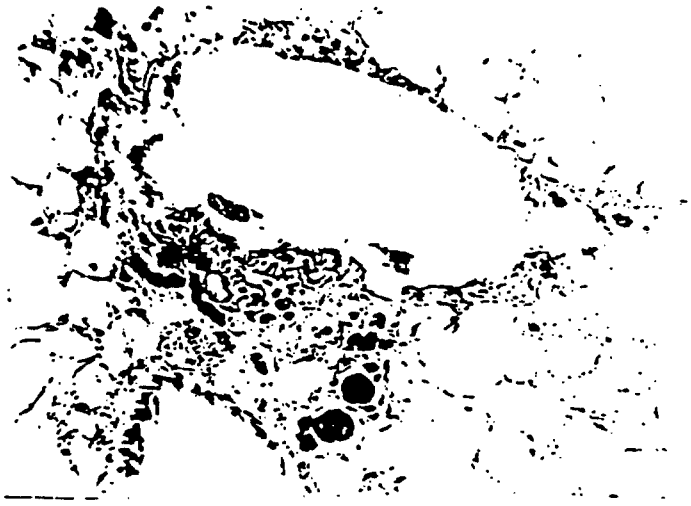


Fig. 3 - 100 Per Cent Ball-Milled Asbestos Inhalation, Guinea Pig, 30 Months.

This field shows a rather large bronchiole, virtually without reaction. A few adjacent alveoli contain phagocytes, packed with particles of the dust. 200X

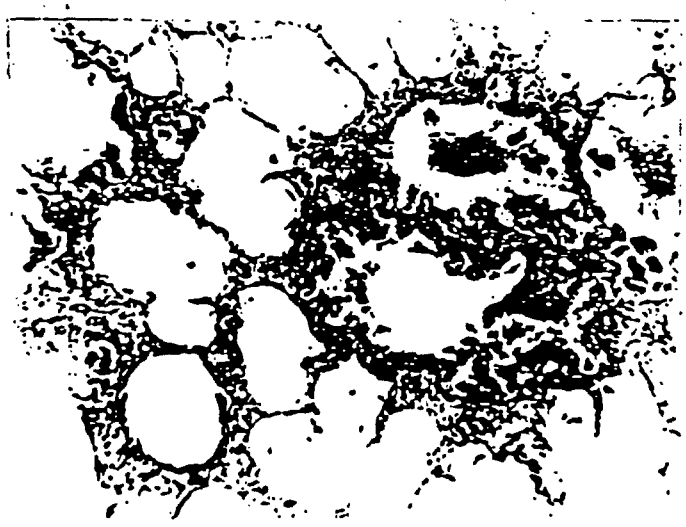


Fig. 4 - Long-Fiber Asbestos Inhalation, Guinea Pig, 30 Months.

In the right center is a bronchiole surrounded by cellular fibrosis. At the left is an area in which alveolar walls have been involved by extension of the process. 200X



Fig. 5 - Intratracheal Chrysotile, Guinea Pig, 2 Months.

There is obvious peribronchiolar fibrosis. 200X

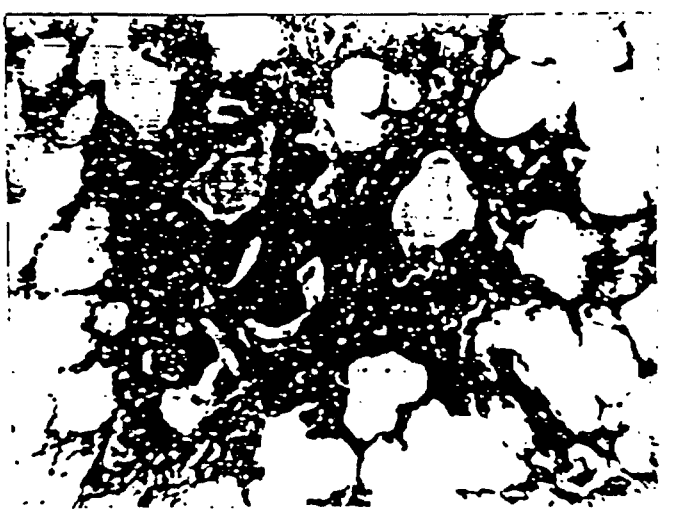


Fig. 6 - Intratracheal Crocidolite, Guinea Pig, 4 Months.

There is obvious peribronchiolar fibrosis of about the same degree as in Figures 5 and 7. 200X



Fig. 7 – Intratracheal Brucite, Guinea Pig, 4 Months.

