SH/HS

ASBESTOSIS RESEARCH COUNCIL

TWELFTH ANNUAL REPORT FOR THE TWELVE MONTHS

BEGINNING 1st OCTOBER, 1968

1. INTRODUCTION

The Asbestosis Research Council was established on the 1st October 1957. This report details the activities sponsored by the Council during the twelfth 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 and again in November 1968 to cover the activities of the Environmental Control Committee.

3. MEMBERSHIP

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

Full Members

BBA 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.
Richard Klinger Limited.

Overseas Associate Members

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

4. COMMITTEES

The affairs of the Council were administered by three Committees; the Management Committee; the Research Committee and the Environmental 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. Case	- The Cape Asbestos Co. Ltd.
	Mr. C.M. Fenton	- RBA Group Ltd.
	Dr. C.C. Addingley	- RBA Group Ltd.
	Mr. D.W. Hills	- Turner & Newall Ltd.
	Mr. R.H. Wilson	- Turner & Newall Ltd.
Secretary :	Dr. S. Holmes	- Turner & Newall Ltd.

Management Committee meetings were held as follows:-

London	- 1st November, 1968
London	- 6th January, 1969

(b) Research Committee

Chairman :	Mr. R.A. Walls	- Turner & Newall Ltd.
	Dr. H.C. Lewinsohn	- Turner & Newall Ltd.
	Dr. C.C. Addingley	- RBA Group Ltd.
	Dr. W.H.A. Beverley	- RBA 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:-

London	- 7/8th January, 1969.
Cleckheaton	- 3/4th June, 1969.
Rochdale	- 23/24th September, 1969

On 4th June, 1969, the Research Committee held a one-day scientific meeting at Rochdale on "The Diagnosis of Mesothelioma". Members of the Medical Branch of the Factory Inspectorate and of the Pneumoconiosis Medical Panel were present, along with research workers in this field.

(c) Environmental Control Committee

Chairman	-	Mr. A.A. Cross	- The Cape Asbestos Co. Ltd.
		Mr. W.P. Rushlin	- Turner & Newall Ltd.
		Mr. M.L. Bentley	- RBA Group Ltd.
		Mr. J.C. Byrom	- Turner & Newall Ltd.
		Dr. S. Holmes	- Turner & Newall Ltd.
		Mr. J.B. Pennington	- Turner & Newall Ltd.
		Mr. R.W. Whitcomb	- RBA Group Ltd.
		Mr. R.H. Wilson	- Turner & Newall Ltd.
Secretary	-	Mr. W.C. Jeaphin	- The Cape Asbestos Co. Ltd.

Mr. R.H. Wilson resigned in July, 1969, his place being taken by Mr. J.P. Parrill of the Cape Asbestos Co. Ltd.

Environmental Control Committee meetings were held as follows:-

Manchester	- 4th October, 1968.
Uxbridge	- 12th December, 1968.
Cleckheaton	- 18th March, 1969.
[illegible]	- [illegible]

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	£25,600
Expenditure	£14,600

6. LIAISON WITH OTHER INTERESTED BODIES

Contact has been maintained with the Department of Employment and Productivity (Safety, Health and Welfare and Factory Inspectorate), and with the Ministry of Technology (Warren Spring Laboratory).

The A.R.C. has collaborated with the Ministry of Housing and Local Government in the production of a recommended Code of Practice to cover the handling and disposal of asbestos waste.

Liaison has continued with the Pneumoconiosis Research Unit of the Medical Research Council. The arrangements for a joint International Conference on "The Tissue Reaction of Asbestos" to be held in Cardiff in April 1970, have proceeded.

The Sub-Committee of the British Occupational Hygiene Society has continued to meet to explore the possibilities of a hygiene standard for exposure to amosite asbestos dust. A one-day Conference organised jointly by the BOHS and the A.R.C. on 18th June, 1969 in London on "The Control of Asbestos in the Working Environment", was very well attended.

A system for the exchange of scientific and technical information has been established with the Pneumoconiosis Research Unit of the South African Institute for Medical Research in Johannesburg.

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

A summary of the year's work is given below. Full reports appear in Appendices 2 to 6. It should be emphasised that these detailed reports represent the individual views of the research workers and not necessarily the official view of the Council.

Sections from the long term animal experiments involving inhalation of the four main types of asbestos and of glass have been examined by optical microscopy. New inhalation experiments on modified asbestos and on dusts other than asbestos, have been started. Collaboration with the Institüt für Lufthygiene in Düsseldorf has continued.

