010538

Committee on Growth
NATIONAL RESEARCH COUNCIL
2101 Constitution Avenue
Washington 25, D. C.

Acting for the

AMERICAN CANCER SOCIETY

APPLICATION FOR A GRANT IN CANCER RESEARCH

(Submit in duplicate, *retain third copy*)

Date: September 28, 1954

1. Name of Institution: The Saranac Laboratory
2. Address of Institution: 7 Church Street, Saranac Lake, New York
3. Name, official position and address of responsible investigator: G. W. H. Schepers, M.D., D.Sc.
Director, The Saranac Laboratory
Executive Vice-President, Board of Trustees, The Saranac Laboratory
4. Subject of investigation: (Brief title of project)

ENVIRONMENTAL CANCER OF THE LUNG :
An investigation of the co-carcinogenic activity of inhaled asbestos dust in experimental beryllium neoplasia

a. Background and present state of problem.

(1) The role of inhaled asbestos in contributing to the growing problem of lung cancer needs experimental exploration.
(2) The Saranac Laboratory has already probed the influence of chrysotile on lung tumor production in mice and now desires to examine the effect of crocidolite and amosite by the same technique.
(3) The Saranac Laboratory has also evolved a reliable method of inducing pulmonary cancer in rats by means of the inhalation of beryllium sulphate and explored the co-carcinogenic influence of various industrial dusts. It is now proposed to examine the influence of asbestos dust by the same means.
(4) For further explanation please refer to the attached appendix 4 (a).

b. Plan of attack.

(1) It is proposed to study the co-carcinogenic activity of asbestos dust in two ways, namely, in a susceptible strain of mice and in beryllium-prepared rats. The experimental procedures to be followed would differ and are explained in greater detail in the appendix.
(2) Appendix 4 (b) attached.

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c. Significance in cancer research and the relation of anticipated results to more general problems in this field.

(1) The beryllium method is a unique and reliable approach to the study of carcinogenesis.
(2) The demonstration of a co-carcinogenic propensity of asbestos or any particular variety of asbestos would have tremendous industrial hygiene, medical, and medico-legal significance.
(3) Asbestos, if proven carcinogenic, would become of its physical characteristics provide an ideal mechanism whereby to focalize experimental lung cancer.
(4) See appendix 4 (c) attached for more detailed explanation.

5. Requirements for investigation:

a. Personnel (professional and technical assistants. Briefly indicate duties and approximate annual salaries).

See attached appendix 5 (a)

b. Materials (equipment and supplies).

Animals and maintenance	$12,400.
Dust chambers and maintenance	4,300.
Supplies	3,150.
Equipment (instruments)	1,800.
Total	$21,650. (2 years)

6. Amount desired:

	1st Year
a. Professional assistants (including institution's contribution to annuity plan)	$ 4,950.
b. Technical assistants (including institution's contribution to annuity plan)	$ 6,600.
c. Equipment	$ 3,100.
d. Supplies	$ 3,150
e. Travel	$ 300.
f. Contingent fund (not to include institutional overhead)	$ 500.
Total	$ 18,600.
Institutional overhead desired (not to exceed 8% of total)	$ 1,488.
Total	$ 20,088.

Applications are considered during the winter of each year and grants recommended become effective the following 1 July.

7. Nature of institutional collaboration in this work:

a. Funds and sources presently available to your group or Institution for investigations in this same field.

(1) Interest on endowment fund approximately $25,000.
(2) Concurrent research grants totalling approximately $100,000.
(3) The proposed project will represent approximately 20% of the total cost of operating The Saranac Laboratory during 1955-1956.

b. Concise description of institutional facilities available for this investigation.

(1) A research laboratory first established by E. L. Trudeau in 1831 and equipped with most of the modern instruments for research of the projected kind.
(2) Sixteen specialized dust chambers and equipment for exposing large numbers of animals to aerosols of various kinds.
(3) Experienced professional associates and technicians. Research on dusts has been pursued for the past 35 years in The Saranac Laboratory.
(4) See also attached appendix 7 (b).

8. Do you have other projects for which you are responsible, or in which you are participating? Specify:

(1) An experimental investigation of the pathology of beryllium workers: A.E.C.
(2) An investigation of the biotoxicity of fiberglas: Industrial.
(3) A study of the effects of amorphous and ultramicroscopic silicas on animals: Industrial.
(4) The biological effects of volcanic glass: Industrial.

c. To what other sources have you applied for support of this project?

None

b. What grants have you previously received for this work?

