THE PATHOLOGY OF MINERS' PHTHISIS.

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It has long been recognised that certain occupations predispose to pulmonary tuberculosis, and that in these "dangerous" occupations the death-rate from this disease is far higher than in the general population. This is particularly so among those who work habitually in atmospheres which are laden with silica dust. Clinically there is overwhelming evidence that silica induces a fibrosis of the lungs which then become susceptible to tuberculosis, and experimentally there is sound evidence supporting the clinical conclusions.

The two problems arising out of the recorded knowledge which have occupied our attention during the last two years are: 1. Why is silica, conspicuous and possibly alone among common dusts, capable of inducing extensive fibrosis? 2. How does the silicotic fibrosis aid the establishment of tuberculosis?

1. There have been many attempts made to answer the first question. For the most part, however, the answers have not been based upon experimental study. The view most often expressed is that silica owes its injurious quality to its physical properties, but for reasons we have set out in detail elsewhere¹ we are in favour of the more modern view that silica causes fibrosis by acting chemically on the tissues and not in virtue of its physical properties.

2. The second problem is even more difficult and much less work has been done on it. The disorganisation of the lymphatic system in silicosis has been recognised by most authors as a potent factor in the increased susceptibility to tuberculosis. It has also been suggested that silica dust and the tubercle bacillus when concentrated in small foci act together as irritants and set in motion a series of reactions on the part of the lung which neither alone is capable of initiating.

Experimental Work.

Our own work on this question is the outcome of investigations into the factors influencing infection and immunity which have occupied our attention for some time. Among other substances we have used silica as a means of breaking down the normal resistance of tissues to invasion by micro-organisms, and while working with *B. tuberculosis* we obtained results which seem to have a direct bearing upon the pathology of miners' phthisis, and suggested further inquiries along these lines. The principal element in the problem of miners' phthisis is that men who are resistant to tuberculosis become susceptible with the development of silicotic fibrosis. It is important to understand the mechanism of this increased susceptibility not merely as a part of the problem of industrial tuberculosis, but also because general tuberculosis presents a similar, though more subtle, problem.

Our work has been based on the facts (1) that colloidal silica is a cell poison; (2) that colloidal silica is the most easily formed soluble form of silica, the circulation of silica in nature depending upon this and (3) that living matter (soil bacteria) is able to break up mineral silicates with formation of soluble silica. We judged it probable that the fibrosis brought about by finely divided silica was due to the slow formation in the tissues of silica sol, either directly or through the intermediate formation of sodium silicate which is decomposed by carbonic acid, the sol formed acting as a cell poison. The direct proof of this has been found impossible, and we are, therefore, compelled to fall back upon indirect evidence.

The indirect evidence has been sought in a careful study of the lesions produced when insoluble silica, silica powder which has molecules of water attached, and soluble colloidal silica are injected subcutaneously. The method of "dusting" animals' lungs by inhalation was not chosen because of the difficulty of forcing a sufficient dose into the lungs in a short time and the consequent inability to create an early local lesion. In subcutaneous injections the dust suspension or the solution can be placed in a small area and the changes in the tissues can be studied from hour to hour until healing has taken place.

Lesions Following Injection of Silica.

It may be said at once that there is no essential difference between the reaction produced by soluble silica and that which follows the injection of the insoluble forms. The only obvious difference is that the reaction is more rapid and more transient with

FIG. 1.

Lesion produced in the subcutaneous tissue of the mouse six days after the injection of silica. Note the central coagulum bounded by a zone of degenerated leucocytes. Outside this there is a secondary zone of necrosis limited by granulation tissue.

colloidal silica, and our findings support very strongly the view that SiO_2 becomes soluble by hydration in the tissues. But, inasmuch as with insoluble silica the reaction is somewhat delayed, the lesions produced by this substance lend themselves rather more readily to analysis than those produced by colloidal silica. The lesion is primarily a destructive one. Within a few hours of the injection of silica the site of inoculation can be recognised as an area of coagulative necrosis at the periphery of which there is an active emigration of leucocytes from the dilated capillaries of the areolar tissue. The condition progresses for some days, resulting in a lesion which is practically specific. (Fig. 1.) It consists of a central acellular area of coagulation necrosis surrounded by a zone of leucocytes, many of which are in varying stages of degeneration. Outside this is a secondary area of necrosis which is limited by granulation tissue. In course of time the necrotic tissue is gradually absorbed and replaced by macrophages, and the final picture is that of an organising inflammatory fibrosis.

Lesions Following Injection of Silica and Tubercle Bacilli.

It now remains to investigate what effect this local necrosis has upon a local infection by tubercle bacilli. In order to study this point it is necessary to employ animals which are normally resistant to tubercle, and for the purpose we have chosen mice. The tubercle bacillus possesses only a very slight degree of pathogenicity for the mouse, and this applies equally to human and bovine strains. It can survive

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and proliferate in the tissues, but it causes very little reaction. When present in small numbers the local reserves of the tissue appear sufficient to cope with it, though when injected in massive doses it calls forth a pronounced exudation of polynuclear leucocytes. It is readily phagocytosed by the fixed connective tissue cells or polyblasts, as well as by wandering leucocytes, but it can exist for a long period in the bodies of such cells without any apparent change; in fact, it seems likely that it can actually proliferate within phagocytes. It seems to cause no cell necrosis or tissue destruction, and though it may be transported, chiefly by the agency of phagocytes, to lymphatic glands and the viscera, in these secondary foci it gives rise only to a very moderate degree of tissue reaction quite unlike that seen in susceptible animals. (Fig. 2.)

