An Address

ON

OCCUPATIONAL AND OTHER CAUSES OF
PULMONARY FIBROSIS.DELIVERED TO THE NORTH OF ENGLAND BRANCH OF THE
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BY

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Four years ago I gave to this Branch a demonstration of the pathological changes met with in fibrosis of the lungs caused by inhalation of dust by men following certain occupations, such as that of ganister mining and crushing, also by gold-miners who had worked in the Transvaal. I now wish to extend my remarks by drawing attention to other forms of illness during or after which, if the patient survives long enough, structural changes occur in the lungs, whereby they lose their spongy character, and, instead of remaining air-filled and elastic organs, they become semi-solid and unable to retract.

In order to appreciate what is meant by pulmonary fibrosis it is well to visualize a type of lung consolidated by an excessive increase of fibrous tissue, such as the lung of a gold-miner who has died of the malady. It was during and shortly after the close of the South African war that men who had previously been coal-miners in the Northumberland pits, and who had gone seven or eight years previously to South Africa, attracted thither by the high wages, were returning home with well lined purses, but, alas! only too frequently to die within a year or two of silicosis, caused by inhalation of dust given off during drilling of the rock in the mines of the Transvaal. As I was consulted by many of these men, they supplied me with the experience which formed the basis of my paper, entitled "Gold-miner's phthisis," published in the *Lancet* in 1902. Some of the men looked rather bronzed and weather-beaten, but the one particular circumstance which caught my attention was the marked dyspnoea which even the slightest exertion induced. On getting up from one chair in my consulting room to move to another, or on taking a few paces in the room, the breathing became short and difficult, so that the patients were glad to sit down and rest. I was impressed, too, by the marked reduction of their respiratory capacity. In many of the men, instead of there being a difference in chest measurement of two to three inches between inspiration and expiration, it was frequently only one inch. Here and there in the chest small areas of dullness were appreciable, especially towards the bases. The respiration was deficient in places, while over other portions of the lungs there could be heard small bronchial râles; but whether râles were heard or not the dyspnoea was always in excess of the physical signs.

If it was a miner whom I was examining in the early stages of the illness, few physical signs might be detected; probably the patient had lost weight, and was the subject of cough as well as of shortness of breath. In the early stages expectoration was not abundant, and on microscopical examination it was found to be free from the presence of tubercle bacilli. In some instances the illness pursued its course to a fatal termination without the lungs becoming tuberculous, as confirmed by *post-mortem* examination. The lungs would be found greyish-black in colour, hard to the touch, stonyhard in fact, and giving rise to a gritty sensation on being cut with the knife. In the lungs of many of the men there were no signs of cavity, large or small, so that silicosis in its inception, and all through its duration, can be, and frequently is, a non-tuberculous disease. Some of the patients subsequently became tuberculous, and this was indicated by a rise of the evening temperature, by sweating, increase of cough, and expectoration in which tubercle bacilli might be found. When the malady had progressed to a further stage, the breathing would be found to have become still shorter; occasionally haemoptysis occurred, or the expectoration would be slightly streaked with blood; the expansion of the chest tended to become

more restricted, owing to extension of adhesions between the bases of the lungs and the diaphragm; dullness on percussion increased in area; moist râles became more abundant, and as digestion became impaired the general health declined correspondingly. On x-ray examination of the chest mottling of the lung in places could be detected.

It is interesting to compare the lungs of coal-miners with those of men who have followed such dusty occupations as ganister mining and crushing, also gold-mining. Ganister is a siliceous clay which is made into bricks for lining iron and steel furnaces, since the bricks are capable of withstanding enormously high temperatures. Of the various kinds of dust inhaled by workmen, that which contains silica is one of the most dangerous. Formerly it was taught that the injury inflicted upon the lung and which ended in fibrosis was the result of the physical action of the particles of dust. Since many of these are sharp-pointed, it was believed that during inhalation these were carried beyond the protective barrier of ciliated epithelium, much of which had probably disappeared as the result of recurrent catarrh, and having reached the small bronchi and the pulmonary alveoli they inflicted damage of a purely physical character. This is no longer regarded as the complete explanation. Professor Haldane of Oxford and Mavrogordato have shown by their experiments that when fine particles of soft coal are inhaled these are met by a reactive resistance on the part of the bronchial mucous membrane and the pulmonary alveoli, during which the large wandering cells lying in the alveoli, or on the inner surface of the minute bronchioles, take up the carbon particles, and as these cells are phagocytic in their function and are subsequently passed up into the bronchi, many of the carbon particles which have been inhaled are in this manner eliminated. Silica dust, on the other hand, is not readily soluble, nor are its particles easily phagocytosed; they penetrate into the lymphatics of the lungs and are carried to the glands at the hilum, or they induce pulmonary fibrosis. Although silica dust is very insoluble, yet Gye and Kettle have demonstrated that silica may become soluble in the lungs, and that the dissolved material is equally capable of acting harmfully upon the pulmonary tissue. The injury thus inflicted upon the lungs would be, according to this theory, not the result of the physical but of the chemical properties of the dust.