(1) The Damon Runyon Fund is currently supporting a study on the carcinogenicity of beryllium sulphate and the co-carcinogenicity of quartz and iron oxide. This grant terminates on November 30, 1954.
(2) The American Cancer Society has supported a study by The Saranac Laboratory on beryllium carcinogenesis, which has recently been transferred to Wayne University, Detroit.

9. Brief biography of principal investigator and professional assistants:

O. W. H. Schepers, M.D., D.Sc.
P. C. Pratt, M.D.
T. M. Durkan, M.E.
M. Roberts, M.E.
L. Scheel, Ph.D.
S. Kaszer, M.E., E.E.

See attached appendix 9.

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10. Bibliography of principal investigator and professional assistants. *(Not more than 15 publications including those pertinent to this application.)*

See attached appendix 10.

11. Additional information which it is desired to offer may be given in this space and on extra sheets.

Please refer to attached appendices: 4 (a), 4 (b), 4 (c)
5 (a), 5 (b)
7 (b)
9
10

Application approved by competent Executive Officer of Institution

O. W. H. Schepers, M.D., D.Sc.
(Please Print or Type)

(Signature)

Executive Vice-President
(Official Title)
Board of Trustees, The Saranac Laboratory

(Signature of Investigator)
O. W. H. Schepers, M.D., D.Sc.
Director, The Saranac Laboratory

This application, if endorsed by the Committee on Growth of the National Research Council will be recommended to the AMERICAN CANCER SOCIETY as the basis for a research grant from the SOCIETY. Under the terms of a contract between the AMERICAN CANCER SOCIETY and the National Academy of Sciences for its agency, the National Research Council, professional aspects of the work conducted under the grant will be a responsibility of the Committee on Growth; while financial aspects will be a responsibility of the AMERICAN CANCER SOCIETY.

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Appendix 4 (a)

Background and present state of the problem

Industrial workers all over the world are constantly being exposed to nocuous dusts of various kinds, some of which are known and others suspected to be carcinogenic. Asbestos dust is a typical and crucial example, in view of the large numbers of individuals concerned with processing asbestos products. The strongest evidence for the carcinogenicity of asbestos is the official British governmental statistics. However, in at least certain geographic localities, particularly in Canada, where some of the world's largest asbestos mines are to be found, reliable observers have failed to demonstrate a comparable increase in the lung cancer rate amongst industrial workers exposed to asbestos dust. Perhaps these differences can be accounted for by the fact that in England the main asbestos product handled is African crocidolite and amosite, whereas chrysotile is more extensively produced in Canada. The former types of asbestos are, however, also used extensively in various textile and industrial processes in the United States.

While asbestos is thus suspected to be contributing to the growing quota of lung cancers, it is by no means yet known in what way it may be thus instrumental as a carcinogen. It may also be that some or other substance, occurring naturally in association with asbestos, is the real cause, thereby accounting for geographic differences in cancer incidence.

A study has already been carried out at The Saranac Laboratory by means of which it was proved that the inhalation of Canadian chrysotile dust produced significantly increased occurrence of neoplasms in mice with a high spontaneous pulmonary tumor propensity (strain C) whereas the same chrysotile had no such influence on mice with a low natural tumor incidence (strain C 57). The chrysotile therefore in this sense acts as a co-carcinogen in mice. It is obviously important to conduct further experiments of the same kind to probe the possibility that other specific varieties of asbestos, particularly the very much suspected African crocidolite and amosite, will have an enhanced influence on the rate of lung tumor production in these mice. Support is sought herewith for such a study.

The American Cancer Society has previously granted generous funds for exhaustive studies by The Saranac Laboratory which have lead to the elaboration of a technique whereby lung cancer can be successfully induced in rats by causing them to inhale beryllium sulphate dust. The Laboratory has extended this study to explore the problem of co-carcinogenicity by exposing rats, which have been caused to breathe beryllium sulphate dust for a period of six months, to other industrial substances. Variations in the anticipated response of the rats to beryllium under these circumstances may serve as an index of the co- or anti-carcinogenicity of the substance under test. Support is now sought for the application of this method to the potential activity of asbestos dust.

Appendix 4 (b)

Plan of attack

A. An investigation of the potential co-carcinogenicity of asbestos dust in tumor-susceptible mice (strain C)

In this proposed study a group of 200 strain C mice (male and female represented in equal proportions) will be exposed by inhalation to crocidolite and another equally large group to amosite asbestos dust for periods up to 18 months in a manner comparable to the previously conducted Saranac Laboratory study on chrysotile. A third group of 200 strain C mice will serve as a control.

