FILE NAME: Metropolitan Life (ML)

DATE: 1950-1995

DOC#: ML312

DOCUMENT DESCRIPTION: Suppression of Saranac Cancer Experiment #2 for QAMA

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~~O.H.M.J.~~
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CONFIDENTIAL

Second Saranac experimental study of cancer potential of asbestos, for DAMA, 1950-1952. Never publicly disclosed.

Hospital
August 31, 1950

C. M. McGaw

Pulmonary Malignancy

I am enclosing copies of a letter and contract received from Dr. Lanza. It will be noted that Dr. Lanza has agreed with Dr. Cartier and I that the program should consist of two parts:-

1 - An epidemiological or statistical study
2 - Animal experiments consisting of:
    (a) Inhalation experiments
    (b) Implantation or injection

I still believe that the statistical study can be carried out by a Canadian authority and thus be more acceptable to various groups in this Province. Also, I believe that the best results from inhalation studies will be obtained through the Saranac Laboratory.

Concerning the Implantation Experiment Program proposed by Dr. Lanza, I believe that their methods are sound and the results will be scientifcally interesting. I would prefer to make no decision until the Saranac proposal is received.

The contract appears to leave little choice to the Donor if the results of the study are unfavorable to Company interests and are submitted for publication. However, I fail to see how they can find anything more unfavorable than that which already has been published by Merewether and Heuper.

KWS/h.n.

Kenneth W. Smith, M.D.

CC - K. V. Lindell
G. K. Foster - Montreal

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9/15

PRODUCED
JM - 83

October 27[illegible]

[redacted]

[illegible]. A. J. Vorwald, Director
The Saranac Laboratory
P. O. Box 551
Saranac Lake, New York

Dear Art:

Confirming phone conversation with Mrs. Blinn this morning, it is planned that we will meet Mr. Sabourin there at Saranac on Tuesday, November 7, to review the proposed asbestos program that has been under consideration by the Q. A. M. A.

When the subject was reviewed here with Mr. Fisher, Mr. Foster, and Mr. Sabourin, following the C. A. M. A. meeting, it was suggested that this meeting be held with you.

It has been difficult to get a day when both Dr. Lanza and Mr. Sabourin could be there, and I hope that the date chosen, Tuesday, November 7, will be satisfactory with you.

Mrs. Blinn said that she or you would call me on Monday, October 30, about the date.

Sincerely yours,

J. P. Woodard

bc: A. J. Lanza, M. D.
A. R. Fisher
Ivan Sabourin
[illegible]. K. Foster

[redacted]

[redacted]

CONFIDENTIAL

MINUTES OF DISCUSSION HELD AT SARANAC LAKE ON NOVEMBER 7, 1950

These present were: A. J. Lanza, M. D.
Ivan Sabourin
A. J. Vorwald, M. D.
J. P. Woodard

The Saranac Laboratory's Proposal of September 21, 1950, to the Quebec Asbestos Mining Association stated the problem as:

> "The specific problem is to ascertain whether or not a relationship exists between the inhalation of asbestos dust and primary pulmonary cancer."

This report proposed a program for trying to get an answer to this problem. The program consisted of two phases:

1. Epidemiological investigation.

2. Experimental investigations, i.e., dusting and checking of animals.

The report to the Quebec Asbestos Mining Association on Pulmonary Cancer, dated September 25, 1950, which was accepted in principle by the Q. A. M. A. at their recent meeting, generally followed, but in brief, Saranac Laboratory's Proposal. A committee of the Q. A. M. A. composed of Messrs. Foster and Sabourin presented this report at this recent meeting.

Following a discussion with Mr. A. R. Fisher, it was left that Messrs. Woodard and Sabourin, and Doctors Vorwald and Lanza would review the Proposal at Saranac to clear up any questions that might be open and arrive at a conclusion as to what is recommended from here on, including who would do what, how long it would take, and how much it would cost.

That was the purpose of this meeting.

I. Short-Range Program - Epidemiological Survey

The short-range program was to consist of a carefully conducted epidemiological survey to determine the incidence of cancer among people exposed to asbestos dust as compared with the incidence among those not exposed.

A. Discussion:

1. Dr. Vorwald's comments were as follows:

   a. We should learn the incidence of cancer among those exposed to asbestos dust and among those not exposed by:

(1) A careful study of the X-rays of people employed in the asbestos industry.

(2) A study of the X-rays made of the general population by the mobile units of the Provincial Department of Health (those not exposed).

(3) A study of post-mortem data on the presence of cancer at death insofar as such information may be available. It was pointed out that in the Province it is the practice not to list cancer as a cause of death even when it is, so that information on this may not be of much help to us.

2. Dr. Lanza commented:

a. The one important point is that we get an expert epidemiologist, i.e., one who can take the job over, do it correctly and adequately, and come up with the correct answer.

b. Dr. Lanza agrees it is important that a Canadian be chosen to handle the job. In case a Canadian cannot be found who can do the job adequately, someone from the U. S. can then be used.

3. Mr. Sabourin suggested:

a. That prior consultation with appropriate Canadian authorities and a request for their suggestions on certain phases of the program would get their tacit backing and that this would materially strengthen the base of the program. Accordingly, Mr. Sabourin agreed to review the matter with Dr. Vidal and also to arrange so that Dr. Vorwald will be able to be in touch easily with the Dean of the McGill Medical School (or Dr. Vorwald will do so, as may be decided between the two of them). By this arrangement, Dr. Vidal and the McGill Dean would know of the program and their help and suggestions would be sought in choosing an able epidemiologist to carry out the first part of the program. Having decided on the individuals who might be considered for the job, it would then be up to Saranac to make final arrangements.

b. In addition to the epidemiologist, a statistician is needed. Miss Rose has been suggested as an assistant. This can be worked out by Dr. Vorwald and Mr. Sabourin in line with the situation and the wishes of the Q. A. M. A.

4. It was the understanding also that X-ray consultants would be needed and it was the consensus that Doctors Smith and Cartier could do preliminary screening of X-rays, which would leave Saranac only

the job of studying those which would be sent to Saranac. It was pointed out that the two company doctors should not be used in any fashion that might lead anyone to question the objectivity of the study and this Saranac can determine.

B. Conclusions:

1. Doctors Smith and Cartier will screen X-rays, then Saranac will make the final study on the X-rays that have been screened out for them.

2. An epidemiologist will be chosen, as outlined above. Saranac will make the approach with a view toward making final arrangements with the man who has been tentatively chosen.

3. The epidemiological report as first made will go to Saranac. Dr. Lanza will evaluate the report in this form and suggest best use of the report, revisions that might be made, and other such matters. There should be discussion between Saranac, the underwriting organizations, and others interested as to the timeliness and propriety of the use of the material developed by this report. It is important that the report be available only to the underwriting companies and not made generally available until it has been reviewed with and by the companies.

4. Saranac Laboratory is responsible for the program.

a. Saranac is to make the final arrangement with the epidemiologist and others to make the study, and is also responsible to head up and supervise the study.

b. The program should be started as soon as it is possible to do so.

c. It was estimated that the job could be done in six months if a qualified epidemiologist can be obtained who can devote a reasonable length of time to the study. It is desirable that the job be done in six months and therefore the person hired for the job should be impressed with the fact that the study should be pushed and conclusions reached promptly.

d. While the original program stated a possible cost of $4,000, it was stated in the discussion that the cost might run between $4,000 and $6,000, it being thought, however, that $5,000 would be adequate.

II. Long-Range Program - A research program of perhaps two years' duration in two parts:

(1) The transplanting of asbestos and embryonic tissue into animals (originally suggested to be under the guidance of Dr. Lanza and his group).

I. INTRODUCTION

An experiment has been in progress at The Saranac Laboratory for some 14 months in an attempt to ascertain the influence of inhaled asbestos dust upon the incidence of pulmonary tumors in mice. The purpose of this study is to obtain experimental data for correlation with experience pertaining to pulmonary cancer in industrial workers exposed occupationally to the inhalation of asbestos dust.

Two strains of mice, one susceptible and the other resistant to the development of pulmonary tumors, have been exposed to the asbestos dust; comparable numbers of control animals of each strain have been kept in normal air but under conditions of housing and diet identical with those of the experimental animals. The experiment has been designed to reveal a possible earlier onset of tumors in the exposed animals than in the control group as well as to determine the total incidence of tumors occurring over the entire period of the experiment.

