General Headquarters
January 28, 1969

C. B. Burnett
E. M. Fenner, Finderne
Bert Goss, H & K
H. M. Jackson
J. B. Jobe
K. V. Lindell, Asbestos
A. B. Marchant
F. L. Pundsack, Finderne
W. P. Raines
Ivan Sabourin, Montreal
C. L. Sheckler, Finderne
A. C. Smith, Finderne
R. R. Standell
M. M. Swetonic
Carl Thompson, Hill & Knowlton
W. L. Van Derbeek, Finderne
Dr. G. W. Wright, Cleveland

Attached is the Eleventh Annual Report of the Asbestosis Research Council for the twelve months beginning October 1, 1967.

F. J. Solon, Jr.

Enc.

SH/HS

ASBESTOSIS RESEARCH COUNCIL

ELEVENTH ANNUAL REPORT FOR THE TWELVE MONTHS BEGINNING 1st OCTOBER, 1967

1. INTRODUCTION

The Asbestosis Research Council was established on the 1st October, 1957. This report details the activities sponsored by the Council during the eleventh year of its operation.

2. CONSTITUTION

The Constitution was revised in August 1965 to extend the field of activities to asbestos operations other than textile and to provide for the admission of Associate Members as well as Full Members.

3. MEMBERSHIP

The Membership of the Council during the year was as follows :-

Full Members

B.B.A. Group Limited.
The Cape Asbestos Company Limited,
Turner & Newall Limited.

Home Associate Members

The Atlas Stone Company Limited.
Bell's Asbestos and Engineering Limited.
T.B. Ford Limited. (In place of Birfield Limited).
Richard Klinger Limited.

The Universal Asbestos Manufacturing Company Limited ceased to be an Associate Member on becoming part of the Cape Asbestos Company Limited.

Overseas Associate Members

James Hardie & Coy. Pty. Ltd.
Johns-Manville Corporation.
The Quebec Asbestos Mining Association.
Griqualand Exploration & Finance Co. Ltd.

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4. COMMITTEES

The affairs of the Council were administered by three Committees, the Management Committee, the Research Committee and the Dust Control Committee. The membership of these committees during the year was :-

(a) Management Committee

Chairman	:	Mr. R.H. Dent	- The Cape Asbestos Co. Ltd.
		Dr. R. Gaze	- The Cape Asbestos Co. Ltd.
		Mr. C.M. Fenton	- B.B.A. Group Ltd.
		Dr. C.G. Addingley	- B.B.A. Group Ltd.
		Mr. J. Waddell	- Turner & Newall Ltd.
		Mr. R.H. Wilson	- Turner & Newall Ltd.
Secretary	:	Dr. S. Holmes	- Turner & Newall Ltd.

Mr. J. Waddell resigned in May 1968, his place being taken by Mr. D.W. Hills.

Management Committee meetings were held as follows :-

Uxbridge	- 27th October, 1967
London	- 5th December, 1967
Manchester	- 6th March, 1968
Rochdale	- 8th May, 1968
London	- 31st July, 1968
London	- 26th August, 1968

(b) Research Committee

Chairman	:	Mr. R.A. Wells	- Turner & Newall Ltd.
		Dr. H.C. Lewinsohn	- Turner & Newall Ltd.
		Dr. C.G. Addingley	- B.B.A. Group Ltd.
		Dr. W.H.A. Beverley	- B.B.A. Group Ltd.
		Dr. A.A. Hodgson	- The Cape Asbestos Co. Ltd.
		Dr. W.J. Smither	- The Cape Asbestos Co. Ltd.
Secretary	:	Dr. S. Holmes	- Turner & Newall Ltd.

Research Meetings were held as follows :-

Rochdale	- 2/3rd January, 1968
Cardiff	- 21/22nd May, 1968
Reading	- 17/18th September, 1968

In November, 1967, the Research Committee held a one-day scientific meeting at Cleckheaton on 'The Early Diagnosis of Asbestosis'. The Pneumoconiosis Medical Panel was well represented, along with research workers in this field.

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(c) Dust Control Committee

Chairman :	Mr. J.M. McFarlane	- The Cape Asbestos Co. Ltd.
	Mr. D. Boyes	- B.P.A. Group Ltd.
	Mr. T.W. Anderson	- The Cape Asbestos Co. Ltd.
	Mr. P.E. Bugge	- Turner & Newall Ltd.
	Mr. R.H. Wilson	- Turner & Newall Ltd.
	Mr. W.P. Bamblin	- Turner & Newall Ltd.
Secretary :	Dr. S. Holmes	- Turner & Newall Ltd.

This Committee was re-constituted in July, 1968, as the 'Environmental Control Committee' under the Chairmanship of Mr. W.A. Gross. It held its first meeting on 22nd August, 1968.

Dust Control Committee meetings were held as follows :-

Rochdale	- 24th January, 1968
Hebden Bridge	- 5th June, 1968

5. FINANCE

(a) Banking Arrangements

The finances of the Council have continued to be administered through accounts operated by the Rochdale Branch of the District Bank.

(b) Budget and Expenditure

Council Budget	£23,500
Expenditure	£19,139

6. LIAISON WITH OTHER INTERESTED BODIES

Contact has been maintained with H.M. Factory Inspectorate and the Panel convened by the Senior Medical Inspector of Factories, on which two of the Council's Medical Officers served, has published its Report entitled 'Problems arising from the use of Asbestos'.

Liaison has continued with the Pneumoconiosis Research Unit of the Medical Research Council. The opportunity was taken during the meeting of the Research Committee at Cardiff in May to have a joint one-day meeting with the Unit to discuss common problems. Arrangements have been put in hand to organise a joint ARC/PRU Conference in April, 1970 on 'The Tissue Reaction of Asbestos'.

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The Sub-Committee set up by the Hygiene Committee of the British Occupational Hygiene Society, on which members of the Council served, published a Report in April 1968, entitled 'Hygiene Standards for Chrysotile Asbestos Dust'.

Liaison has also continued with the U.S. Public Health Service and with the Air Hygiene Committee of the Asbestos Textile Institute.

7. RESEARCH PROGRAMME

The research work of the Council was further expanded during the year by Grants to Dr. Margaret Turner-Warwick of the London Hospital of Diseases of the Chest and Dr. Margaret Swinburne of St. James' Hospital Leeds.

A summary of the year's work is given below. Fuller reports appear in Appendices 1 to 5.

(i) The long term animal experiments involving the inhalation of the four main types of asbestos have been completed during the year, but many of the sections are still to be examined. The studies on the mechanism of asbestos body formation have also been completed. Collaboration with the Institüt für Lufthygiene in Düsseldorf has continued.

(ii) The collection of biopsy material from suspected cases of human mesothelioma has continued and the production of mesothelial tumours in animals has been further studied. Work on the pathogenicity of minerals other than asbestos has been started. Collaboration has continued with Dr. Gross of the U.S. Industrial Hygiene Foundation in Pittsburgh.

(iii) Preliminary work on the effect of asbestos on lysosomal cell systems terminated in June, 1968.

(iv) Work on the surface properties of asbestos has continued.

(v) An immunological study has been started but only preliminary results are yet available.

