Q.A.M.A. Conference on Proposed Research

Institute of Occupational Health, Montreal

(Antigua - November 21st-27th, 1965)

(Neither Dr. Knox nor Dr. Holman attended this meeting.

The Agenda of the Antigua meetings was divided into two main groups of discussions:-

(a) review of objectives, opportunities and priorities and

(b) the organisation and means of achieving objectives.

The first group of discussions was divided into:-

1. Epidemiology
2. Experimental pathology
3. Environmental conditions.
4. Supervision of the health of workers
5. Immediate control measures

This group occupied the greater part of the time of the conference. The opinions expressed and statements made revealed that the climate of opinion and the state of knowledge had not changed materially from the position at the New York conference in October, 1964. The review was valuable in disclosing the objectives of the epidemiological study, proposed by Professor McDonald (McGill), of the population of the two mining areas in Quebec. There was general agreement with the objectives in that the survey should be prospective and retrospective and that it should take into consideration the health of the population in the area not involved directly in mining and milling activities. Full details of the survey were presented for discussion. The review disclosed the arrangements in different countries, (Finland, Italy and Common Market group) for supervising the health of workers, for research, etc. at industry national and international levels. The close agreement of these arrangement with those in the UK and in Canada was interesting though there were some differences in detail. Perhaps more significant in the discussion of this topic were the views put forward in favour of pulmonary function test units at mines and factories for obtaining data on pulmonary function before employment and at intervals throughout the period of employment. It emerged that in many countries compensation boards were putting more emphasi on the results of PF tests in determining degrees of disability and rather less emphasis on radiographic evidence. However, all speakers expressed the belief that PFT and radiographs were not substitutes for, but valuable supplements to, a thorough appreciation of the patient's condition based on clinical observation.

Concerning control measures for dust conditions, it appeared to be accepted that:-

1. the G-S method of dust sampling and the precipitator techniques gave results which differed markedly from each other.
2. any one technique was subject to a margin of error (i.e. in reproducability by the same observer or when different observers counted the same sample) of the order of ± 20 per cent.
3. membrance filter methods were less liable to give 'counting errors' than any other method and give more easily reproducible results. Monitoring methods for instantaneous control over dust concentrations at strategic points were advocated and one speaker drew attention to the good performance of a new

The general opinion was against setting up an arbitrary standard for dust concentrations in mines and mills as such dust contained large amounts (values of up to 85 per cent were quoted) of mother rock particles whose relation to the genesis of asbestotic conditions was at best problematical. Gravimetric methods found only one advocate (Gilson) and his case was weakened by his admission that mill and mine dust had variable compositions (i.e. as between chrysotile fibres and rock particles) and so without subsequent analyses of necessarily large samples, the asbestos hazard could not be assessed. Moreover, it was pointed out that, as dust concentrations fell with adequate control, the value of a gravimetric method was reduced (because of small samples) unless the time of collection was increased to long periods of many days or even weeks in order to secure a large enough sample for analysis.

Although the meeting was untrammeled by press representatives and the spectre of publication, it was not until the last session that there was any attempt made to indulge in forward thinking on the problems of asbestosis. It seemed to me that I had to undertake this crystal-gazing task. Although I was deliberately provocative in challenging present concepts (even those hypotheses put forward by myself) and in putting forward possible implications of the PVC-M oxide work in preventing the development of fibrosis induced by silica, no response was elicited in public, though private discussions later indicated a wide interest in my address. The full text is being duplicated for limited circulation.

The second group of discussions on organisation, initial programme and priorities was compressed into one session. Although the very short discussic on the organisation of the project indicated that one on the lines of the Asbestosis Research Council best fitted the intentions of the Q.A.M.A., a copy of the ARC constitution was given to Mr. Karl Lindell (Canadian J-M) for consideration. Private discussions in which I took part were favourable to my view that the project should not be linked with a specific university but should be independent so that it would continue to be free to decide upon lines of action and priorities.