At regular intervals sample batches of animals from each group, sufficiently large to have statistical significance, will be sacrificed and a histological search will be made for evidence of asbestos reaction in various organs and tumors in the lungs. The results to be obtained will be compared with the observations emanating from the prior study on chrysotile.

B. An investigation of the potential co-carcinogenicity of asbestos dust in beryllium-prepared rats

In conducting this study 500 rats (half of them male and the other half female) will first be rendered lung cancer susceptible by exposing them for six months to a beryllium sulphate aerosol for eight hours per day, five days per week. Two previous Saranac Laboratory experiments have shown that an exposure of this kind constitutes a stimulus sufficient to cause one to several adenocarcinomata to commence to develop in the lungs at periods ranging from five to ten months after the cessation of the beryllium exposure. About fourteen to fifteen months from the commencement of exposure there is a sudden peak production of neoplasmata which is uninfluenced by the duration of exposure beyond six months. These tumors are true cancers of a type which do not occur naturally in rats and it has proved possible to transplant them satisfactorily to other rats of the same species.

After a rest period of one week, during which excessive beryllium is allowed to be excreted, one-quarter of the surviving rats will be transferred to residence in normal air. It must be mentioned that, as found in previous experiments, a variable proportion of rats may be expected to succumb to acute beryllium intoxication during the initial phases of the experiment and certain others may be eliminated from time to time through causes beyond the immediate scope of laboratory control.

The remaining three-quarters of the surviving rats will be divided into three equal groups and transferred to three separate chambers where they will be exposed to chrysotile, crocidolite, and amosite dust, respectively. At regular monthly intervals the rats will be subjected to X-ray examination. At the same time statistically significant batches,

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Appendix 4 (b)

Plan of attack

B. (continued)

including all those showing X-ray indications of lung tumors, will be sacrificed and subjected to histological study for neoplasm and asbestos reaction, biochemical analysis for beryllium in various organs, and quantitative chemical recovery of the asbestos. The statistical results of this proposed study will be compared with data already accumulated in The Saranac Laboratory and should assist materially in elucidating the question of the relative carcinogenicity of different types of asbestos fibers.

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Appendix 4 (c)

Significance in cancer research and the relation of anticipated results to more general problems in this field.

The primary purpose of this proposed experiment is to probe the very vexed question of the relationship of asbestos dust inhalation to the increasing discovery of lung cancer in man. Should a significant statistical result be obtained from this study on rodents combined with the results of previous animal studies on asbestos conducted by The Saranac Laboratory, new evidence either for or against the alleged role of asbestos in causing human lung cancer would be produced. No comparable investigation on industrial co-carcinogenesis has previously been attempted anywhere else. The beryllium method, moreover, provides a unique and reliable tool by means of which to study carcinogenesis. Its chief advantage over all other known carcinogens is that the beryllium itself apparently undergoes no change in the animal tissue and can therefore be relied on to produce a constant calculable effect.

Asbestos is used extensively all over the civilized world. Not only are the miners exposed to it, but so also are the thousands of industrial workers, many of whom are in the upper skill brackets, who are concerned with textile, ceramic, constructional, brakeshoe, paper, transite pipe, etc., industries. Even certain cigarette filters are made from asbestos to shield off alleged carcinogens in tobacco tars!

Should it be proven that asbestos can provoke lung cancer, the efforts of industrial hygiene engineers will have to be intensified to ensure ever lower dust levels than are currently considered compatible with the absence of risk of asbestosis. Physicians will have to study their asbestos-exposed patients with greater circumspection and be on guard against neoplasm for longer periods after cessation of the exposure than is currently the practice. Much medico-legal interest also devolves on this issue.

Should the contrary finding be obtained, there should be further reassurance to asbestos industrialists and employees. Should asbestos be proven to be a decisive carcinogen or co-carcinogen, this would provide a further avenue by means of which the general problem of cancer can be studied, either with an eye to human prophylaxis or therapy or in an effort to elucidate the histochemical and biological basis of carcinogenesis. Unlike many other nocuous agents the asbestos fiber can usually be relied on not to migrate any great distance from its site of implantation and this can serve as an excellent instrument for focalizing the disease process.