(vi) Animal experiments on the ingestion of asbestos have commenced and it is hoped to have some results in the next twelve months.

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8. DUST SAMPLING AND ANALYSIS

While the Royco Automatic Particle Counter has continued to be used as a routine monitoring instrument, the fibre count by membrane filter has remained the standard method in the industry. The method has been published by the Council as its Technical Note No. 1.

Techniques for assessing the asbestos content in other than industrial environments have been further explored. Interest has been shown in this subject by a number of Government Departments and a meeting of those involved was convened by the Ministry of Technology in May, 1968. Representatives of the Council were present.

During the year, the Council has carried out a survey to determine the level of asbestos dust in completed buildings of various types in which asbestos products have been incorporated in their construction. A report has been prepared for publication.

9. DUST CONTROL

During the first part of the year, the Dust Control Committee continued to work on various problems affecting the manufacturing and applications side of the industry. In July, 1968, however, this Committee was reconstituted with the title of 'Environmental Control Committee' and with wider terms of reference to enable it to deal with all relevant matters likely to affect the industry and its customers under the New Asbestos Regulations.

10. THE NEW ASBESTOS REGULATIONS

In April, 1968, representatives of the Council were called to a meeting at the Department of Employment and Productivity to discuss the Council's comments on the preliminary draft of the New Regulations. It was learnt that the Council's suggestions were likely to be given consideration in framing the Statutory Draft. in particular the replacement of the 'no dust' concept by a more practical approach to the problem.

The Statutory Draft was published in August, 1968, and the Council again felt obliged to make a number of comments, which are still under discussion.

11. CODES OF PRACTICE

During the year the Council issued its fourth Code of Practice - 'Recommended Code of Practice for Handling Consignments of Asbestos Fibre in British Ports'.

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The demand for copies of all Codes of Practice has continued steady.

12. [illegible] PUBLICATIONS

"The Mechanism of Formation of Asbestos Bodies"
S.K. Betham and P.F. Holt, J. Path. and Bact. Vol. 96, No. 2, p. 443.

"Interaction of Poly-2-Vinyl Pyridine 1-Oxide and Poly-4-Vinyl Pyridine Oxide with Monosilicic Acid"
P.F. Holt and E.P. Nasrallah, J. Chem. Soc. 1968, p.400.

13. Publication Policy Matters

The work done by the Member Companies in this field has continued to be reviewed by the Research Committee.

14. Visits

In November, 1967, Mr. Waddell, Dr. Gaze, Dr. Knox, Dr. Smither, Dr. Beattie, Dr. Davis and Dr. Holmes attended the Second Antigua Conference organised by the Quebec Asbestos Mining Association.

Dr. Addingley, Dr. Knox, Dr. Smither, Dr. Davis, Dr. Holt, Dr. Lewinsohn, Mr. Hunt and Dr. Holmes attended the International Conference on the Biological Effects of Asbestos held in Dresden in April, 1968.

15. GENERAL

Dr. Knox has continued as Medical Consultant to the Council and has attended the meetings of the Management Committee and the Research Committee.

Dr. Beattie has continued as Research Consultant and has attended the meetings of the Research Committee.

APPENDIX 1

Report on Research at the University of Reading - Dr. Holt

During this year most of the long term experiments started 2 to 3 years ago, in which guinea pigs and rats inhaled four types of asbestos, have been completed. This has required a heavy load of tissue processing and cutting to provide about 3,000 stained sections. It has been impossible to examine many of these sections while the experimental work was proceeding and consequently few final results have been reported. There is now available, however, a library of sections in which the effects on the lungs and lymph glands of reasonably small doses of inhaled amosite, anthophyllite, chrysotile and crocidolite can be studied. There is also a series of slides in which guinea pigs are compared with rats that have inhaled asbestos. These are unique.

The following tentative conclusions need to be confirmed. The asbestos dust is first deposited in the bronchioles, the longest fibres (up to 70 μ long) in the terminal bronchioles only. Remarkably, some fibres subsequently appear to move into the alveoli which is contrary to what would be expected. No histological difference has yet been observed between the effects of the four types of asbestos but a few pleural adhesions were present in animals that had received amosite and crocidolite but none in those that received anthophyllite, chrysotile or glass fibre. No clear morphological difference has been observed between the asbestos bodies produced on the four types of asbestos; those produced by glass fibre are similar except that, since they form round single fibres rather than fibre bundles, they are usually smaller. In a search of other organs for evidence of transport of asbestos from the respiratory system in a guinea pig, so far one perfectly formed asbestos body has been found in the thyroid gland.

The studies on the mechanism by which asbestos bodies are produced have now been completed. The initial effect of the fibre in the lung in the production of haemorrhage and the resulting iron-containing compounds from the haemoglobin in the red cells are taken up by dust cells and deposited on an asbestos fibre in the same cell. The production of an asbestos body does not therefore depend on the chemical nature of the fibre and we have produced bodies from mica fibres and very fine glass fibres. This last experiment is being extended and some guinea pigs have been made to inhale glass fibre and others glass powder of the same chemical composition.

An experiment has been concluded which was set up to investigate whether the progress of pneumoconiosis due to asbestos could be followed in animals by chemically estimating the collagen formed in the damaged lung. The results are disappointing; the variation between animals is at least as great as the variation caused by small doses of asbestos.

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Now that the fundamental work with animals is well established attention is being turned to the methods of modifying the pathological effects of asbestos. Studies are continuing on the possible use of polymeric substance such as poly-2-vinylpyridine 1-oxide, which has proved effective in silicosis in animals and on whether this polymer can alter the rate of fragmentation of asbestos bodies. The possible coating of the asbestos with an adsorbed monolayer, either to modify its effects or to prevent its being retained in the lung, is also being investigated. The initial studies on adsorption are now well under way and early results will be reported during next year.

APPENDIX 2

Report on Research at the University of Cambridge - Dr. Davis

Human Mesothelioma Biopsies

Throughout the year the collection of biopsy material from suspected cases of human mesothelioma has continued, although during the last twelve months only four cases were reported in time to collect the material. Of these cases one has since been confirmed as a mesothelioma at autopsy, two were varieties of bronchial carcinoma, and in one case the suspected tumour mass was found to be inflammatory and not neoplastic.

One of the two bronchial carcinoma cases was especially interesting as before the patient died it was possible to diagnose the tumour as an alveolar cell carcinoma from its cell fine structure. Autopsy confirmed that it was indeed a peripheral lung tumour. This indicates that when sufficient knowledge is available, electron microscopy studies may be useful in mesothelioma diagnosis.

Mesothelioma production in animals

These experiments have continued this year with both mice and guinea pigs. During this period 16 guinea pigs have died and 28 mice. Despite the fact that 13 of the guinea pigs had survived over two years from the time of injection and 11 of the mice had survived more than one year, only one pleural tumour was found. This was in a mouse that had been injected with chrysotile 14 months before death. The histological pattern in this case was not typical of mesotheliomas from other species but mouse mesotheliomas are not yet well documented and more tumours are needed to be sure of the diagnosis.