The first priority was given to the sponsorship of the survey suggested by Professor McDonald and it was agreed that this should be got going as soon as possible. The second priority appeared to be the setting up of a central archives and information unit which would attempt to become a reference centre for the following types of information:-

(a) card catalogues of all published material on asbestosis, lung cancer, dust control methods and medical care of workers in the mining, milling and processing of asbestos (of all types of mineral).

(b) a repository for company records on personnel including medical records and radiographs from each company. The records on file would include only those which concerned men not now employed by the companies. These archives would be available for study.

(c) reports of governmental agencies dealing with the asbestos hazard.

(d) reports, etc. from non-governmental organisations (e.g. ARC, PRU Cardiff and Johannesburg) on research projects. etc

(e) any other source material.

The organisation of such an information service would require the serv of a special library-trained person engaged on a consultant basis for a lis period. A report to be expected in about 3-6 months would provide a basis discussion of this part of the project and its possible cost. The 'archive and records' centre would expand into one giving world coverage which would

Third priority would be given to an exploration of basic research projects but the nature and scope of these would depend on the appearance of suitable full-time workers in university departments with adequate facilities. It was agreed that full-time workers (paid by the new organisation) in specific projects was likely to lead to results more quickly than sponsorship of part-time research work.

The problems of lung cancer and mesotheliomas were discussed briefly. As the Dominion Government had already initiated a nation-wide survey on mesotheliomata, it was agreed that this problem could be left for future consideration. The incidence of lung cancer would be assessed in the McDonald survey and an analysis of the situation would be possible only after the lapse of some years. The Knox-Doll methods were agreed to be the best approach.

After the Antigua meeting visits to Asbestos, Thetford Mines and Montreal provided opportunities to discuss the problems confronting the mining industry in Quebec in more detail than was possible at Antigua. It soon emerged that whatever form the 'Institute' will take, its first duty must be to give advice, based on all available information, to the industry on problems of immediate relevance. To do so the 'steering committee' (corresponding to the Research Committee of the ARC) must build up its information and archives section to provide a basis on which to formulate its advice and by world-wide contacts secure up-to-date knowledge. The idea expressed at Antigua that the 'steering committee' should include among its members some scientists acquainted with the asbestosis problem in all its aspects received universal support. This support was given, not only on the grounds of having around a table some independent informed opinions on problems but also because in cases of conflict of opinion on the value of proposed research work they would be capable of guiding the 'steering committee' towards a decision.

From discussions with Mr. Lindell and Mr. Sabourin in Montreal it was clear that major decisions by the C.A.M.A. could not be expected before the January meeting of the association. I have expressed the opinion that whatever form the 'Institute' may take it should:-

(a) be financially independent and not rely on outside support from any source unless such support is 'without strings'.

(b) be independent of any other institution - university or governmental - so that its policy can be determined by the needs of the industry.

(c) Not indulge in capital expenditure on buildings at least until the needs of the institute for offices, library and other space are known more accurately.

(d) sponsor research in established university departments rather than to create a separate research unit which would be expensive both to build and equip. The principle of investing in the productivity of individual research workers is likely to prove more profitable both in the long and the short term than to attempt to set up a research institute.

(e) provide in its 'steering committee' a forum for discussion of immediate problems and a means to decide how such problems are to be attacked and by whom.

(f) have the resources to finance a modest programme of sponsored research and meet the cost of an information and archives section likely to become a world centre of information on every aspect of asbestos as an industrial hazard. Outside support for this latter programme would be forthcoming provided it is planned with imagination and foresight and administered with efficiency.