Little progress has been made in the examination of human biopsy material from cases of suspected mesotheliomas, due to lack of sufficient specimens, but work on the experimental production of mesotheliomas in animals has continued. Work on the pathogenicity of minerals other than asbestos has continued. Electron microscope studies on the mechanism of asbestos body formation have proceeded and the possible effects of P2O5 on asbestos lesions have been further studied.

Animal experiments on the ingestion of asbestos have continued, so far with encouraging results.

Work on the breakdown phenomena on the grinding of chrysotile, and amosite was terminated at the end of June, 1969. Further work on the surface properties of asbestos is being arranged.

The immunological study has continued. Certain diseases cause recognisable changes in the proteins of blood serum which can be demonstrated by specific tests. In a group of workers exposed to asbestos, Dr. Turner-Warwick has demonstrated a statistically significant increase in blood protein changes in those who show evidence of biological ill-effects compared with those who do not, and also compared to the general population. It is not yet known whether positive tests for these changes follow or accompany the development of pulmonary fibrosis, or whether they are due to an inherent characteristic of some individuals who are more susceptible than others to the disease. If the latter be the case, there is hope that we may have a means of detecting the worker who is the more likely to suffer from the biological ill-effects of asbestos inhalation even before such effects are evident.

8. DUST SAMPLING AND ANALYSIS

This work has been co-ordinated by a Working Group of the Research Committee.

The method of sampling by membrane filter has remained standard in the industry and to take account of recent improvements in technique a revised version of Technical Note No. 1 has been published.

Methods for estimating the mass of asbestos in a dust sample have been studied and what promises to be a very sensitive technique using X-ray diffraction has been evolved.

Work on the assessment of asbestos dust levels in the vicinity of factories and in urban and rural environments has been held up by delays in the delivery of specialised sampling equipment.

The report on asbestos dust levels in completed buildings incorporating asbestos products in their construction has been published in the Annals of Occupational Hygiene.

9. THE ASBESTOS REGULATIONS 1969

The observations made by the Council to the Department of Employment and Productivity on the contents of the Statutory Draft were the subject of discussion early in 1969. The Council, along with other interested bodies, agreed not to press for alterations to the draft and the Regulations were finally enacted in May 1969. They will come into operation in May 1970.

10. ENVIRONMENTAL CONTROL

The study of the implications of the New Regulations and the giving of advice on their implementation has been the major task of the Environmental Control Committee of the Council. A full report of its work appears in Appendix 1.

The Committee has prepared a number of "Notes for Guidance" covering different fields of activity where asbestos and asbestos products are handled, to assist asbestos users in coping with the Regulations. Some of these have already been made available in a preliminary form. Where appropriate, informal discussions on the interpretation of the Regulations have been held with the Factory Inspectorate.

11. CODES OF PRACTICE

During the year the Council issued its fifth Code of Practice - 'Recommended Code of Practice for the Handling and Disposal of Asbestos Waste Materials'.

12. OTHER PUBLICATIONS

'A Dust Survey carried out in Buildings incorporating asbestos-based materials in their construction'
J.C. Byrom, A.A. Hodgson and S. Holmes, Ann. Occup. Hyg. Vol. 12, pp. 141-145.

Two further papers have been accepted for publication, but have not yet appeared in the Journal concerned.

13. PULMONARY FUNCTION TESTS

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

14. VISITS

In April 1969, Dr. Addingley, Dr. Smither, Dr. Lewinsohn and Dr. Holmes attended the Second International Conference on Pneumoconiosis in Johannesburg. The expenses for this visit were borne by the Member Companies of the Council in respect of their own representatives.

Dr. Smither and Dr. Lewinsohn both paid brief visits to Belgium and Holland in connection with asbestos and health problems.

15. GENERAL

Dr. Knox retired in January, 1969. He had been Medical Consultant to the Council since its formation in 1957 and the Council wishes to place on record its appreciation for his outstanding services to the Council and the asbestos industry. His position as Medical Consultant to the Council was taken by Dr. Smither.

Dr. Beattie has continued as Research Consultant to the Council.

APPENDIX 1

Report on the work of the Environmental Control Committee

The first meeting of the Environmental Control Committee was held on 4th October 1968 and five further meetings have been held. Working Groups have been set up as agreed by the Asbestosis Research Council. These were -

I Asbestos Factories

II Asbestos Building Materials

III Asbestos Insulating Materials

IV Friction Materials

V Asbestos Textiles

VI Sprayed Asbestos

Working Group I was required to provide basic information on various aspects of environmental control common to all factories and formed sub-committees to produce advisory notes on -

Dust extraction equipment
Respiratory equipment
Protective clothing
Machine and workroom cleaning
Disposal of waste

Provisional Notes for Guidance on Waste Disposal were produced in time for the BOHS/ARC Conference in June 1969; this provided the basis for the Code of Practice finally published by the ARC in consultation with the Ministry of Housing and Local Government. Draft notes have been prepared and will shortly be published on Exhaust Ventilation and on Protective Equipment (the latter will cover respiratory equipment and protective clothing).