We have observed repeatedly that an injection of tubercle bacilli accompanied by silica into the subcutaneous tissue gives rise to a much greater local reaction than an injection of tubercle bacilli alone, and, further, that general dissemination is earlier and more active. The silica effect, however, is transient, so that we have, in these experiments, inoculated fresh doses of silica weekly into the local lesion, though the dose of tubercle bacilli has not been repeated. In this way we have produced large abscesses containing enormous numbers of tubercle bacilli, far more than were originally injected, but the common silica lesion produced in this way so complicates the microscopic picture that it is impossible to arrive at a clear conception of what takes

FIG. 2.

Lesion produced in the subcutaneous tissue of the mouse seven days after the inoculation of a fine emulsion of tubercle bacilli. There is only a moderate reaction of the fixed and adventitial cells, with little or no emigration of wandering leucocytes.

place. We have therefore resorted to the "early stages" method of analysis. The changes are brought out well in an experiment in which silicic acid was inoculated together with a very fine suspension of tubercle bacilli in normal saline.

Without entering into details it may be said that from day to day an actual local proliferation of tubercle bacilli can be recognised occurring in the central coagulum, which is characteristic of the silica lesion. (Fig. 3.) Whether the coagulum acts merely as a culture medium in which the bacilli are protected from the body cells and fluids, or whether the silica actually stimulates the proliferation of the bacilli, is still uncertain. But there can be no doubt that there is a very active proliferation of the injected bacilli, so that when the final stage of healing is reached almost all the macrophages which enter the lesion at this time contain ingested bacilli. These phagocytes wander into the granulation tissue at the periphery of focus in large numbers and convey infection to a distance.

Conclusion.

The conclusion we draw from these experiments is briefly as follows. The mouse possesses a high degree of natural immunity to tubercle, and even massive doses of bacilli injected beneath the skin can be tolerated fairly well. In course of time the organisms become encapsuled, and though a certain number of them escape this fate, being conveyed to

distant parts by the action of phagocytes, the resulting lesion develops very slowly. With smaller doses of bacilli this tolerance is even more obvious. The isolated bacilli are ingested by leucocytes and also by polyblasts, and in the latter elements they live practically in symbiosis, proliferating freely within the cell, which shows no obvious damage from their presence. When silica is introduced along with the bacilli into the subcutaneous tissues of the mouse there is a very different result. The tissues undergo a considerable degree of necrosis, and though an intense leucocytosis is an important part of the accompanying reaction, the centre of the lesion remains acellular for several days and consists of a structureless coagulum. After a preliminary lag

FIG. 3.

Centre of the lesion produced in the subcutaneous tissue of the mouse six days after the inoculation of silica, together with a fine emulsion of tubercle bacilli. The bacilli are actively proliferating in the central coagulum.

of two or three days the bacilli proliferate abundantly in this coagulum, protected from the cellular defences of the body. This protection is, however, only temporary, and in a few more days the coagulum is absorbed and the lesion becomes infiltrated with mononuclear and polynuclear phagocytes which absorb the bacilli with avidity. In the meantime, however, a small dose of bacilli becomes a dose of considerable magnitude, and inasmuch as an important factor in determining an infectious process is the number of organisms introduced, a simple explanation is forthcoming of the effect of silica upon such tuberculous lesions as we have described.

The abnormal prevalence of tuberculosis among men who are exposed to fine silica dust may, we think, be explained by (1) the destructive action of silica on cells whereby foci of necrosis are produced in which tubercle bacilli can multiply, and (2) the disorganisation of the lymphatic drainage of the lung. Our view that the actual cell poison is a soluble derivative of silica has led us to test whether silica sol can influence the course of general tuberculosis in susceptible animals. In Germany soluble silica in various forms has been used in the treatment of tuberculosis. A discussion of the basis of this treatment is outside the scope of the present article; it may suffice to say that claims have been made that the drug has a specific curative effect in this disease. During the past 15 months we carried out a number of experiments designed to test this claim. The general methods pursued have been as follows. Rabbits have been injected intravenously with human tubercle bacilli in doses which were just sufficient to cause lesions visible to the naked eye two months after injection. Some of the animals were treated—by mouth or by intravenous injection—with soluble silica; an equal number were left as controls. In no instance was the process of tubercularisation delayed or prevented by the silica; in a certain number of the animals the process appeared to be helped by the drug. Reviewing all the evidence, however—derived from experiments on more than 30 animals—it would seem that silica sol circulating in the blood-stream does not materially influence a generalised tuberculosis. It is apparently only where the poison is sufficiently concentrated to form local areas of tissue destruction that the growth of the tubercle bacillus is promoted.