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TRANSCRIPT OF SPEECH BY DR. JOHN BEATTIE AT
Q.A.M.A. CONFERENCE on PROPOSED RESEARCH
INSTITUTE OF OCCUPATIONAL HEALTH IN MONTREAL

21st to 27th November 1965

During the past three days almost every aspect of the problem of asbestosis has been reviewed. I feel however that these reviews seem to indicate that the position has not changed materially since the meeting at the New York Academy of Sciences in October 1964. I cannot agree that this is so, for several significant new lines of work not considered here, have, in my opinion, presented a challenge to our thinking on the whole problem of fibrotic change associated with siliceous dusts and perhaps also to our attitude towards the cancerous changes associated with exposure to asbestos dust. In fact I consider that 1965 may well mark a turning point in the history of asbestosis, as for the first time the possibility that fibrotic change induced by siliceous dust may be controlled by chemical agents, is no longer a pipe dream.

I think we have all accepted the idea that a reduction of the concentration of a toxic dust leads to a fall in the incidence of the disease conditions induced by such dusts. The factual evidence presented by Bamblin (1960) showed that there was indeed a spectacular drop in the incidence of asbestosis after the introduction of efficient ventilation of the working areas in an asbestos textile factory. Coincident with this was a corresponding fall in the incidence of lung cancer in the same working population. I think we should express this in more precise terms by saying as we diminish the amount of dust which is respired per unit time the chances of accumulating in the lungs a toxic dose of asbestos dust are diminished. Paul Gross has emphasised that the capacity of the lungs to rid themselves of inhaled particles is finite for any pair of lungs and if this clearance capacity is exceeded particulate matter will accumulate with progressive diminution of the ability of the lungs to effect clearance. The precise mechanisms whereby this clearance is effected need not concern us here. If the ideal working conditions were to be specified then the concentration of the toxic dust would have to be zero. Paul Gross's work suggests that something less ideal would produce an elimination of the dust hazard. The problem in asbestos mines is not quite as simple as in a factory using separated fibres for in the milling of the rock to separate the fibrous material it is inevitable that the inhaled dust consists of mixtures of varying proportions of crysotile fibre and mother rock. This complicates the picture of lung clearance of the dust. The capacity of the lungs to clear dust may depend solely on the particulate matter inhaled but there may be a differential clearance of the two constituents of the dust in the mills at the mines. A very small concentration of fibrous material in the inhaled air may be toxic because the clearance mechanism is choked by what may be of itself a non-toxic material (serpentine). The situation in the Quebec mining areas must be

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regarded as unique and the approach to reduction of the dust hazard cannot be a simply steady progress towards reduction of all dust. Some attempt must be made to assess the capacity of the lung to eliminate each of the two major constituents of the dust and to determine whether or not one or other constituent accumulates at a greater rate than the other under precisely controlled conditions. If this is to be done, as it must be done, on experimental animals, it will require a well planned programme of investigation which must take into consideration the work of those who have already studied the production of controlled dust clouds and the effect of these on experimental animals.

There is little doubt that such experimental work would influence and be influenced by the programme and the findings of the epidemiological survey proposed by Professor McDonald. It is all the more important therefore that in any organisation set up by the Q.A.M.A. some forum for discussion of work in progress between those engaged in all types of investigative work should be provided. The idea of a prospective and retrospective epidemiological survey has received unanimous approval at this meeting and it is to be hoped that it can be started as soon as practicable. I have the feeling that the development of future investigative work will take place naturally as the survey throws up problems demanding a solution. The survey will, I am sure, throw up many gaps in the information available but as these become apparent steps can be taken to remedy them. It is almost certain that the survey will demonstrate again the need for serial lung function tests on the mining and milling population so that incipient cases of asbestosis showing defects of lung function can be followed before these people show clinical signs and symptoms of the disease and before a charactaristic radiological picture is obtained. The development of "on-the site" centres for the study of pulmonary function seems to be inevitable though the practical difficulties are considerable. The training of competent technicians who can be entrusted to carry out the tests will require time but the results will become more and more rewarding as time passes.