It may be stated here that the evidence obtained reveals no tendency towards an earlier onset of tumors among exposed animals in comparison with control animals. Nevertheless, there does appear to be a trend toward a greater incidence of tumors in the exposed animals than in the control animals. It is important to note, however, that statistical analysis of the data obtained up to the present shows that the differences between the experimental and the control animals are no greater than might be expected to occur by chance alone. The experiment is not completed and it is considered likely that, if the ratios of tumor incidence at the next period when animals

are killed are similar to those for the 14-month interval, the trend which is now noted may finally be shown to be statistically significant because of the larger total number of animals observed.

II. MATERIALS

A. Dusting Material: The dust used in this experiment was received on January 5, 1951, from the Johnson Company Asbestos Mines of Thetford, Quebec, and was given the Saranac Laboratory number MD-136. X-ray diffraction analysis revealed that the material contains a variety of minerals, of which the serpentine group amounted to 70 per cent. Though the particulate mineral serpentine and the fibrous mineral chrysotile yield the same diffraction pattern, petrographic examination showed that there was considerably more chrysotile than serpentine present in the material. Much of the chrysotile occurred in thick unopened bundles, but it was estimated that at least 25 per cent of the chrysotile was present as individual fibers or partially opened bundles. Other components, largely particulate, included a few per cent of magnetite, chromite, brucite, talc, and quartz, and traces of miscellaneous minerals. The quartz content was about 1 to 2 per cent. Of the particulate material at least 85 per cent of the particles were less than 5 microns in size.

Studies of samples of atmospheric dust taken from the animal exposure room revealed, with respect to the length of the chrysotile fibers, that the fibers occurred in the following distribution of sizes:

Fibers less than 5 microns in length	32.3 %
" from 5 to 10 " " "	35.8
" " 10 to 20 " " "	20.7
" " 20 to 50 " " "	8.3
" " 50 to 100 " " "	2.7
	99.8 %

of the asbestos dust by a rotating paddle in a large hopper filled with asbestos dust to approximately the level of the axle of the paddle. The edges of the paddle are equipped with stiff wire brushes to break up the small balls of asbestos which tend to form. The dusting mechanism is kept in operation inside the 8-foot cubical dust room for 8 hours a day, 5 1/2 days per week. Animals live continuously in the room, which is ventilated with fresh clean air when the dust disseminator is not in operation. Atmospheric samples are collected in the room at regular intervals with a Greenburg-Smith midget impinger and dust counts made by the light field technic with a microprojector. The dust counts have averaged 617 million particles per cubic foot of air. In general, the fibers have represented about 6.6 per cent of the total count, or 53.8 million. Of the total number of fibers, about 11 per cent are longer than 20 microns. It will be recalled that, in regard to the production of asbestosis, the fibers greater than 20 microns in length are of the greatest importance.

B. Animals: At the start of the experiment 260 mice were placed in the dust room; 130 of these were Strain C mice, and 130 were Strain C57 black mice. Of each strain 30 were males and 100 were females. This sex ratio was dictated by space requirements, since male mice tend to fight and must be kept in small groups, while many females may safely be placed in a single cage. The total number of control mice was 340, with a sex distribution similar to that of the exposed groups.

In order to follow the development of tumors and to observe any possible earlier onset of tumors among the exposed mice, experimental animals and control animals were killed at regular intervals after the

beginning of the exposure to dust. The intervals chosen were 2, 4, 6, 10, and 14 months; the next interval has been set for 16 months. At each period 34 experimental and 34 control animals were killed; of each group of 34 animals, 17 were Strain C and 17 were Strain C57 black. In each case, the 17 animals included 4 males and 13 females.

IV. RESULTS

The observations made at each of the periods when animals were killed are presented in table 1. It will be noted that the total number of animals examined in each of the different groups varies slightly. This variation is the result of a few spontaneous deaths in each group. The observations made in such cases have been incorporated in the data for the next period. In many instances animals dying spontaneously have been eaten by their cagemates. It has been necessary to discard these animals completely from the record of experimental observations.

It will be noted that within Strain C there is a higher percentage of tumors among animals exposed to asbestos dust than among the controls. The same situation is true within the Strain C57 black. Obviously, the same condition is true also of the over-all figures combining both strains.

The significance of all these percentage incidence figures has been tested statistically by means of the well-recognized formula:

$$S.E. = \sqrt{\frac{P_1 \cdot Q_1}{N_1} + \frac{P_2 \cdot Q_2}{N_2}}$$ where

S.E. = Standard error of difference in incidence between two groups

N_1 = Total number of animals in the group

P_1 = Per cent of animals with tumor in a specific group of animals

Q_1 = " " " " without tumor in the same specific group

(Thus, $Q_1 = 100 - P_1$)

N_2, P_2, Q_2 — Corresponding symbols for another group of animals

It will be recalled that if an observed difference in percentage incidence between two groups is greater than twice the standard error of that difference, the difference may be considered to be significant and due to factors other than chance. If the observed difference is less than twice the standard error, it is very likely due simply to chance. In table 2 the observed difference in the incidence of pulmonary tumor and the critical value of twice the standard error of difference are compared for the various groups. It will be noted by comparing the values that none of the observations made to date are statistically significant. An example of the method of calculation follows.

Calculation of standard error of difference between over-all incidence of tumors in the control animals and in the experimental mice from data in table 1:

Incidence of tumors:	Experimental animals	9.5%
	Control animals	5.5
Number of animals observed:	Experimental animals	179
	Control animals	181

$$S.E. = \sqrt{\frac{9.5 \times 90.5}{179} + \frac{5.5 \times 94.5}{181}} = \sqrt{4.80 + 2.87} = \sqrt{7.67}$$

$$= 2.77$$

$$2 \times S.E. = 5.5\%$$

Thus a difference up to 5.5 per cent is likely to occur by chance. The observed difference of 4 per cent (9.5 - 5.5 = 4.0) may therefore have occurred simply by chance distribution of animals and is not statistically significant.

V. COMMENT

It will be apparent from a review of table 1 that the experiment is now in its most important phase. The incidence of pulmonary tumors has begun to rise for animals killed at the 14-month period, both for the control animals and for the animals exposed to asbestos dust. The increased incidence is more pronounced for the group exposed to dust, but the rise has occurred at about the same time in both groups. The differences between the two groups, however, as has been noted, are not statistically significant.

The impression is gained from an inspection of table 1 that the large numbers of animals killed early in the experiment are weighting the final figures and detracting from the magnitude of the incidence of tumor. It must be noted that this study has been an experimental one and that it has been necessary to make observations by killing animals for study at regular intervals. It appears that by means of a rather involved statistical procedure the disproportionate weighting of the values by the data of the early observations can be eliminated. This procedure will be carried out after final observations have been made, since it is too laborious an undertaking to be performed at the present stage when the values obtained would be only of academic interest.

It may be noted in passing that if the over-all incidence of tumor among the exposed animals had been only slightly greater—11 per cent rather than 9.5 per cent—the difference between the incidence for the exposed group and for the control group would have been statistically significant.

VI. SUMMARY

An experiment concerning the influence of inhaled asbestos dust upon the incidence of pulmonary tumors in mice has been in progress for 14 months. Analysis of the results of this experiment reveals that thus far (after the animals have been exposed to asbestos dust for 14 months), the dust has not exerted an influence of a degree sufficient to cause statistically significant alterations in the incidence of pulmonary tumors. The final phases of this experiment will be of great importance, since at the most recent period when animals were killed for study the incidence of tumors had increased and the increase seems to be more pronounced among the animals exposed to asbestos dust than among the non-exposed control animals.