Note the similarity of the lesion to that in Figures 5 and 6. 200X

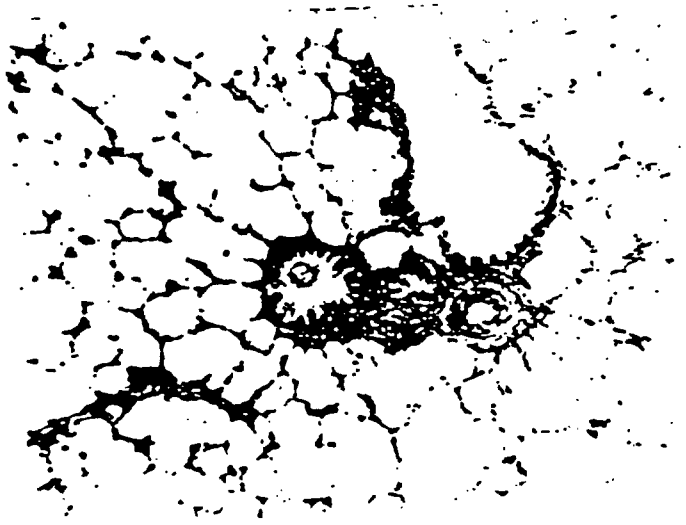
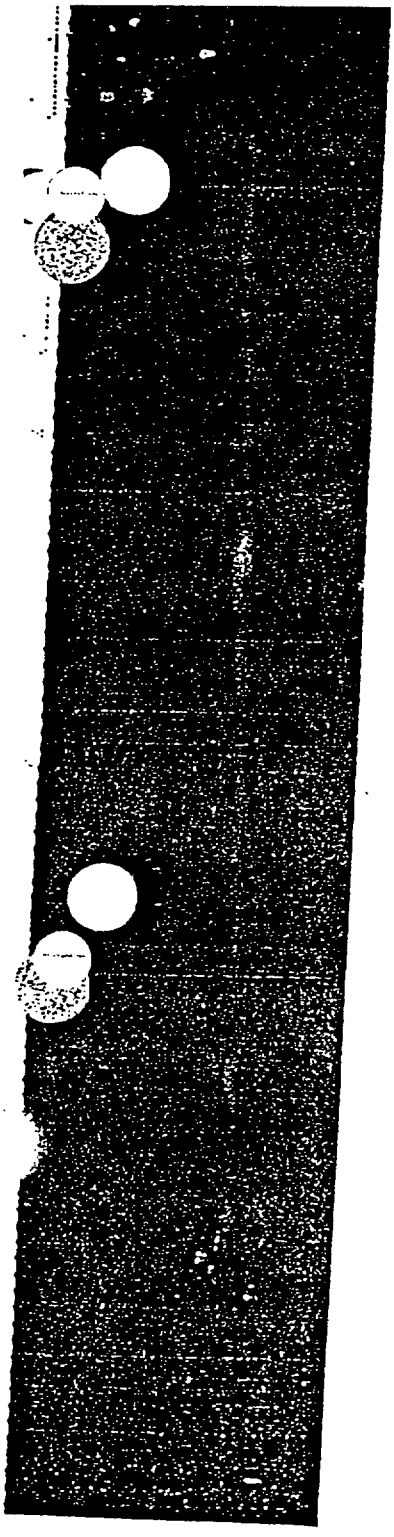


Fig. 8 – Intratracheal Glass Wool, Guinea Pig, 4 Months.

Two bronchioles are present in this field, one seen in cross section and the other in longitudinal section. The associated pulmonary arteriole is present beneath the latter. The structures are virtually normal, although fibers of glass wool would be visible if examined with higher magnification. 200X



(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
zation 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

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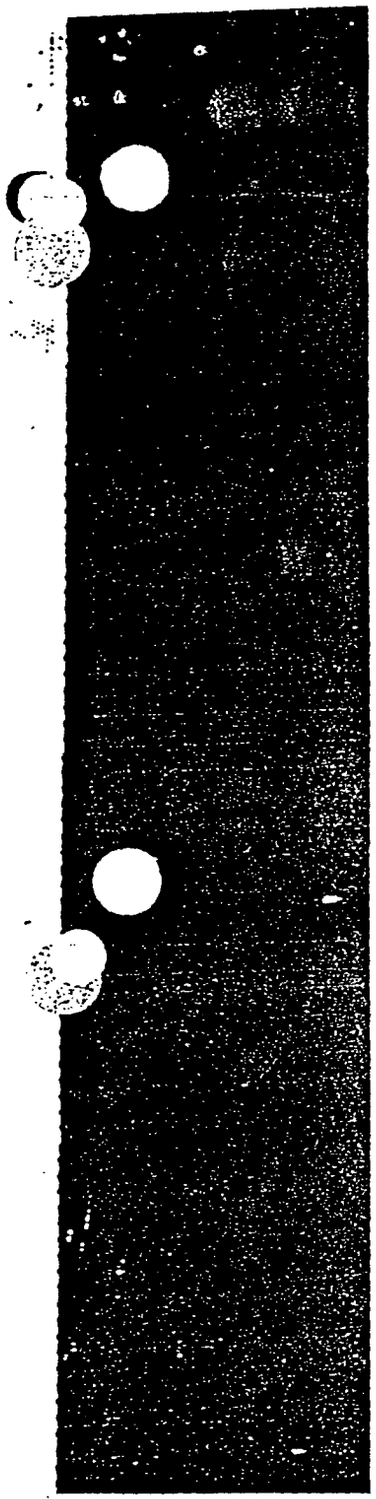

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