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PULMONARY ASBESTOSIS.

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and lassitude. The physical signs in her chest were those of fibrosis of the right lung. In July, 1922, signs of cavitation were noticed, the sputum became more profuse, with sweats and irregular temperature, and she died on March 14th, 1924.

An x-ray plate showed extensive fibrosis, more marked in the right lung, two calcareous glands at the root of the left lung, and two small calcareous particles in the base of the left lower lobe.

Microscopical Appearances.

Right Lung.—The pleura is thickened over the entire surface of the lung, and shows the remains of dense adhesions to the chest wall and pericardium. The lung is firm and small. The glands at the root of the lung are large, and on section are black, show a thickened capsule, and some calcareous particles. On section, the lung is seen to be fibrosed and to a large extent airless, the lung tissue being replaced by fibrous tissue. Dense strands of fibrous tissue from the pleura intersect the lung. In the apex there is a large cavity, the size of a peeled tangerine orange. The middle and lower lobes show numerous small areas—varying in size from a hazel-nut to a pin's head—of caseation, some of which have proceeded to cavitation. The bronchi are dilated.

Left Lung.—The pleura is thickened and shows the remains of adhesions to the chest wall. The thickening and adhesions are not so marked as in the right lung. The lung is firmer than normal. At the root of the lung are two large calcareous masses, one the size of a large hazel-nut, the other about half that size—calcified tuberculous glands. The other glands are black and show peridontitis. In the left apex there is an area of old scar tissue about the size of a sixpenny piece, and a cavity the size of a walnut. Scattered throughout the lung are small areas of denser consistence than the rest of the lung, some of which show definite calcareous particles, others small areas of caseation. There is a considerable increase in the fibrous tissue.

Three outstanding features are presented by sections from this case. The first is the enormous amount of fine granular pigment in the peribronchial fibrous tissue, walls of alveoli, and in phagocytes scattered through the sections. The particles of this dust are similar in size and shape to the black granules seen in the asbestos fibre.

The second unusual feature is the presence of large solid angular particles (Fig. 2). These are situated in areas of fibrosis and in caseating areas. They vary in size from 3 to 360 microns in length. The particles are so large—masses of them are seen in certain areas—that they must have occluded small bronchi. Fibrosis of the alveoli supplied has taken place and later necrosis, as seen in Fig. 3.

We have never seen anything parallel to this in pneumoconiosis due to other dusts, nor have we been able to find such occurrence in literature. On comparing these large particles with asbestos dust there is a striking resemblance in sizes, shapes, and colour. In fact, it is very easy to take each single particle found in the lung sections and immediately find its brother in a slide made from the dust.

We cannot think there is any reasonable doubt that the particles in the lungs are the heavy, brittle, iron-containing fragments of asbestos fibre. The more extensive involvement of the right lung is thus explained. The heavy particles would pass more easily down the more vertical right bronchus than the horizontal left bronchus.

*HISTOLOGY OF PULMONARY ASBESTOSIS.

BY

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(With Special Plate.)

My remarks are confined to the histological appearances in the lungs in this condition, with special reference to certain foreign bodies of most unusual appearance which are present both in the alveoli and interstitial substance of the lungs. The observations are based almost entirely on material supplied from the case described by Dr. Cooke. The investigation has been conducted in the pathological department of the University of Durham College of Medicine.

I may state, however, that the appearances are practically identical with those observed in a second case of this condition, sections of which I have had an opportunity of examining through the courtesy of Dr. I. M. D. Grieve of Armley, Leeds.

Histology.

Numerous sections have been made from both lungs. The changes are more marked on the right side, but the

appearances in the two lungs only differ in degree. They may be summarized as follows:

1. There is well marked diffuse interstitial pneumonia with chronic bronchitis and some emphysema.
2. There is well marked anthracosis.
3. There is an extensive tuberculous condition with chronic phthisis.
4. In the alveoli, bronchi, and bronchioles, and also in the interstitial fibrotic areas, are certain foreign bodies which will be described in detail later (Fig. 7).

As this communication deals specially with the nature of the foreign bodies, the general histological features will be dealt with very briefly.

