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

LEROY U. GARDNER, M.D.
DIRECTOR

February 27, 1947

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

Dear Dr. Lynch:

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

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

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

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

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

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

Sincerely yours,

Lillian R. Blinn

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

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

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

Progress Reports - May 5, 1937
April 13, 1938
December 3, 1938
December 14, 1939
November 30, 1940
December 4, 1940

Proposed Monograph - February, 1943 (accompanying data)

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

Two outlines

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

Experimental data

February 26, 1947

Enclosures to Dr. Lynch

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

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

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

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

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

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

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

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

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

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

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

February 26, 1947

Enclosures to Dr. Lynch

KL

July 23, 1947.

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

Dear Doctor Lanza:

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

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

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

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

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

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

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

With best personal regards, I am

Sincerely yours,

Kenneth M. Lynch, M. D.

KML:kbp.

KLC

July 23, 1947.

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

KKL.

KL20a

T.

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF GEORGIA
ATLANTA DIVISION

IN RE: ALL ASBESTOS CASES PENDING IN ABOVE-STATED COURT BEFORE THE HONORABLE ROBERT L. VINING

Δ-Designations

TT-Designations

The discovery deposition of DOCTOR PHILIP C. PRATT, taken on behalf of the Plaintiffs pursuant to notice on cross-examination before Angelia Wheeler Evert, Certified Court Reporter and Notary Public at Courtroom 3 of the Richard B. Russell Building, Atlanta, Georgia, on the 21st day of June, 1988, commencing at the hour of 9:30 a.m.

Wheeler Reporting Company, Inc.
482 Mt. Paran Rd., N.W.
Atlanta, Georgia 30327
404-256-0338

you want me up there? Which would you prefer?

CHIEF MAGISTRATE DOUGHERTY: You may remain seated if you like.

MR. MOTLEY: All right.

CHIEF MAGISTRATE DOUGHERTY: I have no problem with that.

Q (By Mr. Motley) Doctor, can you see me and hear me all right over here?

A Yes, sir.

Q Thank you, sir.

Will you state your name for the record, please?

A Philip C. Pratt.

Q And your age, sir?

A Sixty-seven.

Q And are you presently employed?

A Yes.

Q In what capacity, sir?

A I'm Professor of Pathology at Duke Medical Center.

Q Are you full-time?

A Yes.

Q And are you in good health?

A Except for having a cold last week, yes.

study?

A Well, I knew that the animals were being exposed in the dust room to several kinds of dust. I knew the schedule at which they would be killed and examined grossly and microscopically. I knew the results of dust counts during the exposures.

Q Did you know about correspondence between the sponsoring asbestos companies and Doctor Vorwald? At that time did you know about it --

A No.

Q -- regarding editing or changing the report in any fashion?

A No. I had no involvement with that.

Q So your observations were solely that of a scientist looking at the tissues that were presented to you by the lab technicians and reporting your results; is that fair?

A Yes; plus seeing the animals at the time they were killed along with the technician.

Q Beyond the science of all of that, what you just described -- observing the animals, looking at the tissue, and recording your findings -- you had no dealings with the sponsors with respect to how, when, and what would be published; is that correct?

A That's correct.

Q Did you see at any time between the years 1946 and 1951 Doctor Gardner's proposed monograph on asbestosis dated February 1943?

A No. I don't think I saw that.

Q Have you seen that recently?

A No.

Q You were not provided with a copy of Doctor Gardner's written observations with respect to both the King's Float studies and the human asbestos disease cases that he was examining for asbestos companies?

A No.

Q You never have seen that --

A No.

Q -- to this day?

A Not that I recall.

Q At any time between 1946 and 1951, did you learn that Doctor Gardner had reported and written that there was an excess incidence of tumors in a certain strain of animals exposed to King's Float?

A Yes.

Q When did you learn that?

A Well, it would have been during the time that we were summarizing those experiments to write up the report.

Q Did you have an opportunity yourself to view the tissue of those animals?

A Yes. I have seen them.

Q When did you see them?

A During the time that we were putting together that report.

Q Did you reduce to writing your observations of what you saw when you looked at that tissue?

A I don't believe it's in writing anywhere.

Q Do you recollect what you observed with respect to what Doctor Gardner described as tumors?

A Yes.

Q And what was that?

A I felt that the lesions he was talking about were what are called benign adenomas of the lung, which are quite common in mice and which vary from one strain of mice to another.

Q Is that a difficult differential diagnosis?

A Not really.

Q Have you subsequently found out that Doctor Lynch recommended that Doctor Gardner's findings and his description of what he claimed to have seen should have been published, quote, as is,

March 15, 1943

Dr. Ludwig Hektoen, Chairman
Committee on Cancer Research
National Cancer Institute
Bethesda, Maryland

Dear Dr. Hektoen:

In analyzing the results of a recently completed inhalation experiment on asbestosis, I was startled to discover that a small group of 11 white mice that had been inhaling asbestos dust from 13 to 24 months showed an excessive incidence (81.8%) of pulmonary cancer. This experience was quite at variance with the results in all our previous long-term dust exposures which were summarized and published by Vorwald and Larr in the American Journal of Pathology, January 1938. I would have attached little significance to this recent finding because of the small number of animals involved, but for the fact that the literature now contains some 10 reports of pulmonary cancer in cases of human asbestosis. Even these I have heretofore attributed to selection of materials as we have found no cases of pulmonary tumor in surveys of employed asbestos workers. However, Gloyne, Merewether and other English observers contend that asbestos has a specific carcinogenic action on the lungs. The question is of considerable importance in industrial medicine because of the associated compensation aspects and from a scientific view point, it interests me a great deal.

In view of this recent finding I have reanalyzed the results of a large number of dust inhalation experiments that we have carried on during the past 25 years. The incidence of pulmonary tumors is above in the appended table. It would appear that, except in mice, tumors have been generally uncommon in the strains of different species that we had used. Guinea pigs have shown occasional adenomas of the lung whose incidence is not influenced by dust exposures or by the type of dust involved. However, in white mice that survived for 13 or more months and in our dust rooms, various forms of lung tumors were much more frequent. The average incidents of such tumors in a group of 143 mice exposed to 4 different quartz-containing dusts was 19.6% but this appears small in contrast to this incidence of 81.8% in the asbestos mice. In 51 younger mice that died or were killed after exposures of 10 or 11 months there was only one instance of pulmonary tumor. Therefore, either age or
of dust exposure must be important.

None of these experiments was planned to study carcinogenic effects. Mice were only used as there was space in the dust rooms and many of these animals that died after short exposure were discarded without autopsy as they could not have developed a sufficient amount of dust reaction to be of interest. The strain of mice kept in the laboratory has changed from time to time by importation of new stock. At one time we did procure from Dr. Maud Slye some cancer susceptible stock but as these animals failed to react to inhaled quartz we lost interest in the subject.