There still remains, however, the probability that the inert or undissolved particles of silica also play a considerable part in inducing inflammatory reactions in the lungs, and this raises the question as to how far the size of the particles can be regarded as contributing to the subsequent structural changes. On examining microscopically a section of a silicotic lung, the fibrotic portions appear as if they had been peppered with very fine dust. By means of a micrometer the size of these particles can be estimated: they are measured to one-thousandth part of a millimetre, the unit being known as a micron (μ). Pathological research in this country has shown that the larger number of particles present in the lungs are below 1 micron, and seldom above 2, although they may sometimes measure 10 microns or more. It would therefore appear as if it was the particles below 2 microns which are the most dangerous, so that while a man may be working in a thick atmosphere heavily laden with dust, readily visible to the naked eye, yet if most of these particles are above, say, 50 microns, there is less likelihood of this dust causing silicosis than an atmosphere in which the particles are smaller than 2 microns in dimension. It is these which, when inhaled, overlap the protective epithelial barrier in the larger respiratory passages and reach the lungs.

During the time I was following up the subject of Rand miner's phthisis from the clinical point of view, it was my wish to become practically acquainted with, as nearly as possible, the conditions under which gold-miners had been working. Accordingly I visited the tin mines in Cornwall, where rock drilling was much in use. The Cornish mines are much deeper than the coal-mines in the North of England, and the rock is harder. Along with an under mine manager, a working miner, who was an experienced rock driller, and the doctor, I went into a mine wherein we crawled through an opening into a chamber from which a certain amount of ore had already been extracted. After

we had squatted as best we could the rock drilling was begun. In a few minutes the atmosphere became so thick that breathing was, to those of the party unaccustomed to dust, somewhat uncomfortable and difficult, and although we were all squatting closely together we could not see each other. Even the glare of our lights could not penetrate the dusty atmosphere. In addition, as no air was circulating through the chamber, the temperature became uncomfortably hot. Subsequently we removed ourselves, as best we could, from the confined space, and travelled into one of the main ways where the air was clear and cool. We inspected other sections of the mine, and in two hours returned to the place where we had witnessed the rock drilling. By this time the dust had considerably settled and the air had become comparatively clear.

We were now to have the opportunity of seeing automatic water spraying carried on simultaneously with the rock drilling. The difference between the two operations was remarkable. Instead of the atmosphere becoming thick and dusty, and the temperature raised, the air remained clear, the temperature low, and we could not only see each other quite well, but could converse without difficulty. As to the utility and efficacy of water spraying during rock drilling there can be no doubt; but while water spraying lays dust, many of the finest particles may yet rise into the atmosphere with the spray, and although these particles may not be visible, yet it is they which, when inhaled, harmfully affect the lungs.