AJV:jc

Table 1

Occurrence of Pulmonary Tumors

in Mice Exposed to Asbestos Dust and in Mice Not Exposed to Dust

Strain of mice	Period of observation	Number of mice with tumor in the group exposed to asbestos dust		Number of mice with tumor in the control group not exposed to dust.	
	months	Male	Female	Male	Female
Strain C (Tumor susceptible strain of mice)	2	0	0	0	1
	4	0	1	0	0
	6	0	1*	1	0
	10	0	2	0	1
	14	1	7	0	4
			12		7
Number examined:		22	72	20	72
			94		92
Incidence of tumor:		12 ÷ 94 = 12.8%		7 ÷ 92 = 7.6%	
Strain C57 Black (Tumor non-susceptible strain of mice)	2	0	0	0	0
	4	0	0	0	0
	6	0	0	0	0
	10	0	1	0	2
	14	2	2	0	1
			5		3
Number examined:		19	66	20	69
			85		89
Incidence of tumor:		5 ÷ 85 = 5.9%		3 ÷ 89 = 3.4%	
Incidence of tumor in both groups:		17 ÷ 179 = 9.5%		10 ÷ 181 = 5.5%	

* Malignant

Table 2

Difference in Incidence of Pulmonary Tumors

in Mice Exposed to Asbestos Dust and in Mice Not Exposed to Dust

Groups of mice compared	Observed difference in incidence	Twice the standard error of difference	Statistical significance of observed difference
	per cent	per cent	
Strain C asbestos group vs Strain C control group	5.2	8.8	Not significant
Strain C57 black asbestos group vs Strain C57 black control group	2.5	6.5	Not significant
All asbestos groups (both strains) vs All control groups (both strains)	4.0	5.5	Not significant
All asbestos groups at 10 and 14 months vs All control groups at 10 and 14 months	8.3	13.0	Not significant
All asbestos groups (total incidence) vs All groups * (total incidence)	3.1	4.8	Not significant

* The values for all groups (total incidence) are based upon observations for the asbestos and the control groups and also for groups exposed to two other dusts--iron oxide and quartz--in another experiment.

American Journal of Industrial Medicine 27:593–606 (1995)

COMMENTARY

Chronology of Asbestos Cancer Discoveries: Experimental Studies of the Saranac Laboratory

Gerrit W.H. Schepers, MD, SCD

This commentary challenges a recently published perception that Dr. Le Roy Upson Gardner had not actually discovered in 1942 that inhaled chrysotile fibers could induce malignant neoplasia in mice. The handwritten laboratory notes and some of Dr. Gardner's slides have recently been found. They verify that the tumors he saw in the mice included truly malignant neoplasms. Gardner had by then also accumulated 11 cases of human lung cancer (two mesotheliomas) derived from Quebec asbestos miners and millers. An inhalation study designed by Dr. Gardner and conducted between 1951 and 1954, using cancer-insusceptible mice, yielded neoplasia risk ratio of 5.7 compared with control animals. The studies also showed that the primary effect of chrysotile is to cause epithelial proliferation in alveoli adjacent to bronchioles. Chrysotile type asbestos bodies were shown to remain only transiently ferruginous, but even though invisible in direct light they can be visualized at high magnification through use of phase contrast and polarized light micrography.

Key words: Saranac laboratory, asbestos, history of medicine, experimental studies

INTRODUCTION

In a recent Letter to the Editor, Dr. Enterline [1993] seems to question whether Drs. Gardner, Vorwald, or Schepers, as directors of the former Saranac Laboratory, ever discovered, through animal experimentation, whether chrysotile asbestos dust is capable of inducing neoplasia. His interpretation of those documents he had available seems to be that Dr. Gardner had found in 1942 only autogenous adenomas in the lungs of mice that had inhaled chrysotile long fiber dust. Perhaps Dr. Enterline, who appears well informed on many matters, has nevertheless not yet read all that is available on this subject. Gardner had written letters and reports designating some of the mouse tumors as malignant and he attributed the tumors to inhaled chrysotile asbestos fibers, even though the mice had not developed asbestosis.

In a companion discussion by Drs. Egilman and Hardy [1993], allusion to corruption of the early scientific literature on asbestos cancers appears. This causes

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me to wonder whether Gardner is posthumously and 50 years later accused of evil doing. Dr. Vorwald is likewise cast in a rather unfavorable light, but this is more difficult to judge, as he actually contributed no personal work to the literature on asbestos' health effects. A further implication may be that Dr. Gardner was an incompetent who could not distinguish a benign adenoma from a malignant neoplasm, and that persons who never studied these cancers are in a better position to assess their true importance than the man who discovered them. Most of these suppositions are questionable. Dr. Le Roy Upson Gardner was the doyen research pioneer and wholly incorruptible scientist of American experimental pneumoconiology. He also was an experienced and very thorough, but conservative, pathologist who never made any judgment unless absolutely convinced of his facts. Most of his studies were repeated many times with multiple variations to get at the truth.

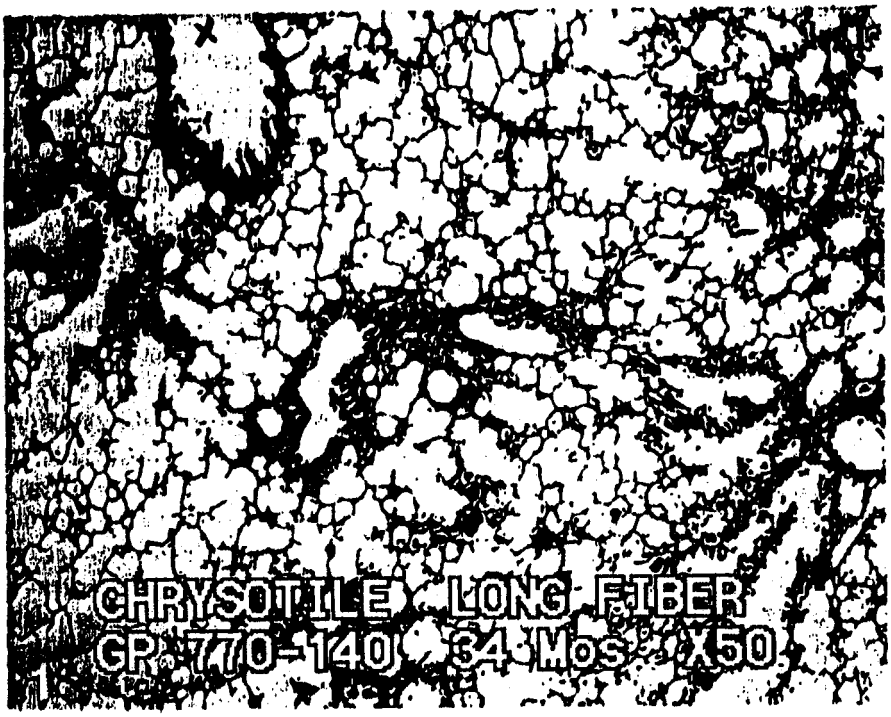
My interpretation is that Gardner had found in 1942 that the majority of the mouse tumors were truly malignant. This is fairly clearly recorded in Dr. Gardner's handwritten notes, the originals of which presently are entrusted to me by court order. His *ipsissima verba* are summarized presented in the accompanying *EXHIBIT*. Fuller details are provided in my (to be published) manuscript on the "Thirty Years of Asbestos Research of the Saranac Laboratory between the years 1928 and 1958."

Dr. Enterline also interprets descriptions published by Schepers on animals that had inhaled KAYLO (asbestos-containing thermal insulation) dust, as indicating that he had said they had developed lung adenomas [Schepers et al., 1955]. This is erroneous. In the referenced paper, it was stated only that animals which had inhaled the KAYLO dust for up to 3 years, between 1946 and 1951, progressively developed peribronchiolar adenomatoid epithelialization. This descriptive terminology was newly coined for the paper, as there was no precedent guidance on what to call such lesions. From about 1930 onwards, Dr. Gardner had described similar dramatic and unique responses of the animal lungs to inhaled chrysotile dust. No nomenclature then existed in standard texts of pathology, this tissue response being something new. Gardner, as the first scientist to study these phenomena, had to devise his own varied terminology, using phrases such as "peribronchiolar dust reactions in lateral alveoli" or "glandlike atelectatic air spaces around bronchioles." These terms, with some minor variations, also appear in quarterly reports to research sponsors over the period 1932–1946. Dr. Gardner did not publish these research findings in technical journals, for his work was performed on behalf of industrial sponsors, from whom he did not have permission to publish. His terminology therefore did not again appear in public media after his initial published report on his studies with "Kings Floats" [Gardner and Cummings, 1931] until Dr. Vorwald published an abbreviated version of parts of Dr. Gardner's 1946 "Monograph on Asbestos," in which Gardner's descriptions were copied across almost verbatim, except that the mouse cancer data are not mentioned [Vorwald et al., 1951]. The next time this very distinctive chrysotilic reaction was published was in the 1955 Schepers report on the KAYLO experiments. Since I had studied the Gardner experimental data previously, I was able immediately to recognize the similarity of the KAYLO lesions to those which chrysotile had evoked in Dr. Gardner's other experiments.