Obviously under such conditions, the results with asbestos mean nothing but in view of the considerations which I have cited, I believe they should be checked. A decisive answer to this question would be of real practical value. From what we have learned about the action of asbestiform minerals in the living body, I would not be surprised to discover that their carcinogenic effects are different from those of other minerals. Their crystallographic structure is unique. They apparently act as mechanical irritants rather than chemically which is the case with quartz and other forms of free silica. On crushing or grinding, asbestos fibres loose practically all their irritating capacity; quartz on the other hand, becomes more irritating as the particle size decreases. Asbestos provokes fibrosis only in the lungs of certain species; quartz excites such reaction in any organ of any species of animal that we have tested. Asbestos seems to have no specific action upon pulmonary epithelium but in some species, it causes an unusual type of diffuse fibrosis which compresses and distorts the epithelial-lined respiratory bronchioles but often fails to obliterate them. However, this mechanism would not appear to be the one responsible for the mouse tumors for this is one of the species which develops no fibrosis on exposure. Possibly, the lack of reaction is due to superior upper respiratory protection against inhaled foreign bodies. The lungs of mice, exposed to asbestos dust for 2 years revealed relatively few fibre and all these are short and coated to form that peculiar structure known as the asbestos body.

In order to verify our accidental discovery of possible carcinogenic action of fibrous asbestos, I would like to repeat the mouse inhalation experiment under properly controlled conditions. I would breed a large number of cancer susceptible mice, splitting each litter into three groups and keep a record of the ages of each. One third of the offspring would be kept in a normal atmosphere as a control; another third would be exposed to quartz dust as a second control and the other third would be exposed to asbestos dust. We

would attempt to obtain 500 mice for each group. The exposures would apparently have to be continued for 15 to 24 months. Our routine in such experiments provides for dusting 8 hours a day, 5 days a week.

We have all the necessary equipment for such experiments and a trained Laboratory personnel. Funds are lacking however. Our previous study of asbestosis which continued for a period of 7 years was financed by the Asbestos Association. Since this group of manufacturers has already invested $30,000, I cannot ask them for further contributions. I discussed the matter with Dr. Rhodes at the Memorial Hospital who favored and was of the opinion that it was worthy of consideration by your committee. I am therefore applying for a grant of $3,000 to cover the cost of the first year's expense.

I had told Dr. Rhodes that I would be willing to do the entire experiment for this amount and ordinarily I should. However, on my return from New York, I found two proposals for investigations of other industrial dusts each of which yield the Laboratory $3,000 a year. As I have only two dust rooms at the present time frame for new work, I cannot afford to tie up one of them for two years for half the amount.

Should you be favorably impressed with this proposal I would appreciate any criticisms or suggestions.

Sincerely yours,

Leroy U. Gardner, M.D.
Director

LUG:RBE

N.C.I. Files No. [illegible]

P R O C E E D I N G S

TWENTY-FOURTH MEETING
NATIONAL ADVISORY CANCER COUNCIL
NATIONAL CANCER INSTITUTE

January 6, 1944
National Institute of Health
Bethesda, Maryland

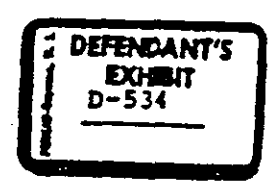

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TABLE OF CONTENTS

National Advisory Cancer Council

January 8, 1944

The Twenty-Fourth meeting of the National Advisory Cancer Council, held at the National Cancer Institute, National Institute of Health, Bethesda, Maryland, convened at 9:48 a.m., Dr. R. E. Dyer presiding.

... The following were present:

Dr. R. E. Dyer
Dr. Ludvig Hektoen
Dr. C. P. Rhoads
Dr. James J. Murphy
Dr. R. R. Spencer
Dr. John E. Wirth
Dr. Max Cutler
Dr. George M. Smith
Dr. J. Shelton Horsley
Dr. Sherwood Moore

...

DR. DYER: Dr. Parran is sick. He has been sick with influenza for the past week. Dr. Draper is also incapacitated this morning. Neither one of them will be here. We have two new members, Dr. Horsley and Dr. Moore. This is the first time they have met with the Council. Dr. Cutler is also with us this morning for the meeting.

I don't know what introductory remarks Dr. Parran had in mind to make, but the minutes of the previous meeting have been circulated. Are there any comments on them? If not, I believe they stand approved as circulated.

Glancing through this hurriedly, Dr. Compton will not be here. He has some comments on some of the proposals that

Without at this time attempting to make a thorough analysis of the published papers and records, a few recent pertinent reports are noted.

In one of the latest, Stoll, Bass and Ingrist[3] report an additional case of cancer of the lung in association with asbestosis and cast up the literature as of 1951. They refer to Merewether's 1947 report, as previously noted herein, and also refer to a report by Myers in 1949 recording a series of 115 cases of asbestosis in which there were 17 instances of associated pulmonary carcinoma, an autopsy series incidence of 14.8%, as compared to Merewether's 13.2%.

Hamburger[4] reported three additional cases of association of pulmonary carcinoma and asbestosis in his autopsy service. In his series of autopsies from 1918-1938 there were 45 cases of pulmonary carcinoma, an incidence of 1.08%. Asbestosis was diagnosed 8 times and in 4 of the 8 cases pulmonary carcinoma was also found.

For such comparison as may be allowable, Higdon and Kirchoff[5] reported in 1951 a pulmonary cancer incidence of 7.5% (67 in 892) in an autopsy series in individuals 30 years of age and older in Tex. They suggest "that frequency of cancer of the lung would best be established from a series of autopsies," on account of the unreliability of death certificates.

Counterbalancing at least some of the weight of evidence of reports of cancer of the lung associated with asbestosis is the widespread increase of pulmonary cancer in the general population that has been recognized during the same period of time. A few references will serve to focus that tremendous problem.

Graham[6], in 1951, says, "Bronchogenic carcinoma differs from other cancers in two important respects: (1) it has shown an enormous increase in the last 35 years; (2) there has been a progressively larger incidence in the male sex."

He states that Adler in 1912 could collect only 374 cases of cancer of the lung from the world's literature, while individual experiences in this country greatly exceed that total of reported cases from the whole world, and that cancer of the lung has advanced to a position of first place in men from one of 8th place in frequency - and this all within the last 35 or 40 years.

Doll and Hill[7] refer to a British government report which shows that for the 25 year period from 1922 to 1947 the incidence of lung cancer in autopsies in England and Wales increased fifteen times over what it had been previously.

An editorial note in The Lancet in January, 1952, strikes a similar note in referring to Hill's report that "in at least 17 out of 29 boroughs (metropolitan), deaths from neoplasm of the lung and bronchus were more numerous than deaths from tuberculosis" and in remarking "This is something quite new."

Smith[8], in 1952, states that lung cancer has shown an increase over and above what could be expected as a result of increases in numbers of elderly persons. He states also that high lung mortality has been recorded for both men and women patients with asbestosis in England.

Perhaps a personal note is permissible to illustrate the apparently universal experience in autopsy services during the last forty years that carcinoma of the lung has changed from a rarity to a commonplace. As a resident in the Philadelphia General Hospital

I had done an autopsy on what I took to be a case of tuberculosis, and had discarded all organs and tissues except the small pieces fr which I prepared microscopic sections. When I showed the resulting slides of carcinoma of the lung to my chief and had to acknowledge that I had thrown the lungs away, he arose sternly from his microscope and literally booted me down the stairs.

Perhaps I may also note that the scarcity of residents in pathology nowadays has brought about a difference in their treatment, although possibly not so much difference in their deserts.