Although only one possible mesothelioma has been found this year, three guinea pigs developed bronchial carcinomas, one a squamous cell carcinoma of the skin and one a spindle cell sarcoma. In the mice two subcutaneous sarcomas were produced. The guinea pig spindle cell sarcoma was definitely caused by crocidolite as part of the injected material had failed to enter the pleural cavity and was found in contact with the tumour. The other animal tumours could not definitely be associated with the asbestos injection, but the incidence of seven spontaneous tumours out of 42 deaths is high for an animal population, and the possibility must be considered that some of these tumours resulted from the asbestos injection even though they developed in sites far removed from the dust.

Apart from definite tumours two interesting facts have emerged from these experiments. In the guinea pigs the intrapleural dust lesions have been found to calcify after about eighteen months to produce typical

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calcified pleural plaques, histologically very similar to those found in human cases. In the mice the pleural fibrosis had often developed to a degree where the pleural cavity was completely full and the lungs encased by masses of fibrous tissue. The macroscopic picture was exactly that of a mesothelioma, but histological examination showed no signs of neoplasia. It would appear that this massive fibrosis is caused by a turnover of dust. When the initial dust granuloma ages the macrophages and gaint cells die and are replaced by fibrous tissue. The asbestos dust is left behind among the collagen fibrils and is rephagocytosed by a new generation of macrophages that actively penetrate the films tissue to pick up the dust. This turnover process appears to continue as long as dust is present and very large masses of fibrous tissue eventually resulted. There is one type of fibrous mesothelioma that pathologists find often difficult to distinguish from normal fibrous tissue. These fibrous masses are in fact only considered tumours because they grow to a very large size. From the mouse evidence it is possible that they may not be tumours but normal fibrous tissue constantly stimulated to new growth by a relatively indestructable content of asbestos dust.

Experiment to test the pathogenicity of minerals other than asbestos

During the last twelve months the following minerals have been tested by intra-pleural injection in mice :- Talc, serpentine, brucite, magnetite, pyroxene, olivine, forsterite and chlorite. So far, all these minerals have failed to produce lesions other than the normal foreign body reactions. The results of injection experiments with fine glass fibre (dia. 0.05 μ) and calcium silicate are still under review. Follow-up experiments involving inhalation on all these materials are planned.

Experiments with P204

During the first part of this year experiments continued which were designed to test the effect of P204 on the development of asbestos lesions in guinea pig tissue. With the chrysotile sample used, no difference could be found between animals treated with dust + P204 and those that had received dust only. For this reason, the experiments were terminated in March. During September, however, some experiments were started using samples of synthetic chrysotile injected intraperitoneally into mice. This dust has proved much more toxic than normal asbestos, and it may be worth repeating the P204 experiments with this dust.

Experiments to determine the chemical processes of asbestos body formation

Two studies are at present in progress in this field. These involve the electron microscope examination of very old calcifying

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asbestos lesions and very young lesions in the guinea pig pleural cavity. Normal asbestos bodies are produced intracellularly and perhaps as few as one in one thousand fibres of dust ever become coated. It has been found, however, that in old calcifying lesions, which are acellular and where the dust is now lying free among the collagen fibrils, all asbestos fibres become coated with a layer of material about as thick as the normal asbestos body coating. This coating is much less dense than the 'ferritin' of normal asbestos bodies although some 'ferritin' granules may be present among the other coating material. From a study of the substances known to occur in calcifying tissues it appears most likely that this coating material is a mucoprotein or mucopolysaccharide. Since colloidal iron is a well known stain for mucin, and is effective because the iron selectively impregnates the mucin, it begins to appear likely that asbestos body formation may be a two stage process, an initial coating of mucoprotein or mucoploysaccharide being followed by the impregnation of this material with 'ferritin'. The density of 'ferritin' in normal asbestos bodies might be due to its high content in living granulation tissue, and the low content in the calcifying tissue bodies may be due to lack of 'ferritin' in these dead avascular area. An examination of very early asbestos lesions is now in progress and already some dust fibres have been found in giant cells coated with low density material containing only a few granules of 'ferritin'.

APPENDIX 5

Report on Research at the Streatham Laboratory - Dr. Barrett
(Work terminated, June 1968)

Work on Macrophages

It has been found possible to maintain mouse peritoneal macrophages for six days in Medium 199 (Burroughs Wellcome) supplemented with 10% unheated calf serum in an atmosphere of 5% CO_2/95% air, on coverslips, but a serious difficulty arose in that the available assay techniques proved not to be sufficiently sensitive to detect the release and synthesis of enzymes by the small number of cells (a few million) that could be isolated and maintained. A more sensitive method has however, only recently been developed and this should prove invaluable in future experiments of this nature.

The Effect of Asbestos on the Stability of Lysosomes

A rat liver was homogenised in 0.25 M sucrose, and a mitochondrial-lysosomal preparation was obtained by differential centrifugation. This was suitably diluted and incubated at 37°, either alone or with a rather dense suspension (10 mg/ml) of finely milled chrysotile asbestos (supplied by Dr. P.F. Holt). Over a period of three hours, the mixtures were gently agitated and samples were removed periodically and centrifuged. Determination of the enzyme activity in the supernatant and sedimented fractions gave a measure of the extent to which the limiting membranes of the lysosomes had broken down, under each treatment to release the enzymes in a free, soluble form. Workers have shown that quartz can act by rupturing lysosomal membranes and it seemed likely that asbestos would have a similar effect, in view of its haemolytic activity, which was comparable with that of silica, but no such effect was detected; parallel release of acid proteinase was obtained in suspensions with or without asbestos. In view of a recent German report on the action of asbestos on lysosomes in vitro further experiments of this type might be justified.

The Cellular Consequences of Phagocytosis

Lysosomes form the digestive system of cells, and in many ways this is comparable with that of higher animals. When a macrophage engulfs a bacterium, it is enclosed in a digestive vacuole, or phagosome, the contents of which are acidified. The lysosomal enzymes, which are active under acid conditions, are then secreted into the vacuole and the bacterium is digested. It is known that the biosynthesis of the lysosomal enzymes is stimulated by the process of phagocytosis in macrophages (and the same may well apply to the macrophages that take up asbestos, if they survive). It is not

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thought that this is solely a characteristic of phagocytic leucocytes since various tissue cell types can show phagocytosis and a lysosomal response, in tissue culture. Generally the lysosomal digestive enzymes produced in response to the phagocytosis are not confined to the interior of the cells, but are released into the culture medium, and in organ cultures of cartilaginous bone rudiments the result is an extensive digestion of the extracellular matrix strongly reminiscent of that seen in rheumatoid arthritis. It is felt that excessive lysosomal activity of this kind may well be involved in the pathology of rheumatoid arthritis and certain other conditions, and investigations have been done on the way in which endocytosis (a general term including pinocytosis and phagocytosis) stimulates the synthesis and release of the lysososmal enzymes.

The biological system used is one in which chick embryonic limb bone rudiments are cultered in a synthetic medium to which sucrose has been added. Surprisingly, the cells are unable to metabolize sucrose, and it causes the formation of persistant large digestive vacuoles within them, but there is no cell mortality and cell division is scarcely inhibited. There is, however, a dramatic increased in the release of lysosomal enzymes. The radiochemical microassay is designed to follow the time-course of the new synthesis with precision, and an inhibitor of protein synthesis, cycloheximide, is being used in an attempt to decide what proportion of the enzyme release represents newly-formed, as opposed to pre-existing molecules.