Figures 1–4 provide examples of the abnormalities which inhaled chrysotile evokes in animal lungs. These photos were recently made from lung tissue sections of guinea pigs prepared in 1940. These animals had inhaled long fiber chrysotile dust for up to 34 months in experiment 770 of the Saranac Laboratory, which ran from

1936 to 1942. The low power view shows that the cellular proliferative reactions in the lungs are focal or patchy and centered on terminal ramifications of the bronchial tree and interspersed between emphysematous, but otherwise unaltered, lung parenchyma. Higher magnification shows that the lesions consist of prodigious proliferation of epithelial cells lining several tiers of alveoli adjacent to the terminal bronchioles. Asbestos particulates are clustered together in desquamated cells in the centers of the abnormal alveolar spaces where ferruginous asbestos bodies can be identified. Ferruginosity of these bodies dissappeared within a few months from cessation of dust exposure, but these chrysotile asbestos bodies could be demonstrated by phase contrast micrography, and tremolite-actinolite fibers in them by polarized light micrography. It is the presence of this foreign matter which differentiates these lesions from neoplasia. The epithelial proliferations look like adenocarcinoma, except for the presence of the causative agent. Identical lesions were evoked in the KAYLO study, of which asbestos was only a 15% ingredient. That these epithelial proliferations should be classified as neoplastic was strongly considered by me in 1955 when the KAYLO paper was written, but at that time I felt that this could not yet be postulated, because the KAYLO particulates were still present and I had no means to know whether these adenomatoid epithelialization reactions would be permanent or transient reactions to the KAYLO dust. I did not call these lesions either adenomata or carcinomata. Had I judged them to be adenomata or carcinomata I would have said so. I did suspect that these lesions would be precursive to malignant neoplasia. Had they persisted and enlarged after cessation of dust exposure I would have called them embryonating carcinomata. This is how chrysotile carcinoma often starts in human and animal lungs. The KAYLO study was, however, not designed to probe the issue of carcinogenesis. For that purpose the animals should have been allowed to live their full life spans in the KAYLO dust environment with one group taken out halfway and allowed to survive in normal air until death. This is not what the Saranac Laboratory undertook to do. The study sponsor, Owens Illinois Glass Company, merely wished to know whether KAYLO dust would be harmful to inhale by their staff or by end users. Dr. Gardner's endeavor therefore was to discover how soon the lung tissues would react to the test substance and how any tissue reaction evolved and whether the responses would likely be permanent. For this purpose he had animal clusters sacrificed at intervals of 3 months, leaving very few at the end, when cancer likely might ensue. His task was to immediately warn industrial sponsors if any adverse reaction occurred, so that they could take immediate needed steps to combat identified problems. His objective was not to find what the worst effects of the test material would be, but how quickly one could detect an adverse response. Cancer was not therefore an issue. Tuberculosis then still was highly relevant and a mycobacterial infection phase study was included, which fortunately yielded rather favorable results.

Did either Dr. Gardner or Dr. Vorwald discover that chrysotile causes cancer? Enterline seems to suggest that they did not. They both most assuredly did! How did I discover this? In 1949 I spent 3 months at the Saranac Laboratory on assignment by Dr. Anthony Lanza, director of the Institute of Industrial Medicine of New York University, where I then pursued post-graduate studies as a Commonwealth Fellow. I was also there as a representative of the Pneumoconiosis Bureau of the South African Government and my assignment from the Bureau was to ascertain whether chrysotile caused human cancer as we already knew amosite and crocidolite did. The South African Government was considering legislation to make cancers of all asbes-



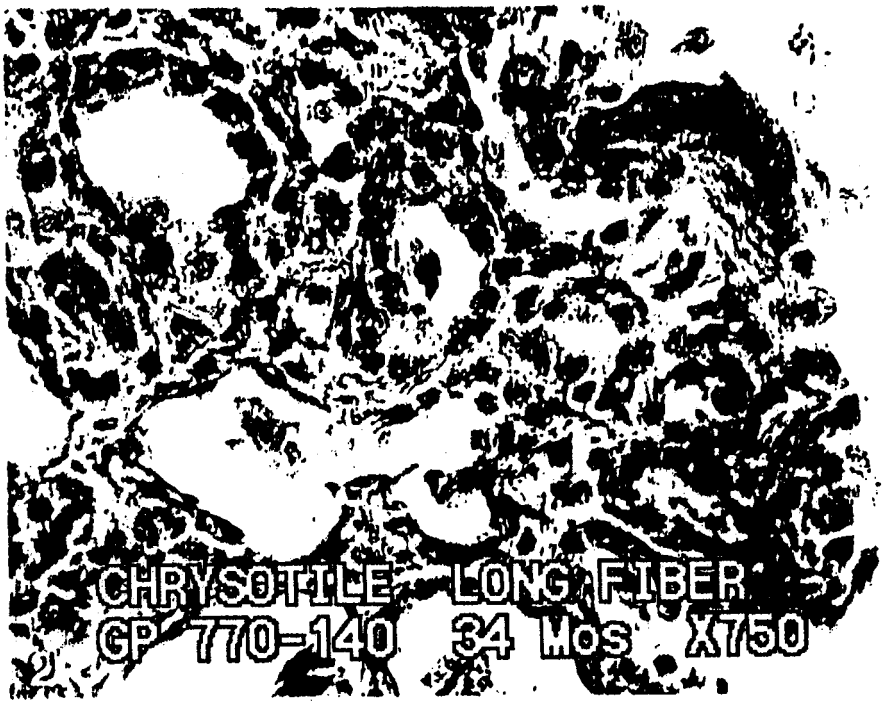


Fig. 1. Photomicrograph of a midcoronal section of a guinea pig lung. Appearance at the end of 34 months of inhalation exposure to an aerosol of chrysotile at about 5 million particles per cubic foot of air at cage level. The dark structures are bronchioles with peribronchiolar cellular proliferation around them. The light areas are lung alveoli, many of which are overdistended. The bronchus shown at X appears unaffected, but a definitive judgment would require higher magnification. (Reduced 1.85× from original photo.)

Fig. 2. 750× power view of guinea pig lung tissue reveals the dense tissue shown in Figure 1 to consist of tiers of alveoli adjacent to the bronchioles, whose surfaces are covered by sheets of large epithelial cells. The lesion is largely an epithelial proliferative response to the inhaled chrysotile fibers. There is mild associated interstitial reaction. (Reduced 1.85× from original photo.)

