OXYGENATION AND TUBERCULOSIS.

BY

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In the course of two investigations published by Moore and Stenhouse Williams¹ in 1909 and 1910, it was shown that the growth of the *Bacillus tuberculosis* is arrested when the atmosphere of the culture tube contains 70 per cent. or over of oxygen, and this has been confirmed by a recent series of observations by Adams.²

The number of micro-organisms showing this oxyphobic property is very small, for out of a list of twenty-six organisms tested by Moore and Stenhouse Williams only the *Bacillus tuberculosis* and *Bacillus pestis* showed it typically, the organisms of the staphylococcic group being only partially inhibited in their growth. To these organisms the more recent work of Adams adds two from the streptothrix group, namely, actinomycetes and mycetozoa.

This oxyphobic property is accordingly a somewhat specific characteristic, and the object of this paper is to point out a possible connexion between it and the seats of election of the bacillus of tuberculosis in the body and its modes of growth and dissemination, and also to indicate certain practical applications which lie outside laboratory work.

An attempt has been made by breathing experiments with oxygen, as well as by respiration experiments on experimentally infected animals, to obtain some effects on the rapidity of tuberculous development in the body. These experiments have given negative results, but a paper recently published by Buckmaster and Gardner³ furnishes an explanation for this failure, by showing that even when oxygen is breathed there is no appreciable increase in the amount of dissolved oxygen in the blood gases.

It is also to be remembered that the seat of growth of the tubercles is only reached after the blood has not only become venous, but when the stream of nutrition has reached the condition of highly venous lymph, and usually in situations when the lymph flow is particularly slow, and the lymph is accordingly at its poorest in oxygen content.

Some other method than oxygen respiration must accordingly be devised for the purpose of bringing more oxygen in contact with the bacilli *in vivo*, such as disturbance of the relative distribution of pressures in the vascular circuit and as between pulmonary and systemic circuits, and by raising the capillary pressure in the tuberculous area, so as to increase lymphatic flow and so carry more oxygen.

It might at first sight seem that the bacillus, by choosing the lung as the favourite seat of its growth in the body, was indicating a preference for a well oxygenated area, but a little consideration of the histological pathology of phthisis, and of the portion of the lung selected in the great majority of cases, supplies convincing proof that this is not the case.

Although the blood is oxygenated in the lungs, the blood coming to the lungs is the most venous in the whole body before it reaches the pulmonary alveoli, and the tubercles containing the bacilli are not situated on the alveolar epithelium or capillaries, but in the lymphatic spaces and about the minute bronchioles in the perivascular spaces.

The pulmonary lymphatics contain lymph which has been separated from very venous blood, and this lymph does not undergo oxygenation in the lungs, so that the favourite situation for the development of tubercles is probably the least oxygenated in the body.

The favourite point of commencement in the lung is, moreover, the apex, where ventilation and movement of the lung tissue is at a minimum, and the lymph flow there is the slowest in the whole organ; the spread of the disease from the apex is usually by the lymphatic channels in a fluid with low oxygen content.

It is of interest to note that in mitral stenosis tuberculosis is very rarely found, whereas it is a frequent cause of death in pulmonary stenosis. Now, mitral stenosis, by introducing a resistance to the blood leaving the pulmonary area, will cause hyperaemia of the lung, with increased pressure in the pulmonary capillaries. This increased

capillary pressure in the lung will lead to an increased velocity of lymph flow and correspondingly increased oxygenation in those perilymphatic areas where the bacillus usually commences its work. The opposite condition of stenosis on the right side of the heart leads to a fall in the pressure in the capillaries and pulmonary arterioles and a slower flow of lymph in the lymphatic capillaries fed by them, so giving typically suitable conditions for the growth of the bacillus.

In the lung, therefore, the bacillus selects the least oxygenated areas. The same is seen in the other organs and situations selected by the bacillus in the body. It is always found in lymphatic areas, where the lymph is venous and the flow slow. It is found in lymphatic glands generally, in joints and in cutaneous areas where the flow of blood and lymph are slow. In the lymphatic glands the lymph, already venous and poor in oxygen as taken up at the capillaries, has become still more venous and is moving slowly. In the joints there is an almost extra-vascular area, and the same holds for the serous cavities such as those of the pleurae and peritoneum.

Amongst the organs affected with tubercle in a general infection are the liver and spleen, especially in the lymphatic Malpighian corpuscles of the latter organ. Both these organs are on a secondary system of capillaries supplied chiefly with very venous blood, although the blood supply is a very rich one.

If consideration be paid to the histological character of the tubercle mass as it grows, it is observable that it is a non-vascular mass, which perishes and caseates as it grows in size for lack of oxygen. It is probable that the giant multinucleated cells which it contains owe their form and development to lack of oxygen—at least that is the type of result which