Further work has led to the preparations of a pure rabbit anti-chicken acid proteinase antiserum with which it is hoped to isolate minute amounts of the enzyme synthesised in culture in the presence of radioactive tracers, as the immunoprecipitate. This would allow changes to be followed in the specific activity of the released enzyme which could give valuable insight into the mechanism of the stimulated release.

APPENDIX 4

Report on Research at the University of Leeds - Dr. Grimshaw

During the last twelve months period the research programme has been directed mainly to studying the release phenomena of magnesium and silicon from chrysotile under a variety of conditions. A raw Canadian fibre was selected for detailed analysis, but other samples have been shown to possess similar characteristics.

Both magnesium and silicon can be extracted from raw fibre under most pH conditions. The amounts were greater in acid solutions but the ratio of $MgO : SiO_2$ in solution bore no relationship to the stochiometric composition of the parent mineral.

Once the fibre had been ground, the amounts of cation release increased enormously and to a far greater extent than would be expected from simple surface area considerations. Chrysotile which had been ball-milled for a few hours still possessed a typical fibrous habit when examined under the microscope, but it was possible to extract virtually all its structural magnesium. Comminution processes also caused marked changes in X-ray, infra-red and differential thermal patterns.

Perhaps the most significant observation of the release phenomenon in treated chrysotile is the fact that the absorption capacity of the mineral was increased considerably. Not only was water absorbed but also cations other than magnesium and many organic compounds and complexes. Stearic acid and some amino-acids were absorbed and the mechanism involved chemical as well as physical phenomena. It has been shown by infra-red studies that the characteristic spectra of certain organic groups changes markedly when absorbed onto the treated chrysotile fibres.

APPENDIX 5

Report on Immunology Study - Dr. Turner-Warwick

In collaboration with Dr. Parkes of the Pneumoconiosis Medical Panel, patients referred to the Panel for assessment have been examined in person and it is hoped that this special series will form the basis of a long-term follow-up study. In addition blood sera supplied by co-operating chest clinics and industry have also been examined. Included in the study so far have been 53 patients and 116 blood sera samples.

Antinuclear factors and rheumatoid factors have been studied. Using the double-layer immunofluorescent technique, 26% were found to be A.N.F. positive, against an expected figure of 5% in a 'normal' population. Assessing rheumatoid factor by the differential agglutination titre technique (DAT), the percentage DAT positive was 37, against an expected less than 4% in a 'normal' population. Using Latex FII tests (Difco Ltd.), the percentage positive was 39. Antinuclear factors and rheumatoid factors have therefore been demonstrated more frequently than expected by chance in patients with asbestosis. Furthermore, the incidence of these antibodies is remarkably similar to findings in idiopathic fibrosing alveolitis. The next study is to analyse the clinical, radiographic and physiological features correlated with immunological re-activity.

A search for lung reactive antibody has been undertaken in 24 patients using the antigloculin consumption test (AGGT). It appears that antilung reactive antibodies are present only in low titre and are unlikely to be an important immunological finding in asbestosis.

Immunofluorescent studies have been carried out on three asbestotic lungs. There was no evidence of antibody nor complement fixed to any structure surrounding asbestos bodies within the lung.

General Conclusion

Circulating non-organ specific tissue antibodies have been found in patients with asbestosis. Moreover the incidence of these is similar to that found in fibrosing alveolitis. These findings suggest that a similar immunological stimulus occurs during the development of both these lung diseases. Whether the immunological response is damaging or protective is unknown. An attempt to get further evidence for or against a pathogenetic role of these antibodies (or some immunological reaction occurring pari passu with them) will now be sought through a study of these antibodies in different stages of evolution of the disorder, using clinical, radiographic and physiological data as the yardsticks to assess the extent and severity of the disease.

ASBESTOSIS RESEARCH COUNCIL

Eleventh Annual Report

1st October, 1967 -

30th September, 1968.

~~Dr. Eoby Pundoock~~

ASBESTOSIS RESEARCH COUNCIL

With the Compliments

of

The Secretary

APPENDIX 5

Report on Research at the University of Cambridge - Dr. Davis

Publications :-

Work on Ferruginous bodies, and calcification in asbestos lesions was completed during this year.

Some aspects of this work were incorporated into two papers. These were:-

(a) The fine structure of 'Ferruginous bodies' produced experimentally in Guinea pigs from minerals other than asbestos.

This has been accepted for publication in the 'Archives of Pathology'.

(b) Asbestos dust as a nucleation centre in the calcification of old fibrous tissue lesions, and the possible association of this process to the formation of asbestos bodies.

This has been accepted for publication in 'Experimental and Molecular Pathology'.

Research Topics

(a) The electron-microscope examination of human mesotheliomas

During the year, three biopsy specimens were obtained, but none of these was finally confirmed as a mesothelioma. Work on this field is still limited by lack of material and has not advanced during the current year.

(b) Production of Mesotheliomas in Animals using asbestos dust

These experiments have continued with both Guinea pigs and mice. Originally samples of chrysotile and crocidolite dust were supplied by Dr. Holt, but now the U.I.C.C. World Bank samples are used. No mesotheliomas have been obtained in Guinea pigs although some animals have now survived for more than three years after dust injection. Two definite mesotheliomas have, however, been found in mice and electron-microscope examination is now in progress. Since nearly 100 mice have so far been used in these studies, and died without producing tumours, a total of two mesotheliomas is still a very small percentage and in no way compares with the high figures produced by Wagner.

(c) Experiments on the pathogenicity of other minerals

These tests using intrapleural injection have continued throughout the current year, and it is now possible to divide the test samples into three categories.

These are :-

1. Minerals which produce an initial foreign body reaction, but which dissolve with or without toxic effects. With dissolution the foreign body reaction declines and may completely resolve. In this class are :- Brucite, Forsterite (produced by heating chrysotile), calcium silicate, and probably synthetic chrysotile.

2. Minerals which produce a foreign body reaction that results in the formation of large granulomas which enclose the dust. These granulomas lie loose in the pleural cavity, do not form adhesions, and appear to cause the animal no discomfort at all. The minerals in this class do not appear soluble and the granulomas do not decrease in size with age. Fibrosis occurs within the granulomas, but not elsewhere in the pleural cavity. In this class are :- Talc, Serpentine, Magnetite, Pyroxene, Olivine, Chlorite, Chromite and glass fibre that has been machine ground.

3. Minerals which produce large spreading granulomas. These lesions adhere firmly to the chest contents and may cause massive adhesions between the lung lobes, the diaphragm and the chest wall. These granulomas are often replaced by fibrous tissue, and in extreme cases the chest contents can appear as a solid mass of fibrous tissue in which are embedded the heart and lungs. In this class are :- All types of asbestos and glass fibre that has been prepared by gentle grinding.