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Appendix 5 (a)

Requirements for investigation

PERSONNEL		SALARIES			
Names	Functions	$-Hourly	1st Yr.	2nd Yr.	Total
G.W.H.Schepers,M.D.,D.Sc.	Principal Investigator	-	-	-	0
L. Blinn	Executive Secretary	-	-	-	0
~~P.C. Pratt, M.D.~~	~~Pathologist~~	~~4.00~~	~~1200.~~	1200.	2400.
O. Dobrogorski, M.D.	Assistant Pathologist	3.00	1000.	900.	1800.
T. Durkan, M.E.	Chief Chemist	4.00	400.	800.	1200.
M. Roberts, M.E., M.S.	Engineer	4.00	400.	400.	800.
~~L. Scheel, Ph.D.~~	~~Biochemist~~	~~4.00~~	~~400.~~	~~800.~~	~~1200.~~
S. Kaszer, M.E., E.E.	Biostatistician	3.00	300.	600.	900.
A.B. Delahant	Research Associate	3.00	900.	900.	1800.
~~A. Redlin~~	~~Assistant Chemist~~	~~2.50~~	~~500.~~	~~500.~~	~~1000.~~
D. Bailey	Petrographer	2.50	500.	500.	1000.
F. Creedon	Histologist	2.50	500.	500.	1000.
E. Gockeler	Photographer	2.50	500.	500.	1000.
R. Clark	Pathology Technician	2.00	600.	600.	1200.
M. Moody	Mechanic, Technician	2.00	600.	200.	800.
E. Fear	Histology Technician	2.00	600.	600.	1200.
~~H. Gay~~	~~Histology Technician~~	~~2.00~~	~~600.~~	~~600.~~	~~1200.~~
~~E. Gordon~~	~~Biochemistry Technician~~	~~2.00~~	~~600.~~	~~1200.~~	~~1800.~~
O. Boula	Animal Caretaker	2.00	400.	200.	600.
R. Whitelaw	Animal Caretaker	2.00	400.	200.	600.
~~G. Nesbitt~~ M. MacINTYRE	Typist	2.00	200.	200.	400.
	Sub-total		10,500.	11,400.	21,900.
Rowley					
	Social Security and Retirement		1,050.	1,140.	2,190.
	Grand Total		$11,550.	$12,540.	$24,090.

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Appendix 5 (b)

Requirements for investigation - Materials

			1st year
Animals			
300 mice (strain C) at $2 each	$ 600.		~~600~~
500 rats (Sherman strain) at $2 each	1,000.		1000
Maintenance 5400 mouse months at $1/3	1,800.		~~900~~
9000 rat months at $1	9,000.		4500
		$12,400.	
Dust Chambers			
One new chamber to increase total available from 4 to 5	~~1,000.~~ 500		500
Beryllium disseminator for use with above	200.		200
Replacements and readjustments	100.		100
Maintenance of 5 beryllium units	~~1,500.~~ 500		250
Maintenance of 5 asbestos chambers	~~1,200.~~ 500		250
		4,300.	
Supplies			
General supplies	250.		150
Glassware	100.		50
Pulverized asbestos	50.		50
Beryllium sulphate -- 50 lbs. at $15	750.		200
Radiographic supplies	800.		400
Histological "	600.		300
Photographic "	400.		~~200~~ 150
Dust counts "	200.		
		3,150.	
Equipment			
Radiographic accessories to adapt a human unit for the serial macroradiographic study of small animals (estimated)	1,000.		500
Petrographic microscope accessories	300.		150
Microphotographic accessories and replacements	200.		200
Miscellaneous lesser items	300.	1,800.	150
TOTAL		$21.650.	

Note: Of this amount, which represents expenditures over a period of two years, it is requested that $2500 be made available about three to four months before the inception of the experiment to enable the construction of the fifth beryllium chamber and the adaptation of the radiographic unit.

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Appendix 7 (b)

Facilities available

(1) Four specially constructed dust chambers for the automatic safe exposure of animals to beryllium, which is particularly dangerous.
(2) Twelve other chambers for exposing animals to constant aerosols or mineral substances for prolonged periods.
(3) An engineering division to control accurately the levels of dust exposure, design new equipment, control hazards, and to identify and quantitatively determine inorganic substances by chemical, petrographic, and X-ray diffraction methods.
(4) A pathological division for the histological study of animal organs.
(5) A radiological unit for serial examination of animals.
(6) A biochemistry department specially experienced and fully equipped for the study of beryllium problems.
(7) The archives of the laboratory house, the experimental records, tissue slides and preparations, representing seventy years of continuous research on tuberculosis, industrial disease, and lung cancer. In addition, there is a specialized library.

Beryllium chambers

The conduct of a dusting experiment with beryllium compounds is a hazardous procedure because of the high degree of selective toxicity of beryllium for man. The Saranac Laboratory experience in coping with this problem extends over the past ten years and specially-designed dusting chambers and techniques and well-trained technicians are available to prevent any serious hazard arising. To cope with the large number of animals which will have to be exposed in a composite experiment of this type, in order to obtain statistically significant results, an additional dusting unit will have to be constructed as the existing four chambers are designed to house 110 rats only. If, therefore, an award be made by the American Cancer Society, it would be appreciated were the funds for constructing such a unit to be advanced approximately three to four months before the anticipated commencement of the experiment.

