PROGRESS IN ETIOPATHOGENESIS OF RESPIRATORY DISORDERS DUE TO OCCUPATIONAL EXPOSURES TO MINERAL AND ORGANIC DUSTS

J.C. WAGNER, M.D., FRCPath

MRC External Staff Team on Occupational Lung Diseases
Llandough Hospital, Penarth, South Wales

INTRODUCTION

Thank you for giving me the honour of introducing the theme on progress of Etiopathogenesis of Respiratory Disorders due to Occupational Exposures to Mineral and Organic Dusts.

In the first place, I would like to say how pleased I am to follow Margaret Becklake in the setting of these themes. We both did our Graduate and Postgrauate training in Johannesburg which was the scene of the first of these conferences in 1930. Of course, we were both too young to attend.

Secondly, I have been given a vast field to cover in a very short time. I will paint with a very thick brush on a large canvas. I will concentrate on my personal experiences and views to offer a provocative base to the further sessions of this conference. I trust this will stir up sufficient controversy to satisfy our sponsors.

I note that my remit covers both mineral and organic dusts. On organic dusts my experience is brief—I do not believe that there is such a disease as byssinosis. The biological effects of cotton dust are part of the vast new field of study covered by the term "Industrial Asthmas," which is now a separate field from pneumoconiosis.

SILICOSIS

There are two facets of silicosis research in which we have developed new ideas since the 1930 conference. One is positive and requires explanation, the other I feel is a false lead which requires most serious scrutiny.

Although historical evidence goes back to neolithic times, it was in the industrial revolution that it was realized that exposure to mineral dust could have fatal consequences. By 1912 South African workers had shown that quartz was responsible for these lesions and by the Johannesburg conference it was proved that tuberculosis was the main killer of silicotics. The problem is how does silica do the damage and why is there this promotion of tuberculosis? My views are now considered simplistic and I hope that at a later stage of this conference someone will produce a more scientific hypothesis. I believe that silicosis is a disease of the monocyte macrophage system and the destruction of numerous macrophages by the inhaled quartz crystals produces a local milieu promoting infection from the mycobacteria when they are present. As far as I will go in explaining this are the studies of Tony Allison and Jack Harington. Briefly the quartz crystal is taken up by the macrophage forming phagosomes with the relevant lyzosomes which are released, but fail to digest either the quartz crystal or the wax coat surrounding the tubercle bacillus. The quartz crystal then by some means disrupts the membrane of the phagosome releasing the "enzyme soup" which destroys the macrophage: the unscathed quartz crystal is freed to destroy further macrophages and the bacillus to reproduce.

The other facet which disturbs me is the suggestion that quartz is an important carcinogen. We have as pathologists studied numerous cases of silicosis and exposed a vast number of animals to quartz dust. In all the human cases I know of where carcinoma does occur in silicotics it is either associated with cigarette smoking or much more rarely with radon release. In the experimental evidence only two series of experiments are quoted in which malignancy occurs. I am responsible for one of these studies and our results have been incorrectly interpreted. In 1960 I inoculated quartz into the pleural cavity of Wistar rats. Some of these rats subsequently died of tumour which were not mesotheliomas. In 1962 the experiment was repeated with two further strains of Wistar rats in which a much higher incidence of these tumours occurred. These tumours were subsequently studied by my wife who showed that these tumours were in fact histiocytic lymphomas of macrophage origin. She was unable to produce a significant number of these tumours by using different routes of exposure. It is unlikely in human exposure that silica would reach the pleural cavity.

The other study was carried out by Dave Smith at Los Alamos where Fischer rats were exposed to very heavy clouds of quartz and developed severe pulmonary fibrosis. Some of these animals subsequently died of peripheral carcinomata. These peripheral tumours occur in the animals with severe pulmonary fibrosis and these lesions are not specific for silica exposure.

COAL WORKERS PNEUMOCONIOSIS

When I first became involved in the study of coal workers pneumoconiosis I was informed that the disease could be divided into simple and complicated forms. The simple form did not cause disability; the complicated form did because

of the production of massive pulmonary lesions consisting of vast chunks of fibrous tissue. All these facts have been disproved. The majority of coalworkers do not develop any pathological change apart from having excessive coal dust blackening their lungs. About 10% of these then develop pulmonary nodulation, so at this stage the disease becomes "complicated," and with further exposure, these nodules tend to form vast coalescent masses if exposure is sufficient. The main disease in these men is not the nodulation *per se*, but the associated emphysema and interstitial fibrosis in some cases. In the massive lesions, the lumps are not fibrous tissue. In fact, the amount of collagen and pre-collagen amino-acids present in them is the same as in the non-involved lung tissues. Working with Dr. F. Wusterman of the Biochemistry Department of the University College of Wales in Cardiff and Professor P. McGee at Oxford, we were able to show that the main constituent of these lesions is fibronectin, a glycoprotein which occurs as 3% of the normal serum proteins.