The finding that the method of preparation of glass fibre samples can greatly alter the pathogenic effects of this dust, represents the most interesting results of the year. The glass samples used contain many small fibres of 250-1000A° in diameter which is within the size range of asbestos crystals. Gentle preparation methods leave these small fibres undamaged and samples so treated produce fibrosis with adhesions. Machine grinding appears to break up the fine filaments faster than the large and these samples produce only granulomas without adhesions. These experiments indicate that the shape of the particle may be more important in fibrosis than its chemical nature. Indications at present are that the dangerous particle may be a fibre several microns in length, but only 250° - 1000A° in diameter. So far in industrial processes asbestos is the only material that has given such particles, but the use of very fine glass fibre may provide another source of these particles. Work in the coming year will be focused on this point. The results from the pleural cavity seem definite. It remains to see if the same results are obtained from lung tissue.

(d) Experiments on the method of production of asbestos bodies

During this year a series of experiments has been completed which give new information on asbestos body formation. These results may be summarised as follows:-

Asbestos body production does not occur actually inside cells as we used to think, but between closely apposed macrophages as they are fusing to form giant cells. Later when giant cell fusion is complete

the bodies are found inside the cells. It has also been found that the first coating laid down on the asbestos fibre is not 'Ferritin' but some form of acid mucopolysaccharide. The iron containing granules later impregnate this coat to form a mature Perl positive asbestos body.

(e) Experiments using P2O4

These experiments have continued throughout the past year and have been extended to rats. The results, however, are still the same as those obtained with Guinea pigs. P2O4 as we have used it so far does not alter the asbestos lesion in any way. It has been suggested however, that dosage may have to be calculated more carefully in relation to the amount of asbestos dust given. This will be considered during the next year.

APPENDIX 4

Report on Work at St. James' Hospital Leeds - Dr. Swinburne

Animal Feeding Experiments

Batches of rats have been followed for 18 months after the ingestion of a course of crocidolite dust at two dose levels. So far, none of these animals has developed any untoward effects. A number were sacrificed early and others later but no dust was traced in the material so far examined either by light microscopy or micro incineration. Three of the control group have died or been sacrificed because of natural disease - one uterine sarcoma and two with nephritis.

Similar groups are receiving chrysotile dust but in order to avoid contamination, this experiment was started later. So far no tumours have resulted.

Asbestos in Pleural Fluids

Macrophages containing asbestos fibres and carbon were found in pleural fluid from one of Dr. Holt's animals. In the light of this finding, pleural and peritoneal washings from rats from the above experiments have been searched, but so far with no results. Fluids from two patients have also been negative.

This work is being extended by studying more samples from patients with suspected asbestosis or early mesotheliomas and material is being collected from such patients to try and determine whether mesotheliomas originated diffusely due to a "field change" or in a localised or multifocal way.

APPENDIX 5

Report on Research in Leeds - R.W. Grimshaw, A.M. Harris

An investigation of the breakdown phenomena on grinding chrysotile has been completed. The release of magnesium has proved most interesting, but it is dependent on pH conditions. To overcome this problem, the free magnesium release has been assessed by titration to neutral pH conditions in all cases. The results on one Canadian chrysotile typify the general pattern:-

Sample treatment	% magnesium released	% silica released
Shredded only	2.0	0.5
Milled for 24 hours	50.5	2.3
Milled for 72 hours	63.0	2.2

The products of the milling have been separated into carefully sized fractions and the release phenomena investigated as a function of particle size. The results of the sample milled for 24 hours may be compared as follows:-

Size range (by settlement)	% magnesium release	% magnesium retained
100 - 64 microns	50.0	50.0
64 - 15 microns	48.4	51.6
- 15 microns	57.4	42.6

A close analysis of the results has revealed that a distorted layer is developed on the asbestos fibres by the grinding process. Within this layer the magnesium is free and can readily be released into solution whilst the silica remains as part of the lattice. The thickness of the distorted layer may be independent of particle size but is related to the intensity of grinding.

The concept of the distorted layer is exactly paralleled by studies of silicosis where a highly reactive layer surrounding ground quartz grains has been postulated as a prime feature.

Associated with the release of magnesium is the absorption of organic components such as amino-acids. That these are absorbed has been established conclusively but the amount and type of absorption appears to be dependent on the pH and buffering conditions within the solution.

APPENDIX 6

Report on Immunology Study - Dr. Turner-Warwick

It is now known that certain chronic diseases of the thryroid, stomach, adrenal gland and other organs are related to the development of immune reactions which in simple terms causes the patient to "reject his own tissue".

Work in this laboratory was originally designed to investigate the possibility of antibodies, specific to lung in certain chronic fibrosing lung diseases of unknown cause and which have histological similarities with other so called autoimmune diseases. The clinical syndrome of Cryptogenic Fibrosing Alveolitis was the subject of our first study.

The results of this study showed that although lung reactive antibodies could be demonstrated in some cases these invariably cross-reacted with other tissues: in other words they were non-organ specific tissue antibodies. It has been established by other workers that there is a group of autoimmune diseases particularly characterised by such antibodies and usually a number of different non-organ specific antibodies can be identified in the same patient. Antibodies reacting with cell nuclei (anti-nuclear factor or ANF) and those reacting to denatured γ globulin (Rheumatoid factors or RF) are two of the most common types found.

Against this background of information, it was encouraging to find that in Cryptogenic Fibrosing Alveolitis ANF and RF were found in about a third of the cases, particularly in the more acute phases of the disease.

We believe that Fibrosing Alveolitis is not due to only one cause, but represents a final common path of pathological change in the lung due to many different agents. The clinical syndrome found in asbestos workers characterised by finger clubbing, widespread crepitations in the lung, widespread radiographic shadows, a restrictive type of ventilatory defect without airways obstruction and fibrosis of the alveolar walls are identical with the features of Cryptogenic Fibrosing Alveolitis found in patients without asbestos exposure.

The next logical step was therefore to study tissue antibodies particularly the non-organ specific group in the serum of asbestosis patients. If they could be identified it would suggest that some types of immunological host reactivity played a part in the development of thisdisorder (in some or all cases), although the exact mechanism of tissue damage would still have to be worked out. Furthermore it might be possible to identify those patients who were more liable to develop lung changes and exclude them from exposure before lung changes have occurred.

Design of the Initial Study

Sera from patients with the classical features of asbestosis were collected from as wide a catchment area as possible to cover different

durations and types of asbestos exposure. It was at this point that the link with the Pneumoconiosis Medical Panel became particularly valuable. By the end of the first year 116 sera had been collected and studied (see Eleventh Annual Report). Our results showed that both ANF and RF were found significantly more frequently than in random populations with an incidence strikingly similar to that found in Cryptogenic Fibrosing Alveolitis. Further detailed study was therefore indicated:-

(a) To obtain further evidence of immunological hyperactivity.

(b) To ascertain whether tissue antibodies occurred as a result of this type of chronic fibrosing condition as a non-specific reaction to tissue damage.

(c) Whether detection of tissue antibodies could identify those patients at special risk to develop lung fibrosis.