One of the dustiest industrial operations I have seen is asbestos crushing, carding, and grinding. Some of you have probably not seen asbestos in its native condition. It is an extremely hard rock with small white fluffy fibres attached to it, almost like finely frayed cotton wadding, and therefore suggesting vegetable origin, but it is really a mineral substance. The rock is crushed in closed machinery, but much fine dust and fibre escape into the workroom. From the finely comminuted pieces of stone the fibre is separated by a mechanical process of teasing, so that the material as it passes away from the machine looks like raw cotton, only the fibres are loose and not so adhesive. During these processes the atmosphere of the workroom is quite cloudy; the hair and clothing of the men become covered with white fluff. Even by brushing I had difficulty in removing the material from my clothes. After having been teased, the material is passed through carding machines, so as to transform it into a cord-like structure; this is subsequently spun or is woven into the flat plaques of asbestos with which all of you are familiar. I was rather surprised when the manager of the works informed me that the men never suffered from respiratory troubles. That such existed I had not the slightest doubt. In the *BRITISH MEDICAL JOURNAL* of July 26th, 1924, this was definitely shown by Dr. W. E. Cooke of Wigan in an interesting article entitled "Fibrosis of the lungs due to the inhalation of asbestos dust." So far as I know his is the first paper on the subject in the English language. Dr. Cooke informs us that asbestos contains, amongst other compounds, calcium and magnesium silicate, and 40 per cent. of SiO_2 or silica. The mineral fibre is translucent, except at the fractured ends, where it is blackened. The patient whose illness and death supplied the basis of Dr. Cooke's information was a woman, aged 33, who had worked in asbestos factories since the age of 13—that is, for twenty years. Between 1917 and 1922 she had remained away from the factory, but subsequently she worked at intervals, and died in March, 1924. An x-ray plate showed extensive fibrosis with calcareous glands at the root of the lungs. On section the right lung was found to be fibrosed and airless; there was a large cavity in the apex and the pleura was thickened. The left lung was adherent and its pleura in places was also thickened; this lung too was considerably fibrosed. On microscopical examination fibrotic changes were very marked; around the caseating areas in the lungs giant cells and tubercle bacilli were found. The case was therefore one of silicosis accompanied by tuberculosis, the tubercle having been a later development, for Professor J. M. Beattie of Liverpool, whose research work on dust and pneumoconiosis is well known, has experimentally produced fibrosis in animals by causing them to inhale asbestos dust.

While mineral dust is a frequent cause of pulmonary fibrosis, the structure of the lung can be similarly altered by micro-organisms or their toxins in such diseases as tubercle and syphilis. Upon some of the less well known associations of these I should like to say a few words. In silicosis the pathological changes occur around the minute bronchi and within the alveolar septa. A little while ago my attention was drawn by Professor Stuart Macdonald to fibroplastic changes which had taken place in the lungs of one of my patients who had died from croupous pneumonia, but therein, and differing therefore from what occurs in silicosis, the initial changes had commenced within the exudate in the alveoli, and were rapidly leading to organization. In some of the alveolar spaces wherein the exudation had become softened, and partly removed by absorption, the leucocytes which had continued to be healthy and active were becoming transformed into fibroblasts, and these, becoming superimposed, lined the interior of the alveoli, and were gradually obliterating them. Had my patient lived long enough there would probably have occurred real fibrosis of those portions of the lung which had been during life the site of croupous pneumonia. This, I admit, is rather an uncommon sequel of pneumonia, for the exudate is usually absorbed, and the lung regains its previous resiliency.

In syphilis a similar thickening takes place; there may be gummata or diffused interstitial fibrosis. In the diffused form there is hyperplasia of the connective tissue. The alveolar walls become thickened, dense masses of fibrous tissue are formed in which the remains of compressed alveoli can be detected, and the walls of small blood vessels are thickened.

Influenza and Pulmonary Fibrosis.

A year ago Dr. Bernard Shaw gave an interesting demonstration, illustrated by lantern slides, of the relationship between influenza and pulmonary fibrosis. After showing how rapidly the epithelial lining of the small bronchi and the alveolar walls becomes destroyed in influenza, he indicated that just as rapidly were reparative processes taking place with, as a result, occlusion of several of the minute bronchi; the alveolar walls, too, were thickened by organization of fibroblasts; newly formed capillaries also could be observed extending into the leucocytic exudate whereby this material became changed into granulation-like tissue. There thus occurs early in some forms of influenza a rapid tendency to the development of pulmonary fibrosis.

In almost a similar manner the bronchopneumonia which accompanies measles is followed by an increase of the interstitial tissue of the lungs. This is the case in children, and is frequently the explanation of the lung troubles from which they suffer in later years. During the recent war similar changes were observed in the lungs of several of the United States soldiers who had been drawn from the agricultural areas. These healthy men when housed in barracks and overcrowded buildings, during their military training, became an easy prey to measles. Many of the men succumbed to the accompanying bronchopneumonia, and in their lungs fibrotic changes were found to have already taken place.