ASBESTOS AND ASSOCIATED DISEASES

There are as we all know, a group of fibrous minerals that can be split longitudinally and have commercial uses. These are chrysotile, crocidolite, amosite, tremolite / actinolite and anthophyllite. The term "asbestos" was originally used for chrysotile. If this had been maintained and the other materials referred to as the amphibole fibres, the present confusion in assessing the risk hazard would not have occurred. In the amphiboles the risk hazard depends on the ultimate length diameter ratio of the fibre and this has been clarified with the studies of the biological effects of tremolite, an amphibole with a widespread occurrence in the earth's crust, usually as a contaminant of chrysotile, talc, anthophyllite, and other minerals. It also occurs in small deposits and is frequently used all over the world as a soil conditioner in agriculture.

The physical features of tremolite vary in all forms from thick flakes to very fine fibres. The electron microscopic appearance of some fibres is shown. Under the transmission electron microscope it can be seen that the finest and straightest of the fibres is crocidolite followed by amosite and the coarse anthophyllite. Now tremolite covers this whole spectrum. By far the finest of all fibres are chrysotile fibres particularly when they break up into fibrils, one chrysotile fibre having the equivalent diameter of at least 100 chrysotile fibrils. However, due to the coiled wave-like configuration the aerodynamic efficiency of chrysotile depends upon that of the full coil. Before venturing into an account of the biological effects of these different fibres, it is necessary to state the hypothesis of selective retention of fibres in the lungs. This contends that it is the fibres retained in the lung parenchyma which are significant in the causation of the disease.

Now I will briefly state our belief in the correlation of disease with fibre type. I am sure this will be contended and defended during this conference.

Asbestos Bodies

Asbestos bodies develop around amphibole and other straight mineral fibres and are seldom on chrysotile fibres.

Pleural Plaques

All types of asbestos are associated with development of pleural plaques particularly tremolite, amosite and anthophyllite. The incidence of environmental plaques is extremely high in agricultural situations and these are usually associated with tremolite.

Asbestosis

All forms of asbestos dust if inhaled in excessive quantities will cause asbestosis.

Carcinoma of the Lung

Initially carcinoma of the lung occurred in people with severe asbestosis with long term survival. Since the 1950's the incidence of carcinoma of the lung has greatly increased due to the association with cigarette smoking. We still contend, and will present supporting evidence, that the association is between cases of definite asbestosis and carcinoma.

Diffuse Pleural Mesotheliomas

Diffuse pleural mesotheliomas are associated with exposure to crocidolite, very fine tremolite, very fine amosite; and if associated with pure chrysotile this must be an extremely rare occurrence. These associations have been occupational, para-occupational or familial.

In 30% of cases of diffuse mesotheliomas in adults, there is no evidence of an association with actual asbestos exposure as defined above. The amount of asbestos in the lungs of these cases is similar to that seen in the the general population living in the same environment.

Diffuse Peritoneal Mesotheliomas

These tumours are not as common as those originating in the pleural cavity.

Experimental Mesotheliomas

We have produced these tumours by the intrapleural inoculation of various types of asbestos dust, including chrysotile. In the majority of the chrysotiles used there was tremolite contamination. The exception to this was the chrysotile that gave the highest rate of experimental tumours. This was a specially prepared preparation containing numerous long straight fibrils and the actual dosage was at least one thousand million times greater than occurs in human exposures. When we used this dust in an inhalation study the tumour rate was similar to that seen in the controls.

Significance of Fibre Body Burden

Chrysotile

Chrysotile fibres are difficult to count as they tend to form clumps, and fibres break up into a myriad of fibrils, so that amphibole fibre is equivalent to about 100 chrysotile fibrils. The present opinion is that exposure to chrysotile has a much milder effect than the amphiboles, and that the association with mesotheliomas is minimal.

Amphiboles

The total amphibole count, a mixture of fibre types, with different length and diameter, can be used in the assessment

of effect, taking 5×10^6 fibres per gram dried weight of lung as the absolute upper limit of non-occupational exposure.