Further Evidence of Immunological Reactivity

Lung reactive antibodies were studied by three different techniques:

1. Conventional complement fixation tests, using homogenates of human lung as substrate.

2. The antiglobulin consumption test using the same substrate.

3. An indirect immunofluorescent test using WI 38 lung fibroblasts.

Our results show that in asbestosis, lung reactive antibodies are only very occasionally found using any of these three systems, and this is in contrast to the pattern of antibodies seen in Systemic Lupus and Fibrosising Alveolitis, where these types of tissue antibodies are not uncommon. However, this contrasts with the two other conditions in whichANF and RF are commonly found, namely Systemic Lupus Erythematosis and Fibrosing Alveolitis where cytoplasmic antibodies can commonly be detected in complement fixation and anti globulin consumption systems. On the other hand study of tissue antibodies in other chronic fibrosing diseases suggests that ANF and RF do not result non-specifically from any type of chronic inflammatory change in the lung and it looks therefore as if ANF and RF are associated with the development of certain forms of fibrosing diseases only, including asbestosis.

Further evidence supporting the suggestion of immunological hyperreactivity in patients with asbestosis is found in our results of quantitative immunoglobulin assay where increases in individual immunoglobulins are not infrequently found occurring in a similar proportion of cases and in similar patterns to that found in Cryptogenic Fibrosing Alveolitis.

Survey of Patients with Asbestos Exposure

To answer the question whether antibodies develop before lung fibrosis will have to be answered by surveying exposed subjects without X-ray changes. We have therefore devised a programme to survey patients

exposed essentially to asbestos in two contrasting ways; one is a factory population and the other employed in the insulation of ships at the Royal Naval Dockyard, Plymouth. So far 127 sera from the factory group and about 73 from Plymouth have been collected. Some 400 further sera will be collected before the detailed analysis is made.

The initial impression is that exposed but unaffected subjects even after many years exposure to asbestos have an incidence of circulating antibodies similar to the normal population, i.e. about 5%. The problem now arises as to whether it is this normally occurring 5% who are at special risk to develop asbestosis or whether lung fibrosis together with tissue antibodies appears in previously negative subjects. Our data perhaps best fits with the suggestion that these subjects may be particularly prone to develop asbestosis so that the incidence of tissue antibodies rises from 5% to 30% as this group becomes selected out, but that other factors are also involved accounting for the numbers of affected patients who have no tissue antibodies.

Further Work

The immunological survey of asbestos exposure has to be completed in the laboratory and then analysed. The detailed correlation between the clinical radiographic, physiological features and the immunological status in patients with asbestosis must be undertaken. This data is already being handled. The radiographs are being classified according to the UICC classification and the physiological data tabulated.

CHRYSOTILE -- HOW REASSURING THE MINING EXPERIENCE?

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Presented to the Asbestos Textile Institute at its Annual Meeting held October 5, 1973, at Wychmere Harbor Club, Harwichport, Mass.

What are the health risks associated with working with asbestos? In quantitative and qualitative terms -- What is the relationship between amount and type of exposure and amount and type of disease? Although a great deal of research has been done on the subject, the picture is still fairly imcomplete because the main evidence has to come from observations on man -- on people who are known to have been exposed to the mineral. Other investigations, such as animal experiments, do a lot to add to the picture but the evidence basically depends on what disease occurs in man and with what exposures. It is complicated, as you realize, by the different varieties of fibers, and because each fiber type may affect health differently. But I will try to give you some picture of the present state of knowledge, which is, on the one hand, complicated, and on the other, uncertain.

*Slide 1 shows the main types and quantities of asbestos produced and the time period over which they have been produced. It also shows the different uses for the mineral.

The first hazard to be observed was asbestosis. In quantitative terms -- What is the risk of contracting asbestosis? How much dust exposure, and over how long a period of time, is necessary before there is a risk of getting asbestosis?

The matter is still rather poorly assessed, except in the study we have been doing in Quebec where we do now have, for chrysotile mining, a fairly good picture of the amount of exposure which will give rise to asbestosis. It appears that all types of fibers and all types of processes (all industrial groups) are at risk of asbestosis.

The problem really lies in lung cancer. There are two main cancers that are associated with asbestos -- lung cancer, which is really indistinguishable from the lung cancer that smoking can give you; and mesothelioma, which is a very rare tumor that involves the surface of the lung and the lining of the abdominal cavity. A very definite connection has been observed between asbestos exposure and mesothelioma.

*The only slides available for reproducing in this written account are shown as Tables 2 through 9.

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TABLE I

Main Industrial Groups and Fiber Exposure

	Chrysotile	Crocidolite	Amosite	Antho-phyllite	Mixes
Mining	±	++?	?	±	M/A
Manu-facture	++?	Not Known	++	Not Known	++
Insu-lation	Not Known	Not Known	Not Known		++ ++

Table I. I'm proposing to look at this in three main industrial groups: mining, manufacture and insulation -- and at the fiber types concerned, i.e., chrysotile, the three main amphiboles, and mixed fiber exposures. Unfortunately, the latter group is the most common.

When we started our studies in Quebec, it was known that very substantial risks of lung cancer and mesothelioma were found in the manufacturing processes and in people working with insulation. This is particularly true for mesothelioma which is very rare and only occurs in one out of a million population -- and yet a substantial number of cases are found with certain asbestos exposures.

Substantial health risks in terms of mesothelioma and lung cancer have been well documented for mixed fiber exposures. When we began our studies in Quebec, there was little evidence of a serious problem in the Chrysotile mining industry.

It was, therefore, very important to look at groups of people who were exposed to only one type of fiber. So we started investigating all persons who had ever been employed in the Quebec chrysotile-producing industry. The main objective, apart from studying pure Chrysotile exposure, was to determine the dose response relationship; that is to say, to try to get some precise information about what exposures could be sustained without a significant risk to health, and at what level was there a significant amount of disease.

As you know, the two main asbestos mining areas in Quebec are Asbestos and Thetford Mines. Slide 2 is a photograph of Canadian Johns-Manville's Jeffrey Mine at Asbestos. Slide 3 is a picture of Smith Street, in Thetford, which is indicative of the extensive environmental exposure to people, locally.

Slide 4. In starting our survey, we obtained personnel records of all of the people who ever had worked in the mines and mills. We documented all of their jobs, recorded as well as possible the amount of dust to which they had been exposed, and allowed for the time during which they had been exposed to these levels. We then divided all of these people into groups, according to the amount of dust exposure.

TABLE II
Dust Exposure Levels and Numbers in each Analysis

Dust Exposure (mpcf - years)	-10	10-	100-	200-	400-	800+	
Number of Men in Each Analysis							Total
Mortality Study	2810	3329	1124	1007	837	585	9692
Radiographic Study	1337	1522	1133	912	718	707	6529
Lung Function and Respiratory Symptoms	91	455	159	134	109	67	1015
Smokers	69	381	144	117	96	59	866
Non-Smokers	22	74	15	17	13	8	149

The above Table II/Slide 5 shows the extent of the study. Looking at the top line, we have six groups, ranging from a total of less than 10 million particles per cubic foot x years through 800 plus. If you take a lifetime of 50 years of employment, the last group on the right would be equivalent to exposure to an average of at least 15 million particles per cubic foot. This is a very heavily exposed group and, of course, such exposures have only happened in the past and do not occur at the present time. Dr. Graham Gibbs, of the Department of Epidemiology and Health, has been studying the correlation between fiber counts and particle counts and we do not find sufficient correlation between the two to give our findings in terms of fiber counts. For this reason and because all epidemiological information is in terms of particle counts, we consider that these should continue to be used until fiber counts have been done for a long period of time. We do not have any direct information about fiber levels in terms of risks of disease.