There is a growing opinion that a silicotic lung is more liable to become affected by tubercle than a non-silicotic. It would almost appear as if a larger percentage of gold-miners affected by silicosis had during recent years become more liable to pulmonary tuberculosis than three decades ago. It may be that the men had been brought into more immediate contact with infection than previously. In a well marked case of dust disease of the lungs the fibrous tissue is hard and thick, and it hardly seems to offer favourable conditions for the reception and multiplication of tubercle bacilli. But while certain portions of lung are fibrosed other portions are the seat of bronchial catarrh, so that it is possibly in those portions of the lung that the tubercle bacillus finds a suitable nidus for its development.

The causes of pulmonary fibrosis with which we have been concerned have in the main operated from within the alveoli inwards—that is, towards their interstitia. Frequently the operative agent has been inhaled dust,

or it has been the presence of toxins in the exudate acting upon leucocytes therein and converting them into fibroblasts.

In my visit to Harvard University a little over a year ago I was extremely interested to learn from Dr. Drinker of some experiments he had been carrying out in regard to pulmonary fibrosis. It had occurred to Drinker that since fibrotic changes in the lungs are the result of inhaled dust having penetrated the alveolar wall and induced irritation of the interstitial tissue, possibly a similar chain of events might take place if particles of insoluble dust were injected into veins not far distant from the heart. Accordingly Drinker injected into the veins of animals extremely minute particles of manganese silicate, and he found that structural alterations were established in the lungs. Since my conversation with Dr. Drinker I have carried out a series of experiments on the Harvard lines, but instead of using manganese silicate I employed finely powdered bauxite, an aluminium ore. This was conveyed into the auricular veins of rabbits, and after a series of injections conducted over a few months we found in the microscopical sections of the lungs, kindly prepared for me by Mr. John Secker of the Physiology Department, large phagocytic cells lying within the alveoli and laden with dust particles, similar cells surrounded by mucus passing outwards by the small bronchi, and the same type of cell in the spleen. Until the series of experiments which I am at present carrying out is concluded, it is somewhat difficult to explain the presence and escape of the phagocytic cells alluded to. They are not leucocytes in the ordinary acceptance of the term. When an injection of finely divided particulate material is made into the veins of an animal not far from the heart the particles are carried along in the blood stream, and as the pulmonary capillaries are those through which, after leaving the heart, they would primarily pass, several of the particles are probably taken up by the endothelial cells. From the size and shape of the phagocytes found in the pulmonary interstitia and alveoli, also in the minute bronchi, the probability is that they are endothelial cells which have broken off from the pulmonary capillaries, and that they were fulfilling their function of eliminating foreign material from the blood. Their presence in the splenic pulp is similarly explained.

PROLONGED MENINGOCOCCAEMIA WITH TERMINAL MENINGITIS.

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THE following record emphasizes the importance of searching for the meningococcus in obscure cases of pyrexia, particularly of an intermittent type.

The patient was a man of 57, an engine fitter, who had been unusually healthy. For thirty-four years he had not lost a day's work; he lived comfortably, and was a teetotaler. About the beginning of May, 1924, he had an attack of so-called "influenza." It commenced abruptly with shivering and fever, but he had no headache or other pain, and no catarrh or pulmonary symptoms of any kind. He had some vomiting, and in a day or two slight diarrhoea came on, which lasted only a few days. Weakness was really the principal symptom. The fever was not continuous, but he had rigors at odd times, apparently almost daily. He was in bed for eight or nine weeks. He was up for about a fortnight before he was admitted to Ward 32, but could hardly walk because of weakness, and he had lost nearly 3 st. in weight. He came into the infirmary on July 8th, 1924.

His only symptoms were weakness and loss of appetite; the appetite returned after a few days in hospital. Physical examination gave entirely negative results, and need not be detailed. All the systems were normal for a man of his age, and remained so throughout. The spleen was not enlarged at any time. For the first two days the temperature remained

normal; on the third day it went up with a slight rigor, but only to 100° F., the next day to 101°, and on that day his white count was found to be 10,400. Throughout the illness this leucocytosis with polymorph increase persisted; the highest figure reached was 29,100, a month later.