The interstitial fibrosis is such as might be expected as a result of a combination of a pneumoconiotic condition and a chronic tuberculous infection. The typical whorled formations seen in a more purely silicotic condition are not present. There is a marked endarteritis in the smaller branches of the pulmonary arteries; some are thrombosed and organized. Many of the smaller bronchi are obliterated; some have still caseous-looking centres. Some of the alveoli show the usual metaplasia of their lining cells into cuboidal form. The fibrosed and thickened walls of the bronchi in many places gradually merge into the areas of diffuse fibrous overgrowth. There are numerous foci of lymphocytic cells among the fibroblasts. Some of these seem obviously derived from lymphoid tissue in the bronchial walls. The interstitial fibrosis is progressive. The tuberculous condition is obvious histologically. Tubercle bacilli were not detected, but the histology is characteristic. The lesions are chronic in character, and there is no special indication of an acute exacerbation. There is well marked caseous bronchitis with lymphatic spread and numerous fibro-caseous deposits with giant cell systems (see Fig. 8). The bronchi, which are not specially the seat of tuberculous change, show catarrh with peribronchial thickening. There are numerous emphysematous areas. The alveoli show, in the majority of cases, some thickening of their walls, and contain many catarrhal cells, apparently derived from the lining cells; a similar catarrhal change is seen in the terminal bronchioles, some of which are dilated.

The Foreign Bodies.

The larger black and irregularly fragmented bodies which have been described by Dr. Cooke were not very obvious in the material I examined, but were clearly seen in some microscopical preparations of his which I had the opportunity of examining. I shall not refer to them specially, but confine my attention to certain highly characteristic and much smaller bodies which are abundant in all the sections examined. Some of these are free, but many are phagocytosed by the large mononuclear cells in the alveoli (Fig. 5). Some are easily included in comparatively small phagocytic cells, but the majority are larger, varying in size from 20 μ to 70 μ , or even more in the case of certain elongated forms. The smaller bodies are rounded and homogeneous, and all have a distinct yellowish-brown colour suggesting blood pigment. The longer forms have a highly characteristic appearance, strongly suggestive of some organic structure. Most have an annular appearance, which on closer examination can be resolved into a closely set series of rounded discoid bodies (Figs. 4, 5, 10, and 11). In some cases the globular forms are arranged along the more filamentous forms and occasionally are clustered at the ends of the rods, simulating sporangia of a hyphomycetes (Figs. 5, 6, 10, and 11). Some have club-like extremities at one or both ends of the filaments. Others, again, suggest the appearance of minute crustacean forms (Fig. 10), but closer examination does not support the idea of either vegetable or animal origin. These bodies do not stain with the ordinary aniline stains, but preserve their original yellow-brown colour. They are seen well in unstained sections. They give a characteristic prussian-blue reaction with potassium ferrocyanide and dilute hydrochloric acid. The reaction is not so obvious unless the solutions are slightly warmed. Where the bodies are too large to be phagocytosed by individual cells they tend to become surrounded by plasmodial masses. Many of the phagocytes contain much carbon pigment in addition. Though these bodies are mainly found in the alveoli and

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debility, shortness of breath, and cough. At present she has no expectoration; her respiratory capacity is one inch. Although the apices of both lungs in front are resonant, there is distinct flattening of the percussion note at the apices. The respiratory murmur at the apices and mid-lung is coarser than usual, and the expiratory murmur is prolonged. At the right base the respiratory murmur is feeble, and small dry friction sound is heard. Towards the base of the left lung and extending into the axilla are heard small moist tinkling sounds, suggestive of cavitation having taken place; here also small friction sounds can be heard. Similar physical signs prevail posteriorly. The apex beat of the heart is displaced upwards and outwards; it is felt external to the nipple, a circumstance which, combined with marked accentuation of the second sound of the heart heard over the pulmonary artery, suggests that fibrotic changes have already occurred in this lung. Although the patient states that she has no expectoration, this was present six weeks ago, and when examined was found to be free of tubercle bacilli. There is no enlargement of the external glands.

The other patient, aged 39, has been an asbestos worker for eighteen years. She had no illness until four years ago, when she developed cough and attacks resembling bronchial asthma. After remaining away from the factory for three months she returned to her employment, and followed the occupation for three years, when she married, and as in the early months of her pregnancy she lost considerably in weight she retired from the factory. Although reduced considerably in weight, and the subject of cough all through her pregnancy, her infant daughter, who is 14 months old, is healthy and well developed.

The patient complains of a dragging in the chest without actual pain. There is noticeable shortness of breath on slight exertion, and she complains of morning cough with expectoration. The sputum has been examined and is negative as regards tubercle bacilli. Her appetite is poor. She weighs 8 st., a drop of 3 st. having occurred within the last two years. Her heart is healthy; the apex beat is not displaced, but the second sound over the pulmonary artery is distinctly accentuated. The apices of her lungs are resonant. Here the respiratory murmur is coarser than usual and the expiratory is prolonged, so that the inspiratory and expiratory murmurs approach each other in equality. Moist râles are heard in mid-axillae and small friction with crepitation is heard at the bases. This woman's mother, who is aged 60, is still working in the factory.