One of the three major studies we undertook was of all men born between 1891 and 1920, to study causes of death and what their death rates were in various dust categories. We did an x-ray study in order to determine which dust groups showed an increased incidence of x-ray changes and at what level the increase started. This, of course, was important evidence of disease. Laboratory equipment was moved down to the mining areas and 1000 men were submitted to detailed lung function studies, again to see what the relationship was between the amount of chrysotile dust to which the men had been exposed and changes in their lung function. Slides 6 & 7 show the apparatus that was used to test their lung functions.

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TABLE III

Age-Corrected Mortality by Cause Per 1000 Men Born 1891-1920 -- Deaths to December 1969

	Dust Group					
mpcf - years	-10	10-	100-	200-	400-	800+
All Causes	365	355	354	313	323	395
Respiratory Cancers, including malignant pleural mesothelioma	10.3	13.1	13.4	15.5	21.4	32.1
Abdominal Cancers	18.0	13.6	18.7	11.6	26.3	28.7
Pneumoconiosis	1.6	1.5	0.8	4.9	4.9	23.6

Table III/Slide 8 shows the main results of the mortality study. Of all causes of disease, it was only in the highest dust group (800+) that there was a considerable excess of deaths. For respiratory cancers, which includes malignant pleural mesothelioma of which there were very few cases in the industry, a rise is clearly present in the 400 to 800+ dust groups with an exposure (to an average concentration of 8 mpcf over 50 years). The rise probably does begin a little earlier. The highest dust group, which as we said was very heavily exposed, has about 3 times as much respiratory cancer as do the people with minimal exposure (the less than 10 group). The latter group includes people such as those working in clerical jobs and who have virtually no exposure to asbestos. But having information for both groups gave us a population with which to compare the people who were substantially exposed to dust.

There was also some indication that abdominal cancers were related to dust exposure. You will see a higher amount of abdominal cancers in the 400 to 800 and the 800+ groups. The same experience has been observed in other studies. It is by no means certain that this is directly due to asbestos since there are other possible explanations. You will see that the rise in asbestosis occurs at around the 200 dust level, indicating an equivalent of an average of 5 mpcf over 50 years.

Table IV/Slide 9. What is thought to be significant disease is irregular small opacities of grade 2/1. For those cases we observed that a significant increase occurred in the 100 to 200 dust group. We conclude, that for a lifetime exposure, an average of 2 mpcf gives rise to radiological change indicative of significant disease in 1% of persons.

Slide 10. In lung function tests in cigarette smokers and non-smokers, the first change occurred in the capacity to breath in and this started with low levels of dust exposure. But a 10% deficit in breathing capacity occurred at about the same level as the radiological changes that I just talked about -- at the level of about 2 mpcf on average over a lifetime.

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TABLE IV

Radiographic Changes - Prevalent Rates (%) Standardized for Age and Years in Industry -- Males Aged 36-65 at time of Radiograph

	Dust Group						
mpcf - years	-10	10-	100-	200-	400-	800+	Average
Thetford Mines							
Irregular Small Opacities - - - 1/0	1.8	3.3	6.3	8.7	12.0	17.2	7.6
2/1	0.0	0.2	2.2	0.9	2.4	9.2	2.0
Pleural Thickening- Grade 1	2.4	4.6	6.5	5.8	8.3	10.5	6.4
Grade 2	1.3	0.7	0.6	1.2	1.3	2.0	1.1
Asbestos							
Irregular Small Opacities - - - 1/0	6.4	3.7	6.3	5.0	6.8	7.0	5.1
2/1	0.0	0.4	1.5	0.8	0.6	3.9	0.8
Pleural Thickening- Grade 1	2.9	2.6	3.0	3.0	4.7	5.8	3.2
Grade 2	0.0	0.6	1.0	0.5	1.4	0.7	0.7

TABLE V

Age-Corrected Prevalence Rates (%) for Bronchitis and Breathlessness by Dust Exposure & Cumulative Smoking Habits

	Dust Index					
mpcf - years	-10	10-	100-	200-	400-	800+
Bronchitis						
Never Smoked	10	19	19	46	21	49
Up to 100 Cigarette Years	18	0	12	0	46	0
100-499	41	28	21	33	42	43
500-999	32	38	44	28	47	58
1000	100	47	45	55	54	35
Breathlessness						
Never Smoked	0	14	24	31	13	44
Up to 100 Cigarette Years	0	12	10	21	41	43
100-499	16	14	8	20	42	18
500-999	9	19	21	19	14	39
1000	0	23	27	31	34	46

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Table V/Slide 11. Lastly, the workers were asked to fill in a questionnaire about smoking. From the answers, we found that there was a relationship between breathlessness and dust exposure not apparently affected by smoking. But if you look at bronchitis and along the line for the "never smoked" and the two groups of smokers, you will note there wasn't any change in bronchitis which increased asbestos dust exposure. Now, if you look at the columns vertically you will see that smoking does a lot of damage in terms of bronchitis

TABLE VI

Distribution of Cases of Mesothelioma by Year of Death and Province (1960-1970)

	Ontario	Quebec	Other Provinces	Canada
1960	0	6	9	15
1961	1	6	3	10
1962	4	4	5	13
1963	9	3	7	19
1964	6	8	3	17
1965	7	7	5	19
1966	8	14	9	31
1967	6	13	6	25
1968	7	18	7	32
1969	12	7	6	25
1970	9	16	5	30
	69	102	65	236
Annual Incidence Per Million Population 1966-1970	1.2	2.3	0.9	1.4
Reviewed by Pathology Panel	57	80	47	194
Accepted as Mesothelioma	71%	42%	57%	55%

Table VI/Slide 12. The other study we did was to survey all mesotheliomas in Canada. At the outset, I should say we had just 5 mesotheliomas out of 3270 deaths in the mining industry. Although this may seem to you to be a small number, there should be no cases of mesothelioma in a general population. One of the problems about mesothelioma is the diagnosis. There is by no means agreement among pathologists about the diagnosis of mesothelioma; so our finding of 5, having searched pretty thoroughly for mesotheliomas, may well be an over-estimate, especially because they were particularly looked for in people with known asbestos dust exposure. Having found very few in the industry, we did a concurrent study -- locating all the mesotheliomas we could in Canada. We obtained from all pathologists reports about all known cases and feel we got fairly full ascertainment. The ascertainment wasn't done until 1967-68. If you look at the graph at the top (Table VI) you will see a gradual rise in the annual number of mesotheliomas across Canada up to 1966. This is

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probably due to poor memory and lack of knowledge about mesotheliomas in these earlier years. We are continuing this surveillance, and between 1966 and 1970 there doesn't appear to have been any change. This is rather a short period of time and we obviously need to know whether this "no change" situation will continue. As you know, the big concern is the lengthy latent period for mesothelioma to develop and the widely expressed fear that we are now going to reap results from exposures which occurred 20-30 years ago and that the rate of mesotheliomas may rise.