Working Groups II to VI undertook the task of carrying out a preliminary survey on the principal products, processes and methods of use of the products covered by each group and then establishing as far as possible the dust concentrations likely to be encountered in these situations.

The Groups were also asked to review the draft Asbestos Regulations in the light of their effect on their product groups and to formulate suitable advisory documents which would take the place of the ARC Codes of Practice. Provisional Notes for Guidance have been produced for four of the five working groups and will shortly be submitted for approval and final publication to the Asbestosis Research Council.

Through the Asbestos Information Committee the availability of advice from the Environmental Control Committee has been publicised and, as a result of this and of the BOHS/ARC conference, considerable use has been made of the services of this Committee either by means

of the provisional Notes for Guidance or by personal advice from Committee members. Individual member companies have in some cases set up their own advisory services which have been supported by the Committee.

Working Group II (asbestos building materials) completed the dust survey carried out in the buildings incorporating asbestos materials in their construction, which had been put in hand by the Asbestosis Research Council prior to the formation of the Environmental Control Committee. A report of the survey has recently been published in the Annals of Occupational Hygiene. The second stage of the survey covering concentrations arising from standard operations carried out on asbestos based materials is approaching completion, and similar surveys are being undertaken by the other working groups.

The Committee was asked to undertake an investigation into the possibility of marking asbestos-based boards, in response to a request from the T.U.C. referred to the A.R.C. by the Department of Employment and Productivity. This was referred to Working Group II and a report has now been submitted to the Management Committee of the A.R.C.

Informal discussions have taken place with the Factory Inspectorate to provide the opportunity for joint study on various aspects of control and the requirements of the new regulations. So far these discussions have covered dust assessment, exhaust ventilation and protective equipment.

The Environmental Control Committee has been able to advise various other interested organisations in their consideration of the effects of the Asbestos Regulations and in the vetting of their advisory documents. Provisional Notes for Guidance on the handling of asbestos fibre by general users has been prepared for the Asbestos Fibre Importers Committee.

APPENDIX 2

Report on Research at Reading - Dr. P.F. Holt

The interpretation of the results of animal experiments started three years ago has continued and a picture of the effects of four varieties of asbestos, glass fibre and glass powder on the lung is being built up. When any of these dusts is inhaled by a guinea-pig, the lung uses several methods to get rid of it. The heavier particles that are deposited in the larger air vessels are removed by cilia, those which get be---d the ciliate epithelium and are deposited are found in the bronchioles, a little is deposited directly in the alveoli. The goblet cells of the bronchioles are activated to secrete mucus which helps to carry the dust into the larger air vessels from whence it is coughed up. Some of the dust moves further into the lung, possibly because of the surface active substance, surfactan, which is secreted in the bronchioles and is absorbed in the alveoli. In the alveoli this dust is rapidly ingested by phagocytic cells (macrophages) but also causes a leakage of red blood cells from the alveolar capillaries. This leakage of red cells is produced (in differing amounts) by all five dusts. Red cells or the haemoglobin of some derivative, are ingested by macrophages.

Some macrophages containing dust and/or haemoglobin-products are shed from the alveolar walls and move outwards from the alveoli into the bronchioles, and many of these cells are eventually coughed up. In this way glass powder is rapidly removed from the lungs. The immediate removal of some dust fibres is sometimes prevented by two factors: (a) some fibres penetrate the alveolar wall, and (b) some macrophages containing dust particles fuse to form giant cells. Some giant cells are also shed from the alveolar walls and leave the alveoli, but others get trapped at the junction of the alveolus and alveolar duct and, at least temporarily, close these alveoli so that they are no longer available for respiration.

When a trapped cell contains asbestos or glass fibres and haemoglobin decomposition products, iron-containing material is deposited on the longest fibre and morphological changes take place with the formation and development of an asbestos or glass fibre body.