A

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Fig. 3. A:
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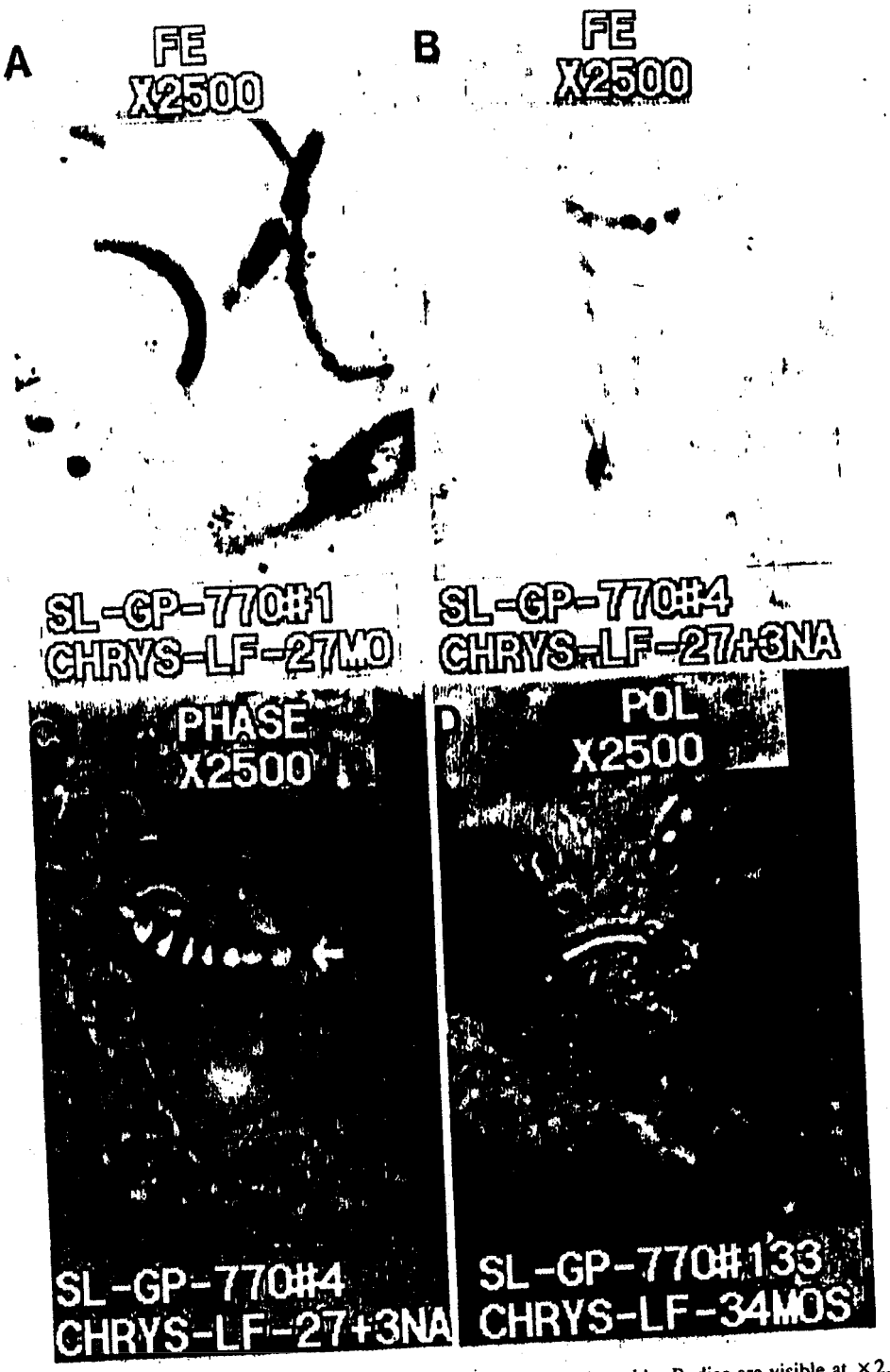

Fig. 3. **A:** Ferruginous asbestos bodies stained blue by the ferricyanide. Bodies are visible at ×2,500 magnification. **B:** Ferricyanide no longer reveals ferruginosity of the asbestos bodies, the guinea pig having lived in normal air for 3 months following inhalation exposure to chrysotile dust aerosol for 27 months. The body outline still is visible at high magnification (×2,500) because of oxidized ferritin. **C:** An asbestos body is again rendered visible despite being aferruginous, phase contrast micrography at high magnification (×2,500) having been utilized to reveal it. This guinea pig had been in normal air for 7 months following 27 months of inhalation exposure to chrysotile dust aerosol. **D:** An asbestos fiber has been rendered visible through light polarization at high magnification (×2,500). This is a tremolite-actinolite fiber. (Reduced 1.85× from original photo.)

tos workers a compensable disease. The advice received from England following publication of Dr. E.R.A. Merewether's 1947 report on 230 cases of lung and pleural cancers in asbestos workers was that the British Government was drafting new workmen's compensation rules concerning asbestos cancers. Dr. Merewether was not a mere laboratorian writing cryptically on cancer for the edification of his colleagues. He was a doctor and lawyer and His Majesty' Chief Inspector of Factories, a responsibility equivalent here to the present directorship of a combined OSHA-NIOSH. His report went officially to the British Parliament. After he had determined that 13.2% of asbestotics had developed lung and pleural cancers (as compared to 1.32% cancers in persons with silicosis), the parliamentarians were constrained to take notice and devise laws to compensate the affected workers and make regulations to lessen further health havoc by asbestos. At that time South Africa was still a Commonwealth of the British Empire. The governor general (Sir Patrick Duncan) received advance notice of what was transpiring in London. The South African Pneumoconiosis Bureau had, up to then, been the largest and most experienced world institution coping with pneumoconiosis problems of industrial workers, but the Bureau's neoplasia experience had been limited to cancer cases from amosite or crocidolite asbestos industries. We needed to know what chrysotile likely would do with respect to lung cancer. Implementation of health conservation measures at the Swaziland-Barberton chrysotile industry had only just begun and I had personally, on behalf of the Pneumoconiosis Bureau, conducted health surveys of all workers in these asbestos industries. At the Penge-Egnep amosite facility I found that past dust inhalation had created such disastrous health havoc that the facility had to be shut down for several years to re-engineer less dusty production methods. By contrast, the chrysotile industry had just started operations, so that in 1949 there were not yet any mill workers who had been exposed to chrysotile dust for more than 4 years. I therefore was asked to inquire in the United States and in Canada what was known about the ability of chrysotile to produce cancer.

Dr. Anthony Lanza, who had published *Asbestosis and Silicosis* in 1938, told me that, although he had experience with chrysotile asbestosis, he had not personally seen any cancers. However, he had read about cancer findings by Dr. Lynch and Dr. Gloyne, whom he knew, and by Germans unknown to him. He sent me to Saranac Lake and Quebec to find more information.

At the Saranac Laboratory no systematic animal research had yet been done to probe the cancer issue, but there was a proposed study protocol which Dr. Gardner had drafted to test the carcinogenicity of lifetime inhalation of long fiber chrysotile

Fig. 4. A: An apparent early carcinomatous response to inhaled chrysotile. The guinea inhaled the aerosol for 27 months and then was allowed to survive in normal air for 9 months before it was killed. There is luxuriant papillomatoid epithelial proliferation into alveolar spaces. ×750. B: A portion of one of the papillary structures at higher magnification. Note the morular pattern of the abnormal cells and their cohesive nature. ×2,500. C: Accumulation of abnormal cells in a bronchial lymph node of this guinea pig. Asbestos structures are not discernible and much of the original lymphatic tissue had been replaced by abnormal cells. ×375. D: A cluster of abnormal cells in the lymph nodes at higher magnification. Lymphocytes have dark nuclei and very little cytoplasm. The abnormal cells are pleomorphic, have abundant cohesive cytoplasm, and assume a morular pattern. They have destroyed the host lymphocytes. ×2,500. (Reduced 1.85× from original photos.)

Figure 4. (Legend appears on opposite page.)

dust on cancer resistant mice. Manfred Bowditch, one of Dr. Lanza's professors, apprised me of this protocol and he told me that Dr. Vorwald had been reluctant to get it going. Bowditch had been the Chief of Industrial Hygiene at the Saranac Laboratory, its deputy, and later interim director until Dr. Vorwald took over in 1947. I asked Vorwald what cancer research was conducted at the Laboratory on chrysotile asbestos. He said none had been attempted, none was contemplated, and none was needed, for in his opinion pneumoconiosis did not cause cancer, as stated in a 1938 paper by Dr. Vorwald and Dr. Kark. However, this paper was on the noncarcinogenic action of siliceous dusts and not on asbestos effects. The negative findings for neoplasia accorded with my own epidemiological findings on silicotic subjects, but provided no enlightenment on chrysotile carcinogenicity.