EXPERIMENTAL STUDIES

Because of the question raised by autopsy observation of associated asbestosis and cancer of the lung, and among the many experimental studies that apparently have been done and are now going on by subjection of experimental animals to respiratory exposure to a variety of suspected substances, I have undertaken to see whether evidence of carcinogenic action on the part of asbestos or of the condition of asbestosis might be gotten in this way. Now in the third year, we have such a project under way, supported in part by a National Cancer Institute grant.

In devising such an experiment, one is, of course, faced with many questions, among which are the choice of experimental animals, the methods of exposure, the mechanical questions involved in methods, the practical matters of time and help, etc., e

Because, so far as I am aware, no animal except man has shown bronchogenic carcinoma of the lung naturally(or experimentally for that matter)

we chose to work with a strain of mice known to develop adenomatous tumors of the lung in regular pre-calculable occurrence. In this animal we have one of short life span, of known lung tumor productiveness that might be susceptible to influence in that natural occurrence, and at the same time as good as any other prospect for bronchogenic carcinoma so far as is known. The strain chosen is the AC_1 hybrid (A male and C female) first generation from breeding stock obtained from the Roscoe B. Jackson Memorial Laboratory. Approximately equal numbers of mice are being exposed and kept as controls. Exposure chambers are of our own devising. Regular dust counts are made, with concentrations of dust as high as may be obtained without risk of killing the animals. As near as feasible, the same asbestos as our human cases experienced is being used as dust.

As the animals are sacrificed they are autopsied and the number, size, and distribution of lung tumors recorded. An attempt to grade these will also be made. It would be premature to give any analysis of this data as yet. However, no epidermoid carcinoma has yet been observed. After 3 years?

Because we wished to also use another and larger animal, a number of dogs are also being subjected to similar dusting in specially constructed chambers. This is, of course, a much longer term experiment, and no report can be made upon it at this time. One of the reasons the dog was selected is that observation of the occurrence of asbestosis bodies in the lung of a dog exposed in an asbestos factory is recorded.

So far as I am aware, there is only one published report of an inhalation experiment exposing mice to asbestos dust as a test

of cancerigenic action. This report, by Nordmann and Sorge,[7] was claimed by the authors as positive evidence of such a relationship and has been cited to that effect by others. Smith,[8] however, analyzes it to the conclusion that it not only produces no proof of a causal relationship of asbestos in cancer of the lung but actually to the contrary. In that report ill-defined epithelial changes were thought to have resulted in the lungs of 9 animals out of an original 100 mice, squamous metaplasia was found in 6, adenocarcinoma in one and squamous cell carcinoma in one. Smith questions whether the interpretation was correct as to the demonstration of actual squamous cell carcinoma and calls attention to the common occurrence of squamous cell metaplasia in old rats with chronic pulmonary infections and in animals deficient in vitamin A.

The only other experiment of which I am aware where animals under exposure to inhalation of asbestos dust developed tumors of the lung in a way suggestive of a relationship occurred in an uncompleted experiment of the late L. U. Gardner that came to my attention through a courtesy from the Saranac Laboratory.

In one of Gardner's experiments in asbestosis he found a high incidence of the type of lung cancer to which mice are dispos Since the strain he was using was unknown as to tumor susceptibilit and since the experiment was uncontrolled from that standpoint, he stopped it, apparently intending to set up a proper experiment to follow up the suggestion later.

* At least it does not appear that any reported experiment can be accepted as conclusive, and I am inclined to the same view as expressed by Smith, that up to the present no experimental proof that the inhalation of asbestos or any other material will cause

bronchogenic carcinoma has been presented.

As the matter now stands, it appears that while additional evidence of the same sort has been collected in the meantime, the question that was raised with our first report in 1935 as to whether asbestosis can act as a producer of cancer of the lung in human beings remains as open as it was when raised.

So far as we are concerned, the conditions in the industry are so much improved that even the problem of asbestosis has become greatly lessened. The grade of exposure to the dust has been so reduced in our territory of experience that we no longer expect to see the extreme of the disease that earlier uncontrolled conditions caused.

Even so, and although our cases were those of medium to advanced asbestosis, if the exposure may be cancerigenic it could not now be certainly said that lesser grades of the primary disease would be immune to the tendency.

In all respects, therefore, the problem remains with us and should be subjected to continued investigation on its own merits, aside from any advantage that would accrue to the investigation of malignant neoplastic disease as a whole if such an etiologic factor were uncovered.

REFERENCES

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3. Stoll, Roger; Bass, Richard; and Angrist, Alfred A.: Asbestosis Associated with Bronchogenic Carcinoma. Arch. Int. Med., 88, 831 (Dec.) 1951.

4. Homburger, F.: The Coincidence of Primary Carcinoma of the Lungs and Pulmonary Asbestosis. Am. J. Path., 19:1943, 797-805.

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8. Smith, W. E.: Lung Cancer With Special Reference to Experimental Aspects. Arch. Ind. Hyg. & Occup. Med., Vol. 5, No. 3, 209, March 1952.

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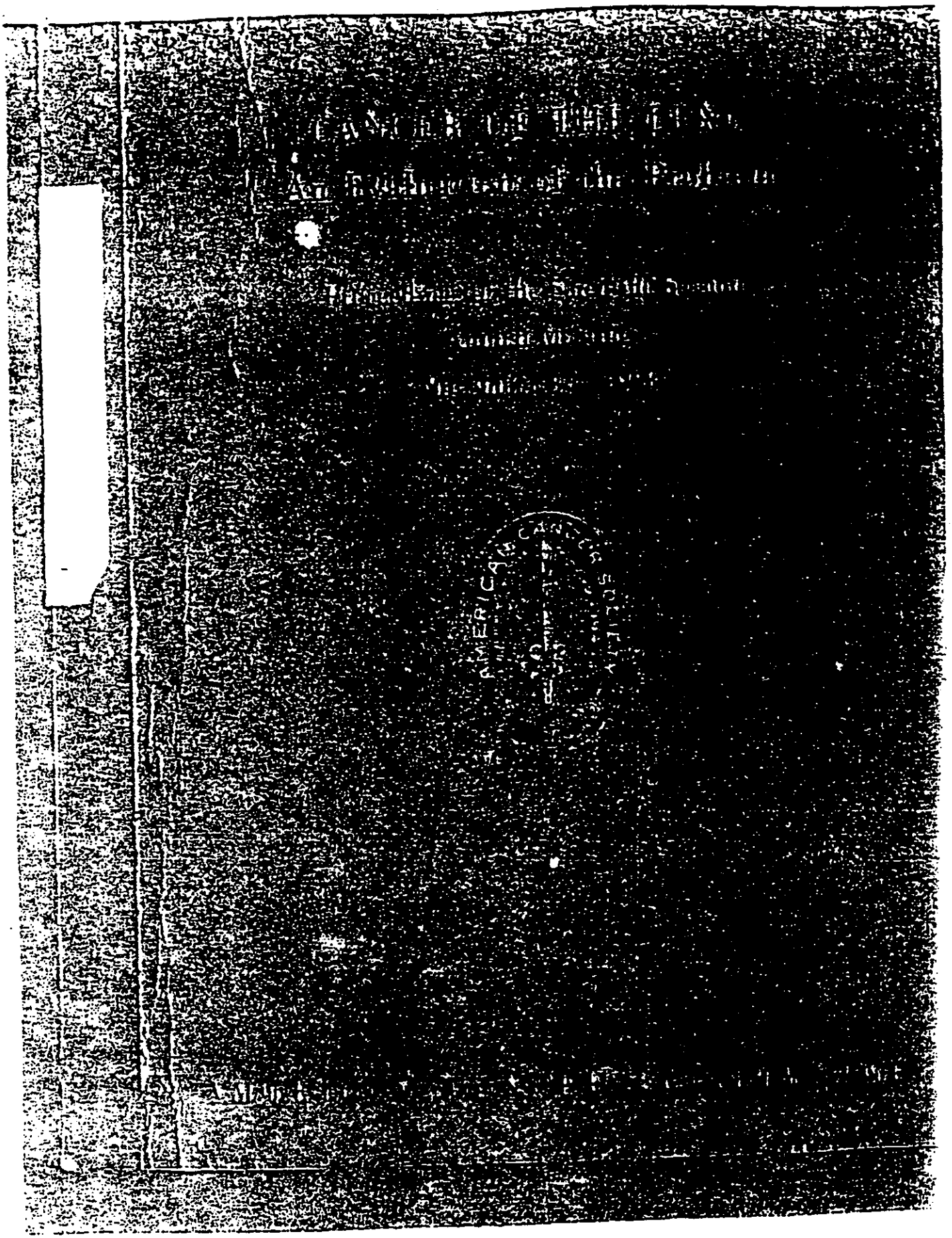