From this time onwards there was, in the way of symptoms, nothing but increasing weakness. The temperature followed a most erratic course; on some days, and sometimes for two or three days together, there would be only a slight rise, say to 100° F., on others, coming singly or in small groups, rigors, when the temperature ran up for a short time to, say, 103°. These occurred at any hour of the day or night; between times the temperature was generally subnormal. From August 26th to September 9th the rigors occurred daily, and were more severe; the temperature was higher, reaching 104° or over on most days. The pulse rate varied strictly with the temperature: when it was subnormal the pulse was in the 60's, when it reached 104° it often ran up over 120. In the same way the respiration rate varied from 20 to 32.

Throughout this period everything we could think of was investigated in the hope of getting some light. The chest was x-rayed, with negative results; the urine was examined daily and was always normal. Though the persistent leucocytosis made enteric or malaria unlikely, the blood was subjected to the Widal test for the usual organisms, with negative results, and examined constantly for plasmodia, equally unsuccessfully. The spirochaete of rat-bite fever was sought in vain; the patient denied ever having been bitten by any animal, and it was only about ten days before his death that his wife remembered that about the middle of April he had been badly scratched on the back of the hand by a "wild" cat that lived by rat-catching. This led to several intravenous injections of novarsenobillon, without improvement. The Wassermann test was negative in both blood and cerebro-spinal fluid, and the latter showed no increase of cells and no organisms on culture. The first blood culture, in July, gave a growth of staphylococci and Gram-negative diplococci. As the staphylococci were almost certainly a contamination, it was thought the diplococci might be so also; but the observation was repeated a few days later and they were found alone, and again on August 12th. A blood culture was not made again till September 8th, and then no organism of any kind was found. Cultures were taken from the urethra, but no diplococci were found.

About September 9th meningeal symptoms began to develop—headache, head retraction, drowsiness, and incontinence of urine and faeces. The temperature was more continuously raised, seldom dropping to normal, but never running above 101°; usually it was about 100°. The rigors ceased. The patient gradually became weaker, emaciated very rapidly, grew more drowsy, and died suddenly on September 16th.

The first lumbar puncture to yield positive results was made on September 11th. The fluid was definitely under pressure, was turbid, and microscopically showed many polymorphs and large lymphocytes. In some parts of the films diplococci were found, practically all intracellular, and always in the large lymphocytes, never in the polymorphs. The same diplococcus which had been found in the blood was grown from this fluid. As lumbar puncture gave relief it was repeated daily. On the 12th the cell count was 5,800 per cubic millimetre. In the later punctures the fluid became clearer.

Post mortem a certain amount of bronchitis and hypostatic congestion of lungs were found. The heart was practically normal; very slight atheroma in the aorta; liver normal, except for some cloudy swelling and perhaps fatty degeneration; spleen not enlarged, apparently normal; cortex and medulla of both kidneys slightly narrowed; other organs all normal except the brain. The pia arachnoid showed areas of localized thickening in various parts, chiefly towards the base and over the cerebellum. These were evidently patches of meningitis, and on section microscopic examination confirmed this view. There was a marked exudate, with numerous polymorphs; slight excess of cerebro-spinal fluid, with slight dilatation of the ventricles internally, but the brain substance was normal.

Cultures made *post mortem* from the heart blood, spleen, and liver remained sterile, but the organism was obtained from the exudate at the base of the brain.

The Micro-organism.

The diplococcus, when first obtained from the blood stream, resembled a meningococcus in its cultural characters, save that it grew more readily on ordinary media than do most strains of meningococcus. On plain agar slopes it grew well, even when inoculation was not particularly heavy, and when no accessory substances could have been carried over from the original medium. Growth on glucose ascitic fluid agar (Thomson's) was profuse. After subculture for some time it lost this readiness of growth to some extent, and finally became indistinguishable culturally from type strains of meningococci, so far as readiness of growth on various media was concerned. Morphologically, it was indistinguishable from the meningococcus or gonococcus.

Its fermentation reactions were those of the meningococcus; it produced acid in glucose and maltose, no change in lactose, saccharose, and salicin. The gonococcus does not ferment maltose,