While reviewing Dr. Gardner's accumulated research data at the Saranac Laboratory, I came across a set of slides of mice, some of them with malignant neoplasms. These mice had been exposed to chrysotile asbestos, but showed no asbestosis, just cancers. I also found nine human lung cancer and two mesothelioma cases in a file identified as "Quebec Asbestos Workers." Dr. Vorwald gave no explanation for these items. Soon after these observations I visited Quebec. Through conversations with Drs. Kenneth Smith and Paul Cartier, the medical directors of the Johns Manville and Thetford asbestos industrial clinics in eastern Quebec, I gathered that these two doctors did not think their chrysotile asbestos caused cancer, since only six lung cancers were known to them in circa 6,000 current asbestos workers. I then told them about the 11 cases at Saranac Lake, which astonished them, for they did not know of their existence. Later I ascertained from Mr. Ivan Sabourin, the chief attorney for the Quebec Asbestos Mining Association (QAMA), that he had confidentially hand carried those case materials to Dr. Gardner during the period 1944–1946. He said he had since then accumulated several additional cases of men who had developed and died of lung cancers after they retired from service at the asbestos mines and mills. He clarified that Drs. Smith and Cartier had responsibility only for health problems of the active employees. Mr. Sabourin was collecting the post employment cases, because the asbestos workers had begun to agitate for compensation for lung cancer in the same manner that gold miners of South Africa received compensation for contracting tuberculosis. Canada also then was a Commonwealth of the British Empire. Adding the 11 Sabourin-Saranac cases to the 6 current employees with cancers, there then were actually 17 known cancers in the chrysotile group. (Such a large number of cases in such a small and well-defined group of industrial employees suggested a significant problem.) At this point I mentioned Dr. Gardner's mice with the cancers, which seemed confirmatory. Smith, Cartier, and Sabourin were all much impressed since they had no knowledge of this aspect of the problem.

When I returned to the Saranac Laboratory about a month later after consultations with officials of Canadian industries, university medical schools, and government departments, Dr. Vorwald took me to task for mentioning the Laboratory cancer data to Smith, Cartier, and Saboufin. This was to me wholly incomprehensible, as the Saranac Laboratory was a consultant to QAMA, whose officers they were. I also found that all the cancerous mouse slides had been lifted from the files. Dr. Vorwald said that Lanza, Smith, Cartier, and Sabourin all had homed in on him immediately after my visit to Canada. Vorwald said he was reprimanded for being derelict in letting me, "a foreigner," see the patently sensitive data on chrysotile carcinogenic-

ity, without being warned not to talk about what I observed. I complied thereafter in the United States.

During my oral examination for a New York University diploma, I commented to Professors Lanza and Bowditch that I did not understand why there was so much secrecy and circumlocution on the chrysotile cancer issue. Next Dr. Lanza took me to Mr. Vandiver Brown, the chief attorney for Johns Manville and also the asbestos consortium which had sponsored Gardner's asbestos research up to the point where he mentioned cancer. Mr. Brown had the original of my university thesis, a copy of which doubled as my report to the South African Government. Brown asked me to withdraw this. I told him I could not and that I already had mailed my report to Johannesburg. Mr. Brown flew immediately to South Africa to retrieve my report from the Department of Mines officials. This merely heightened their interest in what I had to say.

Why this excessive reaction over a few mice with spontaneous adenomas? I think it was that Dr. Gardner himself had made the cancer discovery and had announced this finding in unambiguous terms. If some lesser entity had written officially on finding 81.8% cancers in mice exposed to chrysotile dust, as Dr. Gardner did to Johns Manville in 1943 [Enterline, 1993], far less attention might have been paid. But Dr. Gardner was the number-one authority on pneumoconiosis animal research in the United States at the time. He had been studying the experimental pathology of chrysotile for 24 years. The industries formerly accepted his word on all asbestos matters. It was only when cancer reared its ugly head in his 1943 report that they became frightened and backed off and refused further involvement. They would not have done so for mere mouse adenomas. Dr. Gardner had effectively warned them that malignant neoplasia is a specific effect of inhalation of chrysotile dust. Now, in 1950, I had unexpectedly resurrected a discovery that they perhaps thought had been buried with him.

Dr. Enterline also questions whether Dr. Vorwald discovered any chrysotile cancers. Vorwald did so, perhaps a little reluctantly. Possibly as sequel to my uncontrived meddling, three relevant things had happened. First, Dr. Kenneth Smith, by then Corporate Medical Director for Johns Manville, promptly wrote a report on Quebec asbestos workers mentioning rather laconically that 11 cancers had been found, including 2 mesotheliomas. These were obviously the cancers at Saranac Laboratory. He knew, via Mr. Vandiver Brown, that I had put this detail in my report to the South African Government. Owning up officially to these 11 cancers was preemptive of such information possibly being released in the United States via South Africa. I think this must be the explanation, for Dr. Smith did not publish his own six cases. If he wished to announce that cancer was a health risk for chrysotile workers his own report would have been stronger had he stated that there were 17 cases in 6,000 asbestos workers.

The second consequence was that Dr. Vorwald was impelled to set aside an exposure room for the 1951–1953 mouse study which Dr. Gardner had designed in 1946. He had planned to use this room for beryllium aerosol studies, but Dr. Lanza asked him to implement Dr. Gardner's mouse study instead. Lanza now was vice president of the Trudeau Foundation Board. Vorwald had no option but to comply. This room housed 179 mice which inhaled chrysotile dust daily at about the level of the then threshold limit value (TLV) of 5 million particles per cubic foot of air. After 14 months of dusting, 9.5% of the animals had developed lung tumors. In a control

group of 181 mice which had not been exposed to chrysotile, 5.5% had developed tumors. There thus was a risk ratio (RR) of 1.73. At that point (June 30, 1952), Dr. Vorwald's 5-year contract with the Saranac Laboratory expired. On Dr. Lanza's recommendation, he was allowed to continue working there for another year until the QAMA mouse cancer study would be completed at the 24th month of exposure. Vorwald did not finish the report on this study. Understandably, his mind now was on his future elsewhere.

When I succeeded Vorwald as Director of Saranac Laboratory, one of the first items Dr. Lanza asked me to tackle was finalization of this study on the chrysotile mouse cancers. By then all the mice had died. Mr. Stanley Kaszer, the statistician for the laboratory, presented me with a report on the mathematical findings. The neoplasia response to chrysotile fibers was strongly positive, the cumulative RR for neoplasm having trebled to 5.7 in the final months of the mouse lives. I also tried to check what kinds of tumors these were, but all the animal protocols and slides had been taken to Wayne State University by Dr. Vorwald. I therefore called on him and presented him with Kaszer's statistics and urged him to publish the data, since he now was free to do so, no longer being bound by contract with the QAMA sponsor. No publication on this very important matter ever followed. I also urged Dr. Vorwald to publish all the accumulated human cancer case data. He did not. He died in 1976 still mute on these topics.

The third consequence of my meddling perhaps was publication of the modified version of Dr. Gardner's monograph in 1951. When I was at the Saranac Laboratory from 1949 to 1950, no one was working on this task. I was never told by Dr. Vorwald of the existence of the monograph even though I had been sent to the Laboratory by Dr. Lanza to study all asbestos matters. I had become Vorwald's house guest during all the time I was there and came to know him and his activities very well. He was not working on this project. The monograph had been lying fallow for 5 years. Mr. Tom Durkan, who wrote most of the Laboratory technical reports for Dr. Vorwald, was not working on this monograph either. I would have discovered, since I used his office as my base. He knew of my interest in the former chrysotile research, as did everyone else. Gardner's manuscript was somewhere hidden in a box, which would now be in a forgotten place, if I had not come there to meddle with the past. Perhaps after my exit visit with Mr. Brown, an executive decision was made to get on with the task which seemed to have been dropped after 1948 to judge by the chronology of interactions between Drs. Packard, Lanza, Lynch, and Vorwald.

Did Dr. Vorwald discover that chrysotile caused lung cancer? He most assuredly did, both in mice and men. The fact that he never published anything on such an important matter may be a mystery, but not if one considers that for almost three decades he had served as a defense litigation expert for the asbestos industries. It would hardly have been of value to his sponsors to permit release in scientific publications of the very incriminating data he commanded.

A few years later Brauń and Truan began recounting the Quebec human cancer numbers for QAMA. In their 1958 report they said they had identified 19 cancers in miners. This was a threefold jump over the 10 years since Smith and Cartier had counted only six cases. These 19 cancers again excluded the Saranac cases, which had grown to over 70. However, the Braun-Truan report was limited to the epidemiology of lung cancers in working miners. They likely did not know of the accu-

mulated post-retirement cases at the Saranac Laboratory. Neither Dr. Vorwald nor Mr. Sabourin would have had any reason to tell them and they never came to inquire at the Saranac Laboratory, at least not while I was there.