In significant asbestosis there are 100×10^6 fibres and in severe asbestosis 1000×10^6 fibres.

Significant Fibre Size

Mesotheliomas Diameter <0.25 µm, length >8.0 µm
Pulmonary Fibrosis Diameter <3.0 µm, length >8.0 µm

Diffuse Mesotheliomas

Crocidolite—1 million fibres probably minimal but there have been familial cases with counts of 500,000.

Other Amphibole Fibres

Again, only fibres in the size range of less than 0.25 µm and greater than 8.0 µm in length are regarded as significant. The tremolite and amosite are probably equivalent to crocidolite.

It must be borne in mind that these studies are in a developmental stage and the criteria recorded above are those of our present state of knowledge. Further modifications will be reported as the studies continue.

The number of fibres recorded as millions per gram weight of dried tissue depend on the technique developed by Fred Pooley in Wales in collaboration with Patrick Sebastien in France. There have been modifications of their methods which I understand can be made comparable in some circumstances.

MAN-MADE MINERAL FIBRES (VITREOUS)

I have used the above title deliberately as we have only undertaken extensive studies on samples of rockwool, slag wool, glass wool and sub-micronic glass fibre. I am not in the position to report on detailed studies of the other synthetic fibres such as the ceramic fibres; but hope that later in the conference others will give reports.

In our extensive studies with fibres given to us by both European and American industries, we were only able to produce significant tumour incidents following the intrapleural inoculation of the sub-micron glass fibre. No increased incidence of tumours or significant fibrosis was seen following inhalation experiments.

It should be recorded that in the numerous specimens of lung extracts from tumours that Professor Pooley has studied, only a handful have contained commercially prepared man-made mineral fibre. If the material does not get retained in the lung it is unlikely to cause disease.

ABSORBENT CLAYS

These clays are part of the palygorskite group and are used for cat litter and containing spills on factory floors. Another use is in the preparation of drilling mud for the oil industry. Our detailed studies have been confined to the attapulgite and sepiolite produced in Spain. In our experimental studies only fibres from a small deposit in western Spain were shown to be of a length/diameter ratio to be regarded with suspicion. These fibres produce mesothelioma following intrapleural inoculation into rats. On our advice, the production of this fibre has been discontinued. Other attapulgite fibres and sepiolite fibres did not produce tumours following both intrapleural and inhalation studies. Later in this conference Dr. Kathryn McConnochie will report on a clinical and radiological study of the workers who produce the sepiolite.

ERIONITE

The most fascinating new development in the fibre studies are those on erionite. We all know of Professor Baris' fascinating studies in which erionite was shown to produce a higher incidence of mesotheliomas than any other fibre.

From our experimental studies we obtained fibres from one of the houses in Karain and also from other sources in Oregon State and following intrapleural inoculation it was shown that the sample from Oregon produced 100% tumours and only a slightly lower rate was found in the dust from Karain although it had a lower fibre content.

In inhalation studies the Oregon fibre produced mesotheliomas in 27 out of the 28 animals exposed, 1 animal dying of leukaemia. In repeated experiments tumours rose to 100%.

In comparison to this in our much larger experiments in which animals inhaled asbestos dust, we were only able to produce a very low incidence of mesotheliomas.

Therefore, as I retire from this field, I leave you with a fibre which is a very potent carcinogen and must be of value in unraveling the mineral fibre mesothelioma mystery.

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ADIEU!

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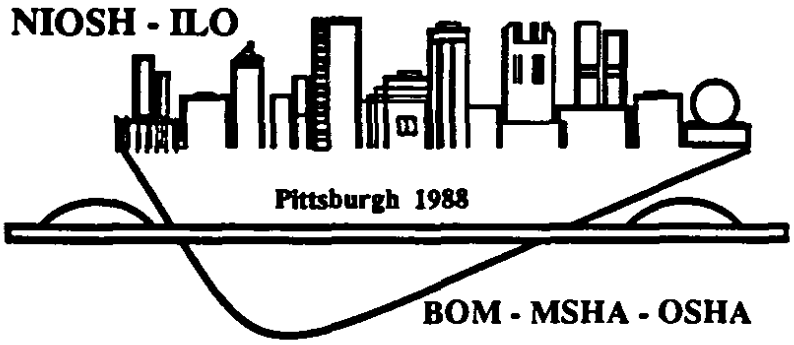

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