Eventually, asbestos or glass fibre bodies become beaded and then fragment into tiny globules. These globules are ingested by macrophages and are removed. So far as can be judged these fragments of asbestos or glass fibre bodies produce no pathological effects; certainly no fibrosis has been found. The fibre body formation is apparently the final method by which the lung attempts to rid itself of fibrous material. What process is involved in the fragmentation of fibre bodies we cannot imagine; the explanations which have been given for asbestos seem inapplicable to glass fibre. No evidence has been found that powdered glass particles become coated, so the coating process appears to depend on the shape of the phagocytosed material. The general sequence that has been described applies to all the fibrous dusts examined. No important features were found that differentiated one from another. What does differ remarkably is the rate at which asbestos bodies form, develop and fragment.

In each group of animals the final animals were killed after the dust had been in the lungs for 18 months. The stage that amosite and crocidolite bodies had reached after that time was reached by anthophyllite after 6-9 months, chrysotile after about 6 months, and glass fibre after 3-6 months. Most chrysotile and glass fibres, then, even if they are not cleared from the lung in the mucus, or by phagocytosis, will disappear through the mechanism of asbestos body formation and fragmentation. Amosite and crodiolite will remain much longer.

Dust, any dust, produces changes in the lung. In particular, there is a proliferation of cells and thickening of the alveolar walls and alveolar septa. This, together with the accumulation of mobile cells such as macrophages and giant cells, tends to block off some alveoli. When glass fibre was inhaled, some thickening of the alveolar walls remained even after 18 months but the changes were not gross, and the majority of air vessels were not blocked. Lungs containing amosite and crocidolite were much more severely congested.

Crocidolite

Experiments in which batches of guinea-pigs were heavily dosed with crocidolite from Koegas and Transvaal respectively, were started at the beginning of the year. These are long-term experiments so there is nothing yet to report except that both groups of guinea-pigs have been depleted by death. One batch of rats also received Kodgas crocidolite; none has died.

Treated chrysotile

A few animals (24) have inhaled chrysotile dust which was pretreated in several ways - extracted with water, extracted with acid, treated with P2O4 and with 4-propylpyridine 1-oxide. There is nothing yet to report.

Asbestos in the rat lung behaves differently from what it does in the guinea-pig lung, particularly in that asbestos bodies are rarely formed. It has been found that the rat is able to get rid of asbestos more efficiently but there is also less leakage of red cells from capillaries and consequently less ferritin produced. The small amount of ferritin in a cell seems to remain separate from any asbestos fibres that may be present; it is not adsorbed.

Calcium Silicate

Two groups of guinea pigs inhaled air containing a high concentration of calcium silicate, one for 50 hours and the other for 100 hours. Sections of the lungs have not yet been studied and the experiment is continuing. The animals appeared to be completely unaffected by the dust; there were no signs of acute toxicity.

The joint experiments with Dr. Beck have continued on the effects of asbestos and modified asbestos on cells. There have been conflicting reports on the toxicity of asbestos to cells in culture, but these experiments suggest the conclusions given below:-

Measurements on the toxicity of dust to cells are usually carried

out by three methods -

(a) leakage of a dye into the cells through the damaged membrane,

(b) leakage of an enzyme from the cell through the damaged membrane, and

(c) the metabolic rate (lactate production).

With toxic dusts like quartz the three agree very well; (a) and (b) are increased, and (c) is decreased.

When chrysotile is tested, tests (a) and (b) indicate a slight toxicity, but test (c) does not. If the chrysotile is extracted with acid, tests (a) and (b) show a considerably greater toxicity but (c) shows none. Csentei at Düsseldorf has shown that quartz haemolyses red cells; chrysotile does so to a much smaller extent, but acid extracted chrysotile produces almost as much haemolysis as quartz.

The results may be explained by the fact that tests (a) and (b) measure the permeability of cell membranes which increases very much when a cell dies, but while asbestos is being taken up, permeability of the cell membrane is also increased. This does not kill the cell, however, so the metabolism (test (c)) is not decreased, (it is, in fact increased because the cell is working harder to phagocytose the dust particles). The increase in membrane permeability is not due to puncturing of the cell wall; if it were, washing the asbestos with acid would have no effect. The increase must be due to the adsorption of the membrane constituents on to the chrysotile surface.

It has been shown that one of the first effects produced by asbestos in the lung is to produce a leak of red cells from capillaries. An explanation of this could be that enzymes leaking from the macrophage affect the capillary wall. Since fibre also produces a leakage of red cells but to a much smaller extent than glass powder. This fits the theory that these enzyme leakages will occur only while the foreign body is passing through the cell wall; a spherical particle will be engulfed rapidly but a fibre takes a long time.

APPENDIX 3

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.

(4) 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.

(c) 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 patterns:-

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 thyroid, 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 this disorder (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 all types 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 100 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.