Did Dr. Schepers discover anything new about the ability of chrysotile to cause cancer? There was not much left for Schepers to discover, for the animal cancer mine had been worked out by Gardner and Vorwald. Schepers did provide the QAMA sponsors of Saranac Laboratory research with Kaszer's statistics and continued to report periodically to them and to their ATI (Asbestos Textile Institute) confreres, on the occurrence and nature of cancers in persons with evidence of asbestos exposure. Some of these case reports were later discovered during the asbestos litigation, which started two decades later, some through raids on residual files and others via subpoenas of company records.

There was only one animal cancer study which Schepers managed to launch to probe whether chrysotile caused cancer directly or as a complication of asbestosis. This was funded partly by the Damon Runyon Foundation. In this study, rats served as test subjects. One group of rats was exposed to chrysotile dust for 6 months and then to beryllium sulfate dust for 6 months, whereafter they were transferred to normal air. In a second group the beryllium and asbestos exposures occurred in reverse order. There also was a 6-month beryllium-only and another six-month chrysotile-only exposure group, while a fifth group of rats with no dust exposure served as a further control. All the animals were killed at 18 months to identify cancers. Through prior and concurrent studies, the Saranac Laboratory had demonstrated that beryllium sulfate would induce a predictable yield of lung cancers within 18 months after 6 months exposure to 1 part per million of $BeSO_4$ aerosol. The theorem to be tested by brief sequential exposures to chrysotile and beryllium, was whether chrysotile would increase the yield of beryllium cancers within 18 months. Had this occurred, it would have been possible to conclude that chrysotile acts as a primary carcinogen, without first inducing asbestosis, which was one of the then current theories of how asbestos causes cancer. Terminating all the animals at 18 months had as a purpose to exclude the possibly confounding factor of asbestosis, which would only manifest in the second year of life following 6 months of dust exposure. This study yielded inconclusive results, since the beryllium interfered with what asbestos did to the lungs and vice versa. The study did not advance knowledge on the carcinogenicity of chrysotile. It seemed not worth publishing, apart from a brief reference [Schepers, 1971].

I also wrote a proposal for a study of cocarcinogenicity of cigarette smoke and chrysotile. This was presented to the National Cancer Institute (NCI) for funding, which it declined. To my knowledge no such study has ever been accomplished. There is considerable physician conviction that concurrent cigarette smoking and asbestos inhalation increase the risk of human bronchogenic cancer. Dr. Enterline suggested that one should not accept that chrysotile causes cancer without published animal confirmation. He did not explain how it is possible to accept the cocarcinogenicity of cigarette smoking and chrysotile asbestos without experimental validation. In vitro experiments recently done in this area yielded rather vague and inconclusive data in comparison with evidence an inhalation study might have accomplished. Apart from the foregoing, it can be safely concluded that Schepers did not independently discover whether chrysotile is carcinogenic for animals. He did not have to. The problem had already been resolved by Dr. Gardner.

In the discussions by Dr. Enterline, emphasis has been placed on whether Dr. Gardner had merely seen some autogenous mouse adenomas, having erroneously misdiagnosed these as chrysotile-induced malignant neoplasms. Although of great practical significance to human victims, it makes little scientific difference whether chrysotile causes adenoma or carcinoma or sarcoma. An adenoma is also a cancer although not malignant. Dr. Gardner did not describe merely spontaneous adenomas in the mice. He was clearly astonished at finding tumors of a more malignant aspect. The slides vanished, so that we cannot currently verify what it is that he saw. I do however have a few of the slides for the guinea pigs of experiment 770, which ran concurrently with the mouse study. Two of these guinea pigs seem to show early phases of carcinoma formation in one of the sites of adenomatoid epithelialization (Fig. 4). This supports Gardner's judgment on the mice.

A question is raised whether Dr. Vorwald expertly judged the cancers differently from the way Gardner did. I do not see how he could have. He had not studied the slides before 1949 and the slides vanished thereafter and are not mentioned at all in his 1951 report on Gardner's asbestos research. None of the animal protocols shows any participation by him in the microscopy reviews of the lung sections during the period 1933–1941, at which point he had joined the Navy. On his return to the Saranac Laboratory, Dr. Vorwald served mainly as the administrator of the Trudeau Foundation and performed no histology tasks. All the photomicrographs in the 1951 paper had been made prior to 1946 by Mr. Edward Gockler, the laboratory photographer, under the direction of Dr. Gardner.

Did Dr. Kenneth Lynch judge the Saramac Laboratory chrysotile cancers to be mere autogenous mouse adenomas? He was briefly involved. Soon after Dr. Gardner's death in November 1946, Dr. Edward Packard, who served as temporary Medical Director of the Saranac Laboratory, mailed Dr. Gardner's manuscript and the animal protocols to Dr. Lynch for editorial refinements. Lynch also came to the laboratory, perhaps to look at the slides. Lynch was an important connoisseur of asbestos matters having published one of the first three American asbestos cancer case reports in 1935 [Lynch and Smith, 1935] and later describing 40 examples of the pathology of asbestosis [Lynch and Cannon, 1943] in deceased workers of asbestos textile factories. Dr. Lynch recommended that Dr. Gardner's manuscript be published unmodified. If he had judged that Dr. Gardner had made a grievous interpretive mistake in calling some mouse tumors malignant, when they should have been classified as benign adenomas, he would have performed a disservice to the science of pathology, of which he was then a leading expert as Professor of Pathology at the University of South Carolina. He seems not to have questioned Dr. Gardner's evaluation of the tumors, but did express puzzlement over Dr. Vorwald's disinclination to release Gardner's cancer data in the planned posthumous publication of the Gardner monograph. This manuscript never was published despite Dr. Lynch's recommendation and even though the Laboratory Board had set aside funds to have it published as a memorial to Dr. Gardner. It is also to be noted that Dr. Lynch initiated his own animal experimentation studies on mice to test for carcinogenicity of chrysotile. These ran for a number of years. By 1957, Dr. Lynch and colleagues had found that chrysotile evoked many tumors, but his paper did not reveal whether these were malignant. However, in 1962, Dr. Lynch invited me to his department in Charleston to advise his staff on how to conduct animal studies in such a manner that "the same malignant neoplasia results" that had been achieved at the Saranac Laboratory could

also be accomplished there. I found that they had not fully fiberized and adequately aerosolized their asbestos, so that their animals had inhaled relatively large chrysotile aggregates rather than separated asbestos fibers. I wrote a detailed methodology for him, but nothing came of this, the pathology department not having engineering staff and facilities to launch a full inhalation study such as had been customary at the Saranac Laboratory. Despite this frustration, Lynch's actions seem to reflect clearly a conviction that the Saranac Laboratory had truly induced malignant cancers in experimental animals. He based this persuasion on what Dr. Gardner had accomplished by 1943 and what Vorwald and I had reported to QAMA in 1952 and 1954, for nothing after that had been published from the Saranac Laboratory. Dr. Lynch, as a research consultant to Raybestos Corporation, would have received copies of reports on the Saranac Laboratory research data. Raybestos was one of the QAMA sponsors of the mouse investigations by Dr. Gardner.

Dr. Enterline suggests that because Gardner sought funding from the NCI to extend the mouse study, this can be interpreted as signifying that he did not believe his own findings on malignant neoplasia. I do not follow this argument as it implies that every time a scientist undertakes a new study of any subject he thereby declares that all he had discovered up to then was invalid. Every scientific study tends to reveal new avenues of inquiry that may be worthwhile. Dr. Gardner specifically had wished to conduct a study in which cancer-insusceptible mice (as compared to cancer-prone mice) would be used, perhaps because human beings are cancer-insusceptible creatures, absent enviromental causes. He also needed a current control group, so that his numerical calculations would be more valid. This does not negate the value of his prior work, but instead reveals his conviction that there was a cogent reason for additional research. This was also 1943, 50 years ago, and all that we know today about cancer and mice and asbestos was not evident then. It was extraordinary for Gardner to attempt such a cancer study. Dr. Gardner had tremendous concurrent research responsibilities on silicosis and tuberculosis, which then were major killer diseases (over 80,000 deaths per year), while the havoc of lung cancer was still of comparatively miniscule dimensions. That he was prepared to deviate from these responsibilities when short of staff during war time and commit scarce resources, indicates how seriously he took the matter. That he should have spent so much effort, as a dying man, to further probe scientific validation of chrysotilic carcinogenicity, was laudatory and consistent with his known objectivity and devotion to the pursuit of truth. He deserves praise instead of the iconoclasm seemingly implied in current comments.