Macroradiography

For the proper control of an investigation of this kind it is essential to control the development of lung tumors by serial radiography of the animals under exposure. The existing X-ray apparatus available for the study is of the conventional type. It will have to be adapted to render possible primary image enlargement up to nine diameters. The radiographic accessories needed for this purpose are available in Holland and Germany, and as The Saranac Laboratory enjoys duty-free import facilities under its charter, it is hoped to obtain the necessary parts for approximately $1,000.

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Appendix 9

Biographies

C. J. H. Schepers

M.Sc., M.B.B.Ch., M.D., Univ. Witwatersrand, Johannesburg, South Africa
D.Sc., Univ. of South Africa, 1945
Commonwealth Fund Fellow, 1949
Diploma Course in Industrial Medicine, New York Univ., 1950
Lecturer, Med.School, Johannesburg, 1934 - 1940
Research Med. Officer, Johannesburg Municipality, 1941
Professor and Head of Department of Anatomy, Univ. of Pretoria, 1942 - 1943
Member, Silicosis Medical Bureau, Johannesburg, 1944 - 1952
Chairman, Pulmonary Disability Committee, Department of Mines, Union of South Africa, 1952 - 1954
Director, The Saranac Laboratory
Publications: 36 papers; 3 books

P. C. Pratt

M.D., Johns Hopkins, 1944
Resident in Pathology, Johns Hopkins, 1944 - 1946
Assistant Pathologist, The Saranac Laboratory, 1947 - 1954
Publications: 7 papers

T. M. Durkan

M.E., Cornell Univ., 1916
Licensed Professional Engineer, 1937
Engineer, Gleason Works, Rochester, 1916 - 1929
Chief Chemist and Engineer, The Saranac Laboratory, 1933 - 1953
Assistant Director, The Saranac Laboratory, 1948 - 1954
Publications: 10 papers

M. Roberts

M.E., 1936; M.S., 1937, Univ. Arizona
Mining Engineer, Nielson Co., Phillipines and China, 1937 - 1940
U.S. Bureau of Mines, Strategic Minerals, 1940 - 1941
Mining Engineer, Phelps Dodge, Morenci, Arizona, 1942 - 1954
Industrial Hygiene Engineer, The Saranac Laboratory, 1954

L. W. Scheel

Ph.D., 1942, Univ. of Wisconsin
Toxicologist, Edgewood Arsenal, Maryland, 1943 - 1944
Chemical Warfare, U.S. Army, 1944 - 1945
Assistant Biochemist, Univ. of Wisconsin, 1946 - 1949
Assistant Biochemist, The Saranac Laboratory, 1949 - 1952
Biochemist, The Saranac Laboratory, 1952 - 1954

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Appendix 9

Biographies (continued)

S. Kaszer	M.E., Univ. Nancy, France, 1912 E.E., Univ. Brussels, Belgium, 1916 Industrial Research, Maintenance and Development Engineer for: Enka Arnhem, Netherlands, Belgium, France Artificial Silk Combine, Warsaw, Germany, Switzerland Member, Polish Supply and Reconstruction Mission in North America, 1946 - 1947 Biostatistician, The Saranac Laboratory, 1952 - 1954
A. B. Delahant	Professional Assistant in charge of all experimental protocols, animal welfare, gross pathology of The Saranac Laboratory for the past 25 years Publications: 10 papers

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Appendix 10

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Vorwald, A.J., Durkan, T.M., and Pratt, P.C. Experimental Studies of Asbestosis. Arch. Indust. Hyg. and Occupational Med. 3:1-43, January 1951

Gordon, J., Zinn, W.B., Pratt, P.C. Bronchography as an Aid in Planning Surgical Treatment of Pulmonary Tuberculosis, J. Thoracic Surg., St. Louis, 22:109-134, August 1951

Gordon, J., and Pratt, P.C. Bronchiectasis: A Comparative Study. Am. Rev. Tuberc., 67:29-44, January 1953

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Vorwald, A.J., Dworski, M., Pratt, P.C., and Delahant, A.B. BCG Vaccination in Silicosis. II. An Experimental Study of the Influence of Inhaled Quartz Dust upon Infection by BCG (Aronson), H37Ra, and M. Marinum Strains of Tubercle Bacilli. Am. Rev. Tuberc., 69:766-789, May 1954

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Appendix 10

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