The classical discipline of pathology using the optical microscope has presented us with a fairly complete picture of the typical changes which take place in the lungs as the asbestotic lesion is formed and developed. With the application of the electron microscope to this same problem a new dimension has been added - the ultra-structure and function of specific formed constituents of the cell itself. It is now possible to follow the development of a macrophage containing minute particles of crysotile into a fibroblast and to determine with accuracy where these particles are situated within the cell. The transformation of a motile cell-the macrophage-into a "fixed" cell which produces filaments of a collagenous material represents not only an alteration of cellular structure but the imposition of a complete new metabolic pattern resulting in the production of the complex protein-polysaccharide polymer known as reticulin or collagen. What is the mechanism which calls into being the set of enzymes responsible for this intra-cellular synthesis, and what part does the crysotile fibre play in inducing this change? Until these questions can be answered we shall not be

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in a position to state precisely how pulmonary fibrosis following asbestos exposure is brought about.

Various speakers have referred to the clear distinction between the pattern of fibrosis produced by silica dust and that produced by crysotile. None however ventured to explain this difference. I think most of us might have ascribed the fibrogenic properties of crysotile to the release of silicon dioxide units from the crystal structure of crysotile and that these units were the ultimate fibrogenic agents. I think most of us would be sceptical of this explanation for we would be faced with another more difficult problem. How does the crystal structure of crysotile disintegrate within the cell? Davis hasshown that it is possible to induce living macrophages in tissue culture to ingest sub-microscopic particles of crysotile and to see these particles lying free within vesicles of the cell sap (cytoplasm). These vesicles are called phagosomes and almost certainly contain fluid. It has been suggested that chemical substances can be secreted by the cell into the phagosomes and that these substances might disrupt the crysotile lattice. The possibility that small amounts of the disintegration products might diffuse back into the cell sap (cytoplasm) has been considered as the stimulus to the production of the fine fibrils of reticulin or collagen and thus effect the transformation of the macrophage into the fibroblast. Schlipkotter has shown that macrophages can take up fine particles of crystalline silicon dioxide and transform themselves into fibroblasts. The macrophages can also be induced to take up (as fine particles) a polymer called poly-vinyl-pyridine N-odixe. When the macrophage ingests silica alone transformation into a fibroblast takes place rapidly but if silica and the polymer are ingested at the same time the transformation does not take place. If instead of ingesting silica the macrophage ingests fine crysotile particles along with the polymer there is no inhibition of the transformation into a fibroblast. Clearly the ultimate fibrogenic substance of crysotile is not free silica units released from the crystal lattice as these would be "mopped up" by the polymer. The intriguing possibilities opened up by these experiments of Schlippkotter and Holt are obvious. Holt has gone further and shown that when silica goes into solution as orthosilicic acid it bonds with the polymer in such a way that the oxygen atom of the polymer links up with a molecule of ortho silicic acid and at the same time forces the polymer chain to expand and expose more oxygen atoms for linkage with the polymer. In this way a single molecule of the polymer can bind a very large number of orthosilicic acid units present in the reacting solution. If this is indeed the mode of action of the polymer within the cell phagosome we may assume that the silica units are not released as such from the crystal of crysotile or, if they are, some ion present in the crystal interferes with the oxygen bonding oy the polymer. It would appear that here is a tool which cannot fail to throw a flood of light on the nature of the fibrogenic action of crysotile. It may also open up the possibility of a therapeutic approach to asbestosis.

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I do not wish to discuss the problems of carcinomatous changes following exposure to asbestos dust for these are outside my province. The studies of Davis on biopsy material from a human case of mesotheliomatosis have shown certain structural peculiarities of the malignant cells whose significance is as yet unknown but which may in the future be of importance in attempting to eradicate such tumours. I mention this work only to draw attention to the need for securing fresh human material from persons exposed to asbestos dust and for examining this material by both the optical and electron microscopes. Only by using such material can the results of experimental work in animals be checked in man. The chances of obtaining human material either at operation or by biopsy in cases of exposure are not great but co-operation with thoracic surgeons can be secured and if only two or three specimens can be examined in a year the results are always rewarding to both the surgeon and the investigator.