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APPENDIX
Typescript Copies of Dr. Gardner's Handwritten Notes

Tumor findings in 11 mice exposed to chrysotile aerosol

Mouse no. 2–12 months. "Tumor mass in right lung—no metastases. Debatable whether a chronic abscess has resulted in acute or chronic organizing pneumonia—epithelial metaplasia or whether there is a true tumor. It is different at least from the ordinary mouse adenoma."

Mouse no. 3–12 months. "Fibrosarcoma? of mediastinal tissue with retrograde extension into the lungs."

Mouse no. 4–18 months. "Well marked epithelial hyperplasia in terminal bronchiole. One small adenoma."

Mouse no. 5–19 months. "A large tumor mass involving almost the entire left lung. Large papillary adenocarcinoma, replacing a lobe of the left lung. Undifferentiated sarcomatoid tissue in the lung next to the tumor and metastases to the liver and spleen."

Mouse no. 6–20 months. "Partial collapse of hind legs. Small localized adenoma in right lung." No microscopy description.

Mouse no. 7–24 months. "Scattered nodules of tumor—round and white in color. Rather large localized adenomatous nodules involving pulmonary parenchyma and bronchi."

Mouse no. 8–24 months. "Focal areas of cellular proliferation in walls of respiratory bronchioles."

Mouse no. 15–18 months. "Small localized tumor—apex of lower lobe—adenoma."

Mouse no. 17–19 months. No tumor described.

Mouse no. 18–20 months. "One tumor about 2 × 3 cm in upper portion of lower lobe on right. Abdomen—Scattered throughout are many tumor masses of varying size—one of which seems to have surrounded and obstructed the large bowel."

Mouse no. 19–24 months. "One large tumor-like mass in middle third of left lung. Well circumscribed and measuring about 6 mm in diameter. Adenoleiomyoma?"

Since Dr. Gardner judged 9 of the 11 mice to have developed neoplasia, he calculated an incidence of 81.8%, which was six times more prevalent than tumors usually encountered in this mouse species at the Saranac Laboratory when used in experiments other than with chrysotile asbestos.

LETTER TO

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First Interim Report

ASBESTOSIS AND PULMONARY CANCER

to

Quebec Asbestos Mining Association

by

The Saranac Laboratory

of

The Trudeau Foundation

Saranac Lake, New York

May 7, 1952

Dr. A. J. Lanza, Chairman
Institute of Industrial Medicine
New York University-Bellevue Medical Center
477 First Avenue
New York 16, New York

Dear Dr. Lanza:

Attached to this letter, as well as to Hugh Jackson's copy, is Saranac's first interim report of May 7, 1952, on the asbestosis and pulmonary cancer study that is being conducted for the Canadian C. A. M. A.

You will note that the conclusions so far do not indicate unfavorable findings. Of course, later conclusions on results of animal exposure beyond the fourteen months here covered may change the picture.

Sincerely yours,

J. P. Woodard

Enclosure

Copy to: Mr. H. M. Jackson

bc: Herbert M. Ball (enc)

NEW YORK UNIVERSITY-BELLEVUE MEDICAL CENTER
OF NEW YORK UNIVERSITY
INSTITUTE OF INDUSTRIAL MEDICINE
477 FIRST AVENUE, NEW YORK 16, N.Y.
ORIGOON 9-3200

November 10, 1950

Mr. J. P. Woodard
Johns-Manville Corp.
22 East 40th Street
New York 16, New York

Dear Page:

I am returning the minutes of our meeting at Saranac Lake. I made some minor corrections in pencil which I think are clear.

I think you did a remarkable job, particularly when we consider the side issues that were discussed as well as the dramatic nature of the conference.

Sincerely yours,

A.J. Lanza, M.D.

AJL:lc
Encl.

FILE COPY

F.U.

6/30

[redacted]

2/15

June 13, 1952

Mr. Ivan Sabourin
Alfred Building
Montreal, Quebec
Canada

Dear Ivan:

A copy of the letter of May 6 from Trudeau to you mentions that the first interim report on ASBESTOSIS AND PULMONARY CANCER supported by the Quebec Asbestos Mining Association was being sent to you within a few days.

I assume you have copies of this report by now and I wonder if you could send a copy of it to Dr. A. J. Lanza and to me.

If you do not have sufficient copies, just let me know and I can get one from Saranac.

Sincerely yours,

J. P. Woodard

Copy to: Dr. A. J. Lanza
Institute of Industrial Medicine
New York University-Bellevue Medical Center
477 First Avenue
New York 16, New York

[redacted] Jackson

B. Conclusions:

1. Sufficiently clear data has been shown under A, "Discussion," above, to show the way in which the program would progress, and the consensus was that the program should be undertaken as promptly as possible in line with the points brought out in the discussion.

III. Other Phases of the Long-Range Program.

A. Discussion:

1. In the Proposal to the Q. A. M. A., four suggestions were made:

a. That the various companies making up the Association see that there is more publicity than in the past about the knowledge of this problem and about some of the many favorable aspects that do exist, but which are unknown to most people. The purpose of this is to combat the adverse and often unwarranted pseudo facts that are put out by others. Dr. Smith and Dr. Cartier should be kept advised by others in the Q. A. M. A. and the asbestos industry of any developments that may become known to them.

b. That our doctors occasionally make talks or lectures at medical schools in the general area.

c. That we see that our doctors get adequate affiliation with research centers such as Saranac and other organizations so that they will get all available information on this and other such subjects.

d. That the companies in the asbestos industry consider the formation of an Institute for Industrial Chest Diseases with other mining associations. In doing this, it was mentioned that the help of Dr. Gregoire of Rosemount Sanatorium, Dr. Burke of the Laurentian, and others be sought.

B. Conclusions:

1. It was agreed that the first three (a, b, and c, above) should be done, it being understood, of course, that judgment must be used in the degree of participation of our doctors under b and c.

However, it was the consensus of the group that the asbestos industry would do well to avoid identifying itself at this time with other mining associations (d, above) so far as chest diseases are concerned. It was pointed out that the problems of the asbestos industry are minor as compared with those of many other mining industries, and that such affiliation might tend to identify the asbestos mining industry with the problems of other mining industries. It was felt that this should be held in abeyance.

cc: Vandiver Brown
A. R. Fisher
L. C. Hart

J. P. W.

November 14, 1950

(2) Utilising the facilities at the Trudeau Laboratory, as in the past, and subjecting animals to high asbestos dust conditions.

A. Discussion:

1. Dr. Lanza said that he is not prepared to carry out a formal project as mentioned in (1) above; that Dr. William Smith, along with Dr. Sutherland associated with him, is doing some of this with finely ground asbestos, as well as with some other materials.

2. Dr. Vorwald gave the following information about part (2) of the program, which, of course, is given in more detail in the Saranac Laboratory's Proposal of September 21, 1950:

   a. Set up a program consisting of 300 animals to be subjected to asbestos and 300 control animals.

   b. The program is likely to last for two years.

   c. It would probably take two months to get enough of the right kind of animals and get under way.

   d. Quoting Dr. Vorwald: "We hope to show or prove that cancer incidence is not increased among these animals even if dusted." It was mentioned that such results are on the basis of animal experimentation, the results are, strictly speaking, true only of animals, and it should be realized that the same results might or might not hold true in the case of humans.

3. It was agreed that, while the long-range program is going on, Saranac would provide each four months a progress report on the work.

   There was some question as to how complete a progress report should be and it was agreed that a progress report might well be of no more than two typewritten pages to show in concise form:

   a. The work that has been completed up to that time.

   b. How the work is progressing at the moment.

   c. What the future work looks like, i.e., as to when completion may be expected and whether or not the program is ahead of schedule or behind schedule, and by how much.

   d. What general conclusions there are, if any, at the moment, without giving detailed data on the work.

4. The present idea is that the two-year program can be undertaken at an estimated cost, as shown in Saranac's Proposal of September 21, 1950, of $16,000 for the first year, and $10,000 for the second year.