PROPOSAL

ASBESTOSIS AND PULMONARY CANCER

$16,000 - 1st yr
$10,000 - 2nd yr

to

The Asbestos Mining Associated Industries
~~Quebec, Canada~~

Jan 1, 1951
Terminates
Dec 31, 1952

---

by

The Saranac Laboratory
of the
The Edward L. Trudeau Foundation

Saranac Lake, New York

Submitted by:

September 21, 1950
approved 11/7/50
Meeting S L - Gabourn Ramsay Wooster

Arthur J. Vorwald, M.D.
Director, The Trudeau Foundation and
The Saranac Laboratory

PART I

INTRODUCTION

1. THE PROBLEM

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

2. GENERAL REMARKS

The rapid increase in the incidence of lung cancer during the past thirty years has become the subject of a great deal of critical study and speculation. Many investigators contend that this increase is merely apparent and can be credited to a shift in the age composition of our population in recent decades, to better diagnostic facilities, and to a keener appreciation by the lay population and medical profession concerning the importance of early detection and treatment. Others maintain that the increase is real and caused by the presence of new carcinogenic factors in our environment, many of which are of industrial origin. This concept of occupational lung cancer receives some indirect support from the fact that the majority of new occupational cancers involve the respiratory system. Some of these cancers have been traced to certain chemical or physical agents. In consequence, there is a growing tendency to incriminate many other agents irrespective of the lack of clear-cut evidence to prove their carcinogenic capabilities.

Evidence regarding many of them, however, although frequently contested, is sufficiently serious to warrant extensive epidemiological and experimental investigation. Asbestos dust is in this category (Hueper, Lynch, Merewether, etc.) and the asbestos industries in Quebec are in a unique position to pursue these epidemiological investigations.

PART II

EPIDEMIOLOGICAL INVESTIGATIONS

3. It is pertinent to point out here that such investigations are indeed complicated and demand the most considered design lest in final analysis the results obtained will have little significance. For example, the incidence of pulmonary cancer appears to vary geographically and racially. A statistical study of a series of individuals exposed to asbestos must be controlled, therefore, by a similar study of individuals of similar geographical distribution and racial type, and of the same age and sex, not exposed to asbestos. Since the incidence of detected pulmonary cancer varies with the degree of effort applied in detection, both groups, the exposed and non-exposed, should be studied by the same technique and perhaps even by the same personnel. As it is not possible to examine a large population by exhaustive techniques such as biopsy, sputum examination, and bronchial washings, it seems most practical to carry out the proposed statistical study essentially as an X-ray survey.

When the presence of neoplasm in an individual is suggested by this technique, he should be further studied with the purpose of establishing or excluding this diagnosis with certainty. Other factors suspected of being carcinogenic, such as cigarette smoking, may constitute variables within the population to be studied. Information as to these variables must be obtained as well as information concerning exposure to asbestos. It appears that cigarette smoking is the most prominent variable factor in the epidemiological study proposed. Other suspected factors such as atmospheric hydrocarbons would be essentially constant for each group of individuals in the same geographic area where asbestos is being mined.

4. In view of these considerations, it is suggested that only certain phases of the epidemiological study be undertaken at this time pending the advice and recommendations of those with a wide experience in the conduct of such studies. Agencies with this experience are: the Medical Research Councils of Canada and the United States, the cancer societies of both countries, the respective tuberculosis societies, the National Cancer Institute of the U. S. Public Health Service, and the Sloan-Kettering Institute of the Cancer Memorial Hospital.

5. The phases of the epidemiological study which might be undertaken immediately include the clinical and statistical data already available for employees in industries such as those at Thetford and Asbestos, where routine physical examination and chest

X-rays have been standard practice for years. In essence, this program should include scrutiny of all medical records, of chest roentgenograms of all employees, of autopsy protocols, and of death certificates for evidence of malignancy. It should be pointed out that statistical calculations relying on clinical records or on death certificates based on clinical diagnosis may contain a wide range of error in the fundamental material and may be unreliable as to the absolute numerical conclusions reached. Similarly, autopsy protocols may represent only a highly selective sample of the total mortality and may constitute, therefore, a weighted index of the incidence of cancer in subjects exposed to asbestos dust.