STATE OF MICHIGAN

IN THE CIRCUIT COURT FOR THE COUNTY OF BERRIEN

BENTON HARBOR AREA SCHOOLS,
Berrien County, Michigan

Plaintiff,

vs. File No. 85-3008-NZ-Z

NATIONAL GYPSUM COMPANY,

Defendant.

JURY TRIAL - VOLUME NO. II

BEFORE THE HONORABLE ZOE S. BURKHOLZ, CIRCUIT JUDGE

St. Joseph, Michigan - Wednesday, March 15, 1989

APPEARANCES:

For the Plaintiff:

MR. JOSEPH B. COX, JR.
MR. PETER KULMALA
Ness, Motley, Loadholt,
Richardson & Poole
151 Meeting Street, Suite 600
P. O. Box 1137
Charleston, South Carolina 29402

MR. PATRICK J. BERARDO P10707
MR. KENNETH HARNED P39170
Thrun, Maatsch & Nordberg, PC
501 South Capitol Avenue
Lansing, Michigan 48901

EXHIBIT I

(At 10:41 a.m., court resumed in the presence of the jury and David Ozonoff resumed the witness stand)

MR. COX: Belatedly, good morning, ladies of the jury. This is Dr. Ozonoff here.

DIRECT EXAMINATION

BY MR. COX:

Q Dr. Ozonoff, would you please, for the jury here, state your full name?

A David Michael Ozonoff.

Q Where do you live, Dr. Ozonoff?

A I live in Boston, or actually across the river, in Cambridge.

Q Are you married?

A I am.

Q Do you have children?

A I have two children.

Q How old are they?

A Fourteen and nine.

Q Where do you work?

A I'm the chief of the environmental health section at Boston University School of Public Health and professor of public health there and professor of community medicine at Boston University School of Medicine.

you conduct your review of the historical, medical and scientific literature on asbestos and asbestos-related disease?

A I reviewed this subject from a period that started at the end of the last century all the way up until the end of 1965.

Q Why did you stop in 1965?

A Well, it was on the very last day of 1965 that a very big book was published on the -- not the history, but the research on asbestos disease. This was the Annals of the New York Academy of Sciences book, and beyond that time, the very last day of 1965, there are few, if any, people who don't acknowledge that the understanding of asbestos-related disease was very widespread in the world. So the interesting historical question was not what was known after 1965, but what was known prior to 1965, using that publication date as a marking point or a milestone.

Q Does that mean that you haven't kept abreast of asbestos since 1965?

A No.

The literature, of course, in asbestos is extensive following 1965, and as a practicing public health practitioner and as a teacher and a researcher, I keep up as best I can with that

subject, as well as I do with many other subjects that are pertinent to my field. But I haven't approached it as systematically in a historical fashion beyond 1965.

Q I believe you indicated you look for these articles in part through the Index Medicus, is that correct?

A Yes.

Q Were there other places you look for articles other than that?

A Yes. That's one of the main tools that we use. But there are a lot of things that you can do to find medical articles about a particular subject, and one of the most effective things is to just walk into a library and go to that section of the library that you know is pertinent to a subject and just browse around, and I used to do that all the time, and invariably when I would do that I would find new material that wasn't listed in an index, but was right there sitting on the shelf just waiting to be found.

Q Are these public libraries, libraries open to the public?

A Usually they are open to the public and many public libraries contain this material. Many of them are medical libraries that are open to any medical person

in the community.

Q What type of articles were you looking for, specifically?

A I confined myself to articles that dealt with asbestos and disease and connections with asbestos exposure and disease. Some articles that had to do with the industrial applications or processes or something like that I did not search the literature for. That's an entirely different engineering or manufacturing literature that I didn't concern myself with.

Q Did you find articles dated prior to 1965?

A Yes, indeed I found many, many hundreds.

Q How many --

Many hundreds?

A Yes. Well, actually, the number on one of my lists, which is not a complete list, is 720 some, up to the end of 1965, but it's certainly not a complete list. There are more articles than that.

Q Could you give me some idea and give the jury some idea of how many of those articles were prior -- dated prior to 1956?

A Yes. Well over 400.

Q Before 1956?

A Yes.

Q Doctor, the reason I asked 1956 is that is the date of the alleged installation of their product, in this case, in the schools of Benton Harbor, and I will be using the 1956 date throughout the rest of this examination.

A I understand.

Q In various places.

And in what types of publications, Doctor, did these various medical and scientific articles appear?

A Well, they appear in all kinds of medical publications, specialty journals, such as journals about diseases of the lungs, specialty journals about cancer, but also general journals like the journal of the American Medical Association, which is a journal that comes along with membership in the American Medical Association and -- so that they went into more than half of the doctors offices in the United States. So it's a wide variety, state, local journals, national journals, specialty journals, review journals.

Q Are these journals that are limited in distribution or are they available to the public at large?

A Well, generally they are available to anybody who would care to subscribe to them or look at them in a

library. Some of them are smaller circulation than in others, of course.

Q Doctor, did you prepare a list of the articles that you researched with respect to asbestos-related disease?

A Yes, sir, I did.

Q Let me show you this 43 page document. It doesn't have a title.

But let me ask you if you could tell the jury what that particular document is?

A Yes. This is a list I prepared, probably some six or seven years ago, and it lists the medical articles that I'm talking about. It's listed chronologically by date, with the date along long the left-hand margin, and then within each year the articles are listed alphabetically by author, and it's 43 pages long, single spaced, with one space skipped between each entry.

Q These are all articles that were pre-1965?

A 1965 and before, yes.

Q Now, Doctor, based upon your review of the medical and scientific literature as you have described, do you have an opinion on when it was first known that asbestos could harm people?

A Yes.

Q Would you tell the jury, please, what your opinion is?