I have been much impressed by the statements on regional differences in the incidence of pleural plaques between the two mining areas in Quebec. We know little or nothing about the reasons why the pleural tissues should produce thick layers of collagenous material nor do we know the cells responsible for producing it. Regional differences in the incidence of plaque formation and in the incidence of mesotheliomata are a challenge to a detailed study of the nature of the inhaled material and its fate within the body. There are many questions which could be asked but until details from the epidemiological survey are available to confirm that regional differences are significantly so, such questions would be irrelevant.

As I see it, the primary question which was posed by the Q.A.M.A. was to review the objectives of an organisation to be set up by the Association and then to advise on how best to achieve these objectives. I think the objectives are clear to all of us and may be summarised as "the reduction and elimination of any hazards to health presented by exposure to asbestos dust in the mining, milling and processing of asbestos". The hazards to health arising from exposure to asbestos dust can be divided into two main categories (a) impairment of pulmonary function due to changes in the ability of the diffusion membrane of the lungs to transmit oxygen and carbon dioxide and to structural changes within the lung which decrease its ability to expand and thus reduce the ventilating capacity of the lung, or which directly reduce the area of the diffusion membrane (b) cancerous changes in the lung and pleural (and possibly peritoneal) membranes associated with known exposures to asbestos dust.

The reduction and elimination of the health hazards are in the first instance an engineering responsibility but this responsibility has to be shared with those who are able to give guidance on possible danger spots for operatives and with those who keep a check on dust levels. Although hazards to health are known to exist within the mining communities in Quebec, the extent of the hazards has not been determined. Within a very short time from its initiation the epidemiological survey will be able to provide an approximation of the extent of the hazards which will come closer and closer to the true

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picture as time goes on. Moreover the survey will be able to determine whether the hazards vary from mine to mine (and associated mills). From such information it will be possible to take steps to reduce the hazards and possibly introduce a purely arbitrary standard to which the dust counts may be referred. It is almost certain that as time goes on attention will be paid as much to the nature of the materials contained in the dust samples and the relative magnitudes of each as to the absolute counts of dust particles. It would be irrelevant here to discuss techniques for dust counting though these will have to be as uniform as possible if the results obtained from the counts are to be of value to the industry as a whole.

Dust counting and dust control by themselves are of little value unless they can be of use to those directly responsible for the health of the workers in the industry. Improvements in the health of the individual worker or at least a diminution of morbidity rates invariably follows when dust levels fall. Periodical health examinations are essential after acceptance into the industry but these should include pulmonary function tests designed to discover if impairment of function has occurred and the nature of the impairment. The organisation should ensure that such tests are made in such a way that results from one site can be compared with those from another. This will demand the training of technicians by an agreed laboratory and the acceptance of the test results by the compensation authority.

It is impossible to set out in any detail the scope of any programme of research designed to obtain an insight into the nature of and causation of asbestosis or the cancerous changes associated with asbestos dust exposure. There is little doubt that the key to any programme of research is the discovery of the right person to carry out a specific project. The projects selected should be linked with problems of a fundamental nature which require attacks by more than one discipline. This is the best way to build up a team of men with a common objective and is in the end the most economical of men and resources. I am satisfied that it is essential to have full time workers supported by grants to them personally. These grants should be made in the first instance for a minimum period of two years renewable annually provided the organisation is satisfied with the progress made. The grants should cover not only a specific stipend for the research worker (which can be reviewed at intervals) but also the costs of technical assistance and laboratory expenses. Capital grants for equipment may be required from time to time but these should be considered on the merits of the case at the time and not included in the annual grant. Such equipment could remain the property of the organisation until it determines otherwise.

I have given already some of the lines of fundamental work which seem to me of importance at present. If these or any of them are to be followed it may be necessary to supplement the grant to the individual concerned to enable him to travel

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and work with those who are already working along these lines. Visits of this kind should be of sufficient length to ensure that the worker is able to master any new technique or better to work in collaboration on a problem for a sufficient time for him to make a significant contribution which can be published.

In emphasising the need to sponsor fundamental research I do so in the knowledge that the basic research of today is the applied science of tomorrow.