PART III

EXPERIMENTAL INVESTIGATIONS

6. The Saranac Laboratory with its background of study concerning chronic pulmonary disease, especially that resulting from the inhalation of industrial dusts including asbestos, is uniquely qualified to pursue certain phases dealing with the problem of asbestosis and pulmonary cancer.

7. For purpose of completeness and general information, certain brief comments seem justified for guidance in the design of the experimental approach which we propose.

A number of experimental methods may be employed to test the capacity of asbestos to produce cancer. It is desirable to keep in mind, however, certain facts concerning asbestosis which affect the selection of the method:

(1) Asbestosis is a chronic pulmonary disease resulting from the deposition of asbestos fibers in the lung; therefore, the experimental method employed should direct emphasis on the lung.

(2) The weight of evidence is that asbestos fibers produce their irritation by a mechanical rather than by a chemical mode of action. The mechanical action is intimately related to the movement of the lung during respiration. Thus, an experimental method which neglects movement of the lung and thereby excludes the mechanical action in all probability would be highly inconclusive and subject to criticism.

(3) Asbestosis is a disease resulting from widespread dissemination of asbestos dust in the lung. Reliable conclusions in an experimental investigation with asbestos cannot be drawn solely from experiments with the intratracheal injection technique whereby a high concentration of dust becomes localized in a restricted portion of the lung and stimulates excessive focal irritation. When the asbestos dust is introduced into the animal in that manner, the injected dust may miss certain potentially cancer-producing sites in the lung which are remote from the

localized area of implantation of dust. It is further possible for the excessive focal irritation, which is not a characteristic feature of human asbestosis, to induce pulmonary cancer which would not have developed had the dust been uniformly distributed throughout the lung. Thus, the intratracheal injection technique alone might lead to unwarranted conclusions. The intratracheal method has been used for cancer studies by a number of investigators, probably because of the relative difficulty and tediousness of methods involving inhalation of the potential carcinogen. The inhalation method, however, has been employed by eminently recognized investigators of carcinogenic agents.

8. In passing, it might be said that lung tumors can be produced by numerous means in susceptible mice, i.e., mice possessing the tendency to develop tumors spontaneously. Some of the methods garnered from the literature are: repeated applications of coal tar to the skin; subcutaneous injection of carcinogenic hydrocarbons; intravenous injection of serum and charcoal dispersions of carcinogenic hydrocarbons; feeding large doses of dibenzanthracene; and introduction of carcinogenic hydrocarbons into the rectum, vagina, peritoneal cavity, or pleural cavity. For explanation of the occurrences of lung cancer following such methods, it has been suggested that the introduction of carcinogenic compounds into the body of the mouse alters the body state so that tumors arise at points of incidental irritation. The more plausible explanation advanced by certain investigators is that the lung tumors are pro-

duced because very small amounts of the carcinogenic agent leave the site of application and come in contact with extremely susceptible alveolar epithelium. If this is true, it is unlikely that such methods could be used for investigation of cancer and asbestos, a dust which remains within pulmonary tissue, which is not transported systemically as are soluble chemical agents, and which produces its irritating effect by a mechanical rather than by a chemical mode of action.

9. Reference has been made to inbred strains of mice in which the spontaneous occurrence of tumors of the lung is a characteristic feature. Strains are available in which the incidence of spontaneous lung tumors is accurately known. In some strains the incidence is low, so that an increase in the incidence after an experimental procedure is easily detectable. Other strains with high incidence of spontaneous tumors are suitable to determine whether the procedure has caused tumors to appear at an earlier age and whether the number of tumors per mouse has been increased.

The susceptibility of the pulmonary tissue in selected inbred strains of mice is such that they serve as excellent test animals for checking an alleged extrinsic carcinogen such as asbestos. A reasonably delicate assay of the potency of asbestos as a carcinogen is possible because of the unique multiplicity of tumors formed.