A Well, I will skip the ancient world, because it was noticed in fact in ancient times that slaves who worked with asbestos died from it. But in the modern literature, the literature really starts around the year 1900, which is very shortly after the beginning of the modern asbestos industry in this western industrial society. And at that very first publication, which is the inspector of factory reports for the year 1898, published in the year 1900, it was noticed that breathing asbestos dust was a harmful and dangerous kind of workplace. So I would have to say, in answer to your question, that from the very first notice of it it was understood that breathing asbestos dust would cause harm to people.

Q That first article, was that the first article, the 1900 article, that you made reference to in your bibliography?

A Yes, that's the very first entry.

Q What kind of people are harmed by asbestos as reflected in the medical articles?

A Well, any human being that breathes asbestos fiber. Asbestos disease is a disease of asbestos breathers.

It's not a disease of particular kinds of workers. So that the literature reflects all sorts of people, people who are involved in mining and milling and manufacturing, various kinds of processes. People who lived nearby asbestos facilities. People who worked in facilities but not with the asbestos itself; for example, a cashier or a warehouseman or somebody who was a bystander, in essence. The spouses of asbestos workers. They -- for example, the wife or a child that was involved in doing the laundry of an asbestos worker and was exposed to the dust on the clothes. There is even a wirehaired terrier that's mentioned several times in the literature. This is a dog that worked as a guard dog in an asbestos factory and came to the attention of some medical people after it died of asbestos disease, and an autopsy done, and it was described in at least two different medical articles that I'm aware of.

Q Thank you.

Well, based upon your review of this medical literature, when was a possible association between asbestos and cancer first noted?

A The relationship between asbestos and cancer was first noted in 1935 in an article about lung cancer

in an asbestos worker in Charleston, South Carolina. And I think that article brought to the attention to the medical world the possible connection, but I wouldn't say that it established that connection by any means, although I think warning flags started to fly at that point.

By 1942 this relationship was being mentioned in textbooks, textbook on occupational cancer, to be specific. And I would say no later than 1949, I would suspect that some people might put it earlier, but I would say, to be conservative, no later than 1945, I would say that it was generally accepted in the medical profession that asbestosis was connected with cancer.

Q What was the significance of 1949?

A Well, 1949 was the date, first of all, of a study by a Dr. Merewether on cancer and asbestos disease, and as a result of that study an editorial was written in the journal of the American Medical Association, which was one of the most widely circulated medical journals in this country. And that editorial set out the relationship then, on the basis of the Merewether study, accepted the relationship between asbestos and cancer.

Q Did the medical literature that you reviewed also

building exposures?

A Well, it's -- it's pretty -- it would be pretty hard to do a school-specific study, but there are some cases reported in the literature in which the only exposure seemed to be schools. For example, Dr. Karen Antman, who's actually from the same city that I am from, at the Cancer Institute, has published an article on the treatment of mesothelioma. And in this article which was published in 1985, she notes that a number of her cases there -- there were four women in this group. And two of the women had no exposure, occupational exposure at all, except for the fact that they went to a school, according to Dr. Antman, that was noted to have excessive asbestos exposure in it. So, to that extent, yes, there are cases that are appearing in the literature, and I think virtually our only way of locating cases will be through work such as Dr. Antman's work where she treats patients and inquires somewhat into their background.

Q Doctor, I want to go back for a moment now to the early medical articles that you have reviewed to ask you a couple of questions.

Were the medical articles that you discussed as existing in the 1930's, for example, the

Stewart article with respect to plaster, and the Russell article with respect to maintenance people, were those medical articles available to manufacturers such as the National Gypsum Company, who might wish to take a look at them?

A Well, certainly they'd be available to anybody who had access to these libraries, and access to general and medical libraries is pretty much unrestricted.

Q So I gather the answer --

A I guess the answer is yes.

Q Now, based on all the articles that you have reviewed, Doctor, if manufacturers such as National Gypsum wanted to find out more about asbestos hazards, let's assume that they look at those articles in the early 1930's, would one reasonable way to do that be to conduct animal studies?

A Well, certainly that is one route that's taken, to do research on the effect of chemicals.

Epidemiologists look at the -- you know --

MR. SUOJANEN: Objection, Your Honor.

Dr. Ozonoff hasn't been qualified as an expert in any kind of animal study. He reads books. He doesn't test animals.

MR. COX: Your Honor, this question is going to lead into literature that the doctor

Pulmonary Tumors in Mice Exposed to Asbestos Dust

KENNETH M. LYNCH, M.D.; GEORGE A. HUEPER, M.D., and JAMES S. CAIN, M.D., Charleston, S. C.

Since the first case of carcinoma of the lung associated with asbestosis was cited by Lynch and Smith in 1933,[1] there have been numerous reports in the literature of similar cases. Authors reviewing the literature describe an incidence of carcinoma of the lung associated with asbestosis ranging from [illegible] to 16%.[2-4] Individual reports, usually dealing with relatively small numbers of cases, describe an incidence ranging from [illegible]% to 50%.[5-8] In an editorial in 1953, Hueper[9] stated that 127 cases of asbestosis carcinoma of the lung were on record and described the occurrence of 114 cases of pulmonary carcinoma in 738 autopsies of asbestosis cases collected from the literature (1952).

Experimental work has not kept pace with the accumulation of clinical data. An increased incidence of pulmonary tumors has been recorded in mice following the subcutaneous injection,[9] intratracheal injection,[9] intravenous injection,[10] and inhalation[11] of a variety of substances, but only one published statement has been found suggesting the induction of tumors in experimental animals by the inhalation of asbestos.[12]

The purpose of the investigation to be described in this report was to correlate, if possible, the effect of asbestos on the lungs of experimental animals with the suggested carcinogenicity for human subjects.

Received for publication Nov. 19, 1956.

From the Department of Pathology, Medical College of South Carolina.

This work has been supported by a research grant, No. C-474, from the Public Health Service.

Present address (Dr. Melver), University of Wisconsin School of Medicine, Madison; (Dr. Cain), St. Joseph's Hospital, Atlanta.

Experimental Study

Animals.—Mice were selected for this work because the use of inbred strains would eliminate some of the uncertainties inherent in the use of other animals. Furthermore, the published report of Nettleman and Sorge, which has been previously mentioned,[9] and unpublished data left by Dr. L. U. Gardner,[1] of Sarsaac Laboratories at his death suggested that mice might be suitable test animals. Dr. Gardner mentioned that of 25 mice inhaling chrysotile asbestos for not more than 12 months, 3 (12%) developed lung tumors. Fifty-one mice exposed to other dusts for 10-12 months developed lung tumors in 2%. In both of these studies the number of animals used was small, and the strains employed were not mentioned or apparently varied.

In the study to be described, it was decided to use the F_1 generation offspring of Strain A male mice[14] and Strain C female mice.[15] It was felt that this hybrid strain would possess the genetic purity of the parent stock but would be hardier and hence more suitable for long-term studies.

Strain A breeding stock was obtained from J. J. Bittner, of the University of Minnesota, and Strain C female breeding stock was obtained from Lloyd W. Law, of the National Cancer Institute. As soon as the Roscoe B. Jackson Memorial Laboratories had recovered from the disastrous fire of 1947, all breeding stock was obtained from that source.