From what I have seen clinically of pulmonary asbestosis it resembles silicosis of the lungs in the marked shortness of breath on slight exertion, deficient respiratory capacity, physical debility, and, in examination of the sputa of not too far advanced cases, absence of tubercle bacilli, but since fibrotic changes are developing in both of the patients to whom I have alluded, there is almost sure to develop, if such has not already taken place, pulmonary tuberculosis.

The clinical picture of pulmonary asbestosis differs slightly from that presented by a patient the subject of ordinary tuberculosis of the lungs, in so far as there is a pronounced deadening of the skin varying from mild bronzing to slight blueness, a degree of shortness of breath in excess of the physical signs, a greater amount of general disability, little expectoration, and comparative absence of night sweats.

AN ACTIVE CONSTITUENT OF THE PREPARATION CALLED "GLUKHORMENT."

BY

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AND

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In May of this year Professor von Noorden published in the *Klinische Wochenschrift* an account of a new pancreatic preparation which had a controlling effect on carbohydrate metabolism, but, unlike insulin, was effective when administered by the mouth.¹ To this preparation the name "glukhorment" had been given, and the title of the paper made it clear that the substance was regarded by the author as containing a new anti-glycosuric principle, naturally performed in the body. On information, evidently supplied to him by the chemist responsible for devising "glukhorment," Professor von Noorden stated explicitly that, in spite of indications in the patent specification, which might suggest some connexion of the active principle with a guanidine derivative, no such derivative, and in particular no synthalin,² had been added; and, further, that the finished preparation contained no guanidine derivative of any kind in recognizable amount. Professor von Noorden drew the cautious conclusion that, if the activity were due to a guanidine derivative, it would have to be one of extremely high activity. In July of this year one of us (H. H. D.) received a communication from the Horment Company, who were manufacturing glukhorment, stating that they were sending material in the hope that clinical trials of it could be arranged. In due course this and several subsequent consignments of glukhorment were sent by the Horment Company, with a request for their trial.

A consideration of preliminary reports, on the mode of action of this preparation on the human being and on laboratory animals, suggested a strong similarity between its effects and those with which we had become familiar, through experiments then for some time in progress, on the action of synthalin. Some of the glukhorment

was immediately placed in the hands of one physician, who will presumably report his experience with it in due course. The physiological resemblance to synthalin was so pronounced, however, that, before the question of wider clinical trials was considered, it was thought desirable to make a simple chemical examination, in order to confirm the fact that the preparation was free from synthalin and similar guanidine derivatives, as stated in the paper by Professor von Noorden, of which copies had been submitted by the Horment Company in support of their request. The result of this first test showed clearly that a guanidine derivative strongly resembling synthalin was present in substantial amount in the glukhorment tablets as submitted for trial. The evidence thus early obtained was at once so clear and so surprising that it was considered desirable to use a further quantity of the material submitted, in order to obtain precise information as to the nature of the substance in question. The isolation of the substance was made easy by the fact that the nitrate of synthalin is a remarkably insoluble salt.

Chemical Isolation from Glukhorment of a Guanidine Derivative closely resembling Synthalin.

Two hundred glukhorment tablets were powdered; the powder, weighing 60 grams, was thrown into 1 litre of boiling water and the mixture was kept gently boiling for fifteen minutes. The liquid was then filtered, while still hot, from a large mass of insoluble protein.

The filtrate was evaporated *in vacuo*, with the addition of octyl alcohol to prevent frothing, to a volume of 120 c.cm. On standing, it set to a jelly; this was warmed to 40°, when it became fluid, and concentrated nitric acid was added until the reaction of the liquid was strongly acid to Congo red. A white crystalline nitrate separated from the solution on standing, and the liquid no longer set to a jelly when cold. The crystalline material was collected by centrifuging, washed in the centrifuge with a small quantity of dilute nitric acid, and dissolved in about 25 c.cm. of hot water. This solution was boiled with charcoal and filtered. To the hot filtrate 0.5 c.cm. of 6 per cent. nitric acid was added, and the nitrate crystallized on cooling. This was filtered off and dried; it weighed 1.135 grams. It was then converted into the picrate by dissolving it in water and adding a saturated solution of sodium picrate until no further precipitate was produced. The picrate was filtered

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¹ "Synthalin" is the synthetic compound, decamethylenediguandine, introduced by Frank, Nohmann, and Wagner, as an antidiabetic remedy for oral administration, and already the subject of numerous reports.