We now feel quite happy that a fairly good base line has been established for this surveillance and we shall be able to know within the next few years what is happening in Canada. If you look at the bottom line (Table VI), we looked to see whether mesothelioma occurred more in one part of Canada than in other sections of the country. There was, in fact, more in Quebec -- over 2 per million population, compared with just over one in Ontario and slightly less than one in the rest of Canada. But we must revert to the question of the diagnosis. When the mesotheliomas were submitted to pathologists, a much lower proportion was accepted as mesothelioma by the pathologists' panel -- not only in Quebec but in all of Canada. It looks as though, for cases that are accepted by the panel as mesotheliomas, there is little or no difference in the various parts of Canada.

TABLE VII

Distribution by Age of Cases and Matched Controls

(The number in parentheses designates those successfully investigated, epidemiologically)

Age (Years)	Men		Women	
	Cases	Controls	Cases	Controls
20-29	0 (-)	0 (-)	2 (2)	0 (-)
30-39	3 (2)	2 (2)	4 (4)	4 (4)
40-49	6 (5)	6 (6)	4 (4)	5 (5)
50-59	12 (12)	12 (11)	6 (6)	5 (5)
60-69	8 (8)	10 (10)	6 (6)	8 (8)
70-79	7 (7)	5 (5)	7 (7)	8 (8)
80-89	2 (2)	3 (3)	3 (3)	2 (2)
90-99	1 (1)	1 (1)		
Total	39 (37)	39 (38)	32(32)	32 (32)
Mean	58.7	59.2	58.9	59.0
Standard Deviation	12.9	13.2	18.2	15.2

Table VII/Slide 13. There are two objectives in this mesothelioma study -- to continue to watch the incidence and to examine to what extent the mesotheliomas are caused by asbestos. Here you see that more than 2/3 of the cases are in males, as is expected, and

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TABLE IX

Types of Occupation in which there was Definite or Probable Asbestos Exposure

	Men				Women			
	Occupational		Domestic		Occupational		Domestic	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Mining & Milling	1	--	1 father	--	--	--	1 father	--
Asbestos Products Manufacture	4	--	--	--	--	--	--	--
Insulation Work	2	--	--	--	--	--	3 1 father 2 husbands	--
Other Occupations	4	4	--	--	--	--	--	1 husband

Table IX: If you will look at the top line, you will note that we did find some indication of domestic exposure. There were a few people who had been exposed to a father or a husband working with asbestos. The diagnosis of mesothelioma may be more likely to be made in such a situation, but nevertheless, this risk is probably real and, especially for children. But there is no indication that the general population is at any risk.

So we found that the mesothelioma study backed up what we found in the mining industry, namely that there is a small excess of mesotheliomas in mining but it was manufacture and insulation that were mainly associated with mesothelioma in Canada rather than the mining and milling of chrysotile.

This has been borne out in other studies of chrysotile mines in Cyprus, Northern Italy and the USSR. Although the information is somewhat incomplete, they indicate a similar experience to that found in Quebec with regard to lung cancer and, in fact, practically no mesotheliomas. The evidence, insofar as the chrysotile-producing industry goes, is good in that the risks are low, and probably controllable.

Now, referring back to Table I -- I'm going to put a + for chrysotile mining. For anthophyllite mining in Finland, the picture is similar in that they find no mesotheliomas in that country. There does appear to be some lung cancer associated with mining but it isn't the high rate that appears in manufacturing and in insulation work.

Our information about crocidolite and amosite mining is fragmentary because it doesn't depend on surveys of people working in the mines. It depends, rather, on a surveillance of all types of cases which come from the mines and surrounding areas.

It does appear, however, that there have been a substantial number of mesotheliomas around crocidolite mines in the Northwest Cape. So, I'll put a ? for crocidolite mining (Table I) because the evidence isn't too secure, especially in regards to rates; i.e., how many cases in relation to how many workers and residents.

Regarding the amosite mines in the Transvaal, there is a very minute + (Table I). There does appear to be some lung cancer but practically no mesothelioma -- which is very different from the Northwest Cape area.

The relationship between mesothelioma and chrysotile has been confirmed in studies by the electron microscope -- studies in which fiber types in the lungs of cases of mesothelioma have been identified by Dr. Fred Pooley, of Cardiff in South Wales. In these studies, practically all of the fibers detected were of the amphi-

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bole variety. So far it has not been possible to distinguish crocidolite from amosite fibers, but chrysotile can be detected. All the cases thus far examined have substantial amounts of amphibole fibers and relatively few chrysotile fibers.

There are reports that persons exposed to chrysotile only in the manufacture of asbestos, have had similar rates of mesothelioma and lung cancer to those found in persons exposed to a mixture of fibers. The evidence isn't any too sure, in fact it's pretty doubtful, that these men were exposed only to chrysotile. So, we must put a ? (Table I) against the risk of cancer in the manufacture of asbestos products using only chrysotile.

Some additional comments to the data in Table I: Dr. Selikoff reports a high rate of mesothelioma and lung cancer in persons exposed only to amosite. Information on the manufacture of anthophyllite is unknown because single types of fiber have not been used in the process. Mixed mining is not applicable. And, we lack satisfactory information about manufacturing with pure crocidolite or with pure anthophyllite.

As you know, there are differences in the nature of each fiber type but experimental work has produced some possible explanations of the varying effects. Chrysotile is a long, thin and curly fiber and there is some evidence that it easily gets held up in the larger airways and, therefore, does not penetrate so well as other fiber types which can enter the smaller airways and reach the pleural surface.

In comparing crocidolite and amosite fibers, both are straight, rather than curly. However, when mined they apparently have quite different diameters; crocidolite having the narrower diameter and amosite being much wider in diameter. This fits in quite well with the findings from studies in the Northwest Cape. There are a lot of mesotheliomas in the Northwest Cape where the diameter of the fibers is small; whereas in the Transvaal area, where amosite is mined, and the fibers are broad, there appear to be practically no mesotheliomas. This doesn't fit with the story of the manufacture of amosite, and, frankly, I really do not know the reason.

Fiber differences could be an explanation; but on the other hand, the big differences between chrysotile mining and the manufacture of asbestos products and insulation certainly cannot be laughed off. Some of the possibilities for the differences between chrysotile mining and manufacture and insulation are . . . .

1) It is possible that during manufacture the fibers may be broken up into much smaller pieces and, therefore, lose their capacity to be caught up in the bigger airways, thereby penetrating further into the lungs.

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2) It is possible that the culprits are crocidolite and/or amosite.

3) It also is possible that in the process of manufacturing and insulation, that other carcinogens are involved.

Smoking has been raised as a possible additional factor in causing cancer of the lung; but for mesothelioma it has been pretty clearly shown that smoking is not an added factor. If there is something else that increases the risk of mesotheliomas, it is not smoking.

So I have to conclude that the chrysotile mining experience cannot really be said to be reassuring. It is certainly possible that if one were able to show that the manufacture of pure chrysotile gave cancer rates, similar to those in mining and milling, the picture would certainly be brighter.

But, it isn't brighter at the moment!

- end -