ACF, animals from the breeding colony were divided into approximately equal groups, and at the age of 2 months one-half were placed in the cages exposed to asbestos dust. The other half were maintained as a control group. Male and female mice were kept in separate cages to avoid breeding in both the control and the dusted groups.

Of the hundreds of mice bred for this work, a great many succumbed to cannibalism, intercurrent infection, or other accidents, but 776 mice were subjected to parenteral examination. Of this number the largest groups were the control and test animals carried at 19 and 24 months of age. The observations in these groups will be emphasized in the discussion which follows.

In order to study larger animals with a tracheobronchial tree more comparable to that found in

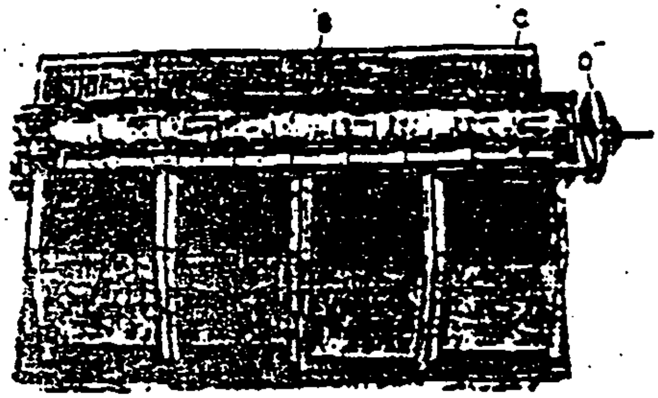


Fig. 1.—Dusting apparatus for mice: (A), mouse cage; (B), trough for asbestos; (C), copper tubing with minute holes directing compressed air toward cages, and (D), pulley used to rotate U-shaped wire paddles.

men, dogs have also been subjected to dusting with asbestos. The results of this study will form the basis of another report.

Methods and Materials.—Test animals were kept in wire cages on racks in an especially constructed room. Usually 10 or fewer animals were placed in each cage. In the early stages of the work a single metal bin, with a paddle wheel near the bottom, was loaded with asbestos to provide a cloud of dust for the entire room. Later a trough filled with asbestos was run behind each row of cages (Fig. 1), the asbestos was stirred by a series of small rotating metal agitators, and dust was blown toward the cages by multiple fine streams of compressed air. Most of the test animals were dusted in this manner because heavier concentrations could be obtained.

The asbestos used in this work was generously supplied, as was much of the information concerning its composition, by the manufacturers. This material is referred to commercially as Asbestos Flakes 7-TF-2. It is described as a "very fine flake with little fibrous content" but was selected because of its similarity to "King's Fibers," used in other asbestos studies,[4] and because no material with a greater fibrous content in the 10μ-100μ length was available. Kenneth W. Smith, M.D., provided the information that 91.5% of Asbestos Flakes 7-TF-2 passes a 200-mesh wet screen. This large proportion of the dust appears

Fig. 2.—Asbestos Flakes 7-TF-2. Photograph shows that portion of the material which failed to pass through a 200-mesh wet screen. × 102.

PULMONARY T[illegible]

to be mostly irreg[illegible] serpentine rock. C[illegible] portant material n[illegible] not passing the 20[illegible] chemical compositio[illegible] bestos, 3MgO·2SiO[illegible] 1 which was suppli[illegible] represent high and [illegible] centage.

TABLE 1.—Chem[illegible] Che[illegible]

Dust counts were [illegible] and for extended pe[illegible] cubic foot of air w[illegible] according to time [illegible] factors, but it was p[illegible] concentrations of 1[illegible] ticles per cubic foot [illegible] permanent. Dusting [illegible] 4 to 12 hours daily [illegible] ples were collected [illegible] cages by means of [illegible]

Particle-size deter[illegible] collected in water (w[illegible] that particles and [illegible] formed 18% to 2[illegible] sample of air colle[illegible] and sent to the lal[illegible] Ville at the Cent[illegible] showed the follow[illegible] sizes: less than 3μ[illegible] 3μ, 38.2%, and gre[illegible]

Control Animal[illegible] work was started [illegible] AC F_1 mice, and [illegible] these animals was [illegible] able interest. In [illegible] was maintained [illegible] and most of the an[illegible] at 19 or 24 mont[illegible] mortality was in[illegible] sulted, apparently, [illegible] difficulty was also [illegible] summer months w[illegible]

It was originall[illegible] mals to live out a[illegible]

...le mostly irregular pieces of inert granular ...ementing rock. Chrysotile asbestos is the important material in that portion of the substance ...passing the 20-mesh screen (Fig. 2). The ...mical composition of Canadian chrysotile as ...ported, $3MgO \cdot 2SiO_2 \cdot 2H_2O$, is represented in Table ... which was supplied by the producers. The data ...present high and low limits expressed in per...ntages.

TABLE 1.—*Chemical Analysis of Canadian Chrysotile Asbestos*

...	SiO_2	H_2O	FeO	Fe_2O_3	Al_2O_3	CaO
...	...	...	...	...	...	...

The figures in each column represent high and low results ...ported in five tests.

Dust counts were done on numerous occasions, ...d for extended periods 300,000,000 particles per ...bic foot of air were maintained. Counts varied ...cording to time of day, humidity, and other ...ctors, but it was possible to maintain atmospheric ...ncentrations of 150,000,000 to 200,000,000 par...icles per cubic foot throughout most of the ex...periment. During experiment was exercised for ... to 12 hours daily for 5 days each week. Sam...ples were collected in water within the mouse ...tes by means of a standard midget impinger.

Particle-size determinations on samples of air collected in water from mouse cages in 1950 showed that particles and fibers 10u in size and over formed 18% to 21% of the total. In 1952 a ...mple of air collected in 99% isopropyl alcohol ...nt to the laboratory of Dr. J. M. Dalla Valle at the Georgia Institute of Technology showed the following distribution of particle sizes: less than 2u, 13.3%; 2u-10u, 34.0%; 10u-20u, 26.7%, and greater than 20u, 26.0%.

Results

Control Animals.—At the time that this work was started little was known about AC F1 mice, and the biologic behavior of these animals was observed with considerable interest. In general, the control colony was maintained without undue difficulty, and most of the animals survived until killed at 19 or 24 months of age. The greatest mortality was in the male group and resulted, apparently, from fighting, but some limicolity was also encountered during the summer months with infectious diseases.

It was originally planned to permit animals to live out a full life span, but examination, especially microscopically, of animals which were found dead proved very unsatisfactory, and eventually only killed animals were considered in the statistical studies.

The microscopic appearance of the lungs of control animals is shown in Figure 1. Alveolar septa are delicate; alveoli are well expanded, and macrophages, when present, are small and eosinophilic. One or two small collections of lymphoid tissue are frequently present, and inflammatory changes are found but are uncommon. Large foamy macrophages are occasionally found in areas of inflammation.

In Table 2 the occurrence of pulmonary tumors in control mice killed at 19 months of age is recorded. Only those tumors considered histologically are included. It should be pointed out that on rare occasions a nodule regarded as a tumor grossly proved to be inflammatory on microscopic examination. On the other hand, tumors were occasionally found on microscopic examination which had not been detected grossly. For practical purposes the results on gross and microscopic examination in the control group were the same.

It is interesting to note that there seems to be a significant difference between the number of male and female control mice

Fig. 1.—Lung of control mouse at 19 months—Mouse 158 (female). Photograph shows a portion of the wall of a bronchiole and related alveoli. Alveolar walls are delicate, and there is a relative absence of intra-alveolar macrophages. ×433.

Table 2.—AC F₁ Hybrid Mice: Controls at Nineteen Months

Sex	No.	Mice with Pulmonary Tumors		Mice with Extrapulmonary Tumors		Mice with Multiple Tumors	
		No.	per Cent	No.	per Cent	No.	per Cent
Female	119	28	23	28	23	4	3
Male	122	36	29	28	23	12	10

The tumors have not yet been examined histologically. Only tumors suitable for histologic examination are reported.

bearing pulmonary tumors at 19 months of age. Males developed pulmonary tumors in approximately 47% and females in 28%. However, in a smaller group of mice 20 months and older this ratio was reversed, and, of 43 female controls, 29 developed pulmonary tumors (67%). Of 41 male controls in this age group, 24 developed pulmonary tumors (58%).

The nature of the pulmonary tumors observed in AC F_1 mice has been a matter of considerable interest in this study, and we have not felt warranted in referring to the neoplasms observed as carcinomas. The tumors are basically papillary adenomas, although some are very compact and in some fields do not reveal a papillary appearance. Tumors may be surrounded by small neoplastic masses which we have described as "satellite nodules"; their margins may be sharp or ill-defined, they may extend into the lumen of bronchioles, and they may show very few or many mitotic figures, but we have never found evidence of metastasis. This absence of metastasis is true of all age groups examined, but the largest numbers of mice, as mentioned previously, were in the 19- and the 24-month categories. Some of the tumors do present a relatively malignant histologic appearance, but in 23 consecutive control mice bearing 31 pulmonary tumors, which were studied in great detail, not a single one was classified as malignant, even on a histologic basis.

Other findings of interest in the control animals at 19 months included an abnormality of the reticuloendothelial system in 7%. This entity is characterized by splenic enlargement in most cases and also in some by excessive lymphoid accumulations in the lungs, markedly enlarged lymph nodes, or hepatomegaly. Blood counts were not done. Four animals, all females, developed extrapulmonary tumors, one of the breast, two of the ovary, and one of the skin. Other breast tumors were seen, but the affected mice did not survive to be killed at 19 months.

Test Animals.—The microscopic appearance of the lung of a mouse dosed for 17

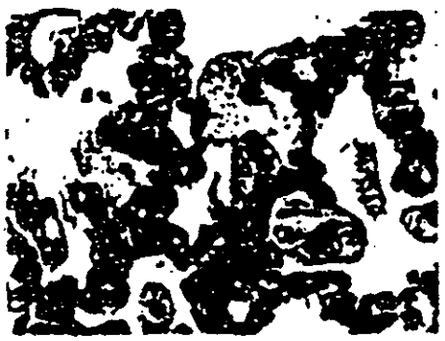
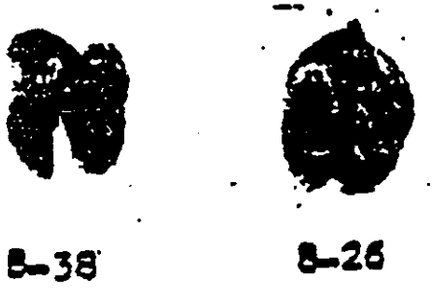


Fig. 4.—Lung of test mouse at 19 months (Mouse B-38) (female). Photograph shows normal organized and thickened alveolar walls [illegible] "dusty" macrophages are prominent. × 445.

Fig. 5.—Lungs of a control animal (Mouse B-38) and of a test mouse (Mouse B-26). Both animals were killed at 19 months of age. In both specimens the hearts are sectioned and partially hidden by the lungs. The test lungs are larger and heavier and present a mottled gray pleural surface.



months and killed at the age of 19 months is illustrated in Figure 4. The lungs of dusted animals appeared grayer and larger than normal (Fig. 5). Alveolar walls were thickened; macrophages were a great deal more numerous and were usually foamy and contained a great deal of tiny granular material, "dust." Coarse granular particles of brown material, probably blood pigment, were found in test animals as well as in controls, but larger golden brown particles within macrophages were found only in the dusted animals. These were thought to be

Fig. 4.—Asbestos body in mouse lung—Mouse [illegible] (female). Each asbestos body is incompletely surrounded by a large macrophage, and each reveals the typical "stacked coin" appearance. × 1000.

asbestos bodies about small chunks and very short fibers of asbestos. Elongated asbestos bodies (Fig. 6) were found in the lungs of almost every dusted mouse, and 10 to 20 bodies were not infrequently found in one microscopic section. At times one end was globular, but more frequently they were straight or curving golden brown bodies partially engulfed by large "dusty" macrophages. The "stacked coin" appearance, usually described in human asbestos bodies, was also frequently observed in mice. Bodies more than 20μ in length were frequently seen, and the longest recorded length was 40μ. The great majority were shorter than 20μ. Hilar nodes were not noticeably enlarged and apparently were not involved by any specific process related to asbestos. Pulmonary fibrosis did not occur, and squamous metaplasia of bronchial epithelium was not found. Inflammatory changes and bronchiectasis were commoner than in the control animals.

The occurrence of pulmonary tumors in dusted mice killed at 19 months of age is shown in Table 3. Only those tumors confirmed histologically are included.

The microscopic appearance of these tumors was in no significant way different from those described in the control animals. Asbestos bodies were rarely encountered within the substance of the neoplasm.

Comment

Studies referred to previously dealing with human cases of asbestosis strongly suggest that there is an increased incidence of associated carcinoma of the lung. It is important to bear in mind, however, that there are no very large groups of cases, and one is beset with the problem of deciding whether the cases reported are weighted in favor of a high incidence of carcinoma by selection. On the other hand, no consistently high incidence of pulmonary carcinoma has appeared in reports of cases of silicosis. In fact, the incidence of pulmonary carcinoma in silicosis seems to be relatively low, and one writer [17] suggests the possibility that silicosis may protect the patient from the likelihood of carcinoma of the lung.

TABLE 3.—*AC F₁ Hybrid Mice Test Mice at Nineteen Months*

Sex	Number	Total Mice with Tumors		Mice with Primary Tumors		Mice with Metastatic Tumors	
		No.	per Cent	No.	per Cent	No.	per Cent
Female	48	21	37	14	29	7	14
Male	44	15	34	11	25	10	23

The tumor figures are preliminary observations. Only tumors confirmed by microscopic examination are reported.

The references which describe animal studies are not regarded as acceptable evidence for the experimental production of asbestosis carcinoma of the lung. Nordmann [4] reports a number of instances and types of epithelial change but found only two pulmonary tumors in 10 mice living to the "cancer age" of 240 days. The number, therefore, is very small, and no suitable control animals are mentioned. Gardner [5] apparently regarded his observations as merely suggestive. The work was done in a study of pneumoconiosis, and the incidence of naturally occurring pulmonary tumors was not established for the test animals or for the controls.

The animals used in this study, mice, are probably poorly suited for the purpose. The tracheobronchial tree is of small diameter, and the nasopharyngeal filtering apparatus is probably highly efficient. Mice readily form asbestos bodies, but pulmonary fibrosis is not produced. The latter change could be a feature essential to the anticipated epithelial alterations. At least, in studies now in progress in which dogs are used, pulmonary fibrosis is produced and there is a profound associated squamous metaplasia of bronchial epithelium. It is quite possible that future work should be planned about the use of primates. The occurrence of newly developing asbestosis in man is fortunately very low at this time, and so the animals best suited for future studies seems to be the monkey.

Asbestos Fionia 7-TF-2 is a difficult material with which to work in a climate with high humidity because of its hygroscopic nature. By the use of heat lamps, however, it was possible to keep the storage bin reasonably dry, and all dust counts were certainly far above those in which human asbestosis develops. Even the low counts of 150,000,000 particles per cubic foot are 15 times greater than levels at which human asbestosis is thought to be a danger.

Particle length is a factor in human asbestosis. The quantities of asbestos material of various lengths reaching the lungs of test mice are not known. It is known, however, that a sufficient quantity of fibrous material reached the mouse lungs to produce asbestos bodies in great numbers and that the same material is capable of producing fibrosis in dogs. If the ability to produce asbestosis, therefore, were associated with carcinogenicity, then Asbestos Fionia 7-TF-2 should be capable of producing pulmonary tumors.

If the anticipated life span of a healthy mouse is considered to be 30 months, then the exposure of our animals for periods of 17 and 22 months should correspond to very adequate periods of human exposure. As was mentioned earlier, animals were exposed to the dust at 2 months of age, and the larger groups were killed at 19 and 24 months, respectively.

The results summarized in Table 4 show that there is no striking difference between the total number of control and test animals bearing lung tumors, the figures being approximately 46% for dusted animals and 36% for control animals at 19 months. There are 7 possibilities in 100 that this difference might be due to chance. This difference is not statistically significant.*

There was a considerable occurrence of multiple lung tumors in both the dusted and the control groups. Table 4 shows that this incidence is 13% and 8% for the two groups, respectively. Using the same formula, there are only 0.31 chances in 100 that the difference is a chance difference. This variation is statistically significant. A possible interpretation of this observation is that, given a group of animals with a similar tendency to develop pulmonary tumors, this

* In evaluating the recorded statistics, the standard error is computed on the basis of the following formula:

$$\sqrt{pq\,(1/N_1 + 1/N_2)}$$

where

p = general percentage occurrence

q = $1 - p$

N_1 = number in first sample

N_2 = number in second sample

The probability of occurrence of the stated results on the basis of chance is computed from the number of standard errors with Pearl's table.

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Total Control....

Total Tissue Number

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Summar

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The largest
consisted of 12
after exposure
was compared w

L. A. S. et al.

TABLE 4.—AC F₁ Hybrid Mice: Summary

Group	No.	Total Mice with Tumors		Mice with Lung Tumors		Mice with Multiple Tumors	
		No.	per Cent	No.	per Cent	No.	per Cent
Total Dusted....	137	45	46	25	26	25	18
Total Control....	222	80	36	45	20	8	4

[illegible] the findings presented in Tables 2 and 3, and all animals lived [illegible] conditions of thorough examination.

tendency is accentuated by the inhalation of asbestos dust, and multicentric foci of origin become evident. Such an interpretation fits into the widely held belief that one requirement for the effectiveness of a carcinogen is a susceptible host. The weaker the carcinogen, the more important becomes the factor of host susceptibility.

No appreciable difference is noted in the histologic characteristics of pulmonary tumors in the dusted and the control groups. In the absence of any evidence of metastasis the term carcinoma should be applied to such neoplasms with great caution. Specifically, the presence of small neoplastic formations in the vicinity of larger ones is insufficient evidence of malignancy, as is the occurrence of invasion of bronchial lumens. The former is more likely evidence for multiple foci of origin, and the latter is a result of growth in the direction of least resistance. Both findings may be noted regardless of the histologic or cytologic appearance of the primary lesion. Irregularity of tumor margins, the appearance of "infiltration," is similarly unrelated to the cytologic evidence of possible malignancy. Enlarged lymph nodes are encountered not infrequently, but metastasis from pulmonary tumors has not been found.

Summary and Conclusion

AC F₁ mice were exposed to dusty atmospheres containing Asbestos Fines 7-TF-2 for various lengths of time.

The largest single experimental group consisted of 127 animals killed at 19 months after exposure for 17 months. This group was compared with 222 control animals.

Primary lung tumors were demonstrated microscopically in 46% of the dusted mice and in 36% of the control animals.

Multiple pulmonary tumors were demonstrated in 18% of the dusted animals and in 8% of the control animals.

No significant histologic or cytologic difference was observed between tumors in the control and the dusted groups.

No clear-cut proof of malignancy was found in any of the lung tumors studied.

We have been unable to demonstrate any proof of the carcinogenicity of asbestos under the conditions of this experiment, but the increased incidence of multiple lung tumors in dusted animals must be regarded as a possible accentuation by the inhalation of asbestos dust of an existing tendency to develop lung tumors.

Future experiments with asbestos should include the use of larger animals, probably monkeys.

The equivocal nature of this report does not answer the questions raised by accumulating clinical evidence that asbestosis is strongly associated with, and therefore a possible cause of, pulmonary carcinoma in man.

In the choice of experimental animals very helpful advice was supplied by H. B. Andervont, Walter Nungester, and Lloyd W. Law, of the National Cancer Institute. C. D. Coleman, Building Superintendent at the Medical College of South Carolina, provided valuable assistance in designing and maintaining the mechanical equipment. Advice and assistance in the technique of dust counting were provided by W. G. Crosby, of the South Carolina State Board of Health, and Dr. L. M. Parks, of the Georgia State Board of Health. Further assistance was rendered by Robert A. Brown and Miss Ethyl McAfee, of the Department of Medical Illustration, Medical College of South Carolina.

University Hospitals, 1300 University Ave., Madison 6, Wis. (Dr. McIver)

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pertinent comment of Dr. Murphy's? What are the facts regarding the control of these animals reported by Gardner as the basis for his request?

DR. MURPHY: You notice he calls it an uncontrolled experiment, so I doubt if he knows the normal lung tumor rate for his animals. He gives 18 per cent in 143 animals. It is very hard to get a strain of mice that gives much lower than 3 or 4 per cent, and we have some strains that give as high as 50 to 60 per cent normally. I wouldn't consider that figure, uncontrolled, as of any significance whatever, unless I knew the strain of the animals, knew it was a low strain; and of course that is the whole danger in having a project of this kind carried on in an institution where they have absolutely no experience with animals in planning cancer experiments. It may be well worth doing, but I doubt if this is quite the way to do it.

DR. SPENCER: After you establish cancer in certain strains of inbred mice, and maybe others are more resistant or less resistant, you still can't reason from that to human beings, from such an experiment to human beings. Isn't that true?

DR. MURPHY: I think so.

DR. SPENCER: Wouldn't this experiment be just establishing another carcinogenic agent, when we know new ones are being found nearly every week or so.

EXHIBITS TO DEFENDANTS' REPLY BRIEF
IN SUPPORT OF MOTION TO DISMISS
CONSPIRACY CLAIMS