PART IV

PROPOSED EXPERIMENTAL INVESTIGATION

10. METHODS TO BE EMPLOYED

In view of the considerations mentioned in the preceeding paragraphs, the Saranac Laboratory proposes to conduct an experimental investigation employing the inhalation method and also, for supportive evidence, the intratracheal injection method. Two groups of pure inbred strain mice will be used, i.e., the low spontaneous lung tumor "strain C 57 black," and the high lung tumor "strain A" (obtained from the Roscoe B. Jackson Memorial Laboratory). The animals of each group will be divided into subgroups, equivalent as to sex, age, and weight at the time of inauguration of the actual experiments. After mixing, part of each subgroup will be exposed to atmospheric suspensions of long-fiber asbestos dust of controlled concentrations; part will be injected intratracheally with measured amounts of the dust suspended in sterile normal saline; part will be set aside in normal air for controls. Each animal will be numbered and a separate record will be kept.

Animals from each subgroup will be sacrificed at intervals, and the other members will be permitted to live out their natural life span. After death the lungs will be fixed by intratracheal injection of Zenker's formal or formalin solution. Sections passing transversely through both lungs and the mediastinal structures will be prepared for microscopic study.

11. EVALUATION OF EXPERIMENTAL RESULTS

Carcinogenicity is to be evaluated by comparing the following five factors in all subgroups:

(1) The per cent of mice with lung tumors.

(2) The average number of tumors per mouse.

(3) The number of tumors arising in the asbestotic areas versus the non-asbestotic areas of tissue in the exposed mice.

(4) The induction time for tumors.

(5) Evidence for direct origin of tumor from asbestos, i.e., the histological appearance of tumor will be compared with the non-cancerous epithelial hyperplasias that may be present.

12. COMPARATIVE ANALYSIS WITH OTHER INVESTIGATIONS UNDERWAY

The studies concerning asbestos will be integrated with other investigations of the Saranac Laboratory. Those investigations concern the carcinogenic properties of inhaled quartz and of non-irritating dusts, such as carbon and iron oxide. The data obtained will form a basis for statistical study of the occurrence of pulmonary cancer in mice exposed to dusts other than asbestos.

13. ESTIMATED DURATION OF THE EXPERIMENTAL INVESTIGATIONS

The investigations proposed involve disease processes which develop very slowly. This applies to asbestosis as well as to pulmonary cancer. With respect to asbestosis, previous studies indicate that at least sixteen months of continuous exposure to dust are necessary in order to produce definite fibrosis in a highly susceptible

animal such as the guinea pig. In contrast, the mouse is more resistant and develops his reaction even more slowly under similar conditions of exposure. The development of asbestosis in mice may be speeded up considerably by increasing the concentration of the dust to which they are exposed. Thus, it is anticipated that rather definite results can be obtained in not less than two years by the inhalation method, and in not less than one year in mice receiving an intratracheal injection of the dust. Regarding the latter method, it must be stressed that although the injection experiment is of shorter duration, the results are inconclusive. An inhalation study of relatively longer duration should be performed to obtain reliable results.

With respect to pulmonary cancer, there are many complex problems inherent in any study of the subject. The very nature of the disease and the experience of other investigators dictate that at least a two-year, and preferably a five-year program, should be envisaged. This should not discourage the sponsorship of the program by the companies, as unfortunately there is no other alternative if reliable results are to be obtained.

14. REPORTS OF EXPERIMENTS – Short letter every 3 mos.

Progress reports will be issued from time to time during the experiment and a comprehensive report will be submitted at the conclusion of the investigation. These reports will be forwarded to the proper authorities identified by the sponsoring agencies.

15. PUBLICATIONS OF RESULTS OF INVESTIGATIONS

The Saranac Laboratory reserves the right to publish the results of its investigations in the recognized manner commonly employed by the scientific fraternity and in accordance with established practices, whereby the manuscript, prior to its publication, is submitted to the sponsoring company for its review and approval.

16. COST ESTIMATE

The combined project including both the inhalation and the intratracheal techniques requires the services of a number of staff members, the use of an exposure chamber or room and special apparatus needed for control, the purchase of a large number of mice of a pure inbred strain, the use of special mouse cages, and a large quantity of expendable materials such as chemicals, glassware, microscopic slides, and cover slips.

The cost for this comprehensive study will approximate $16,000.00 for the first year and $10,000.00 for the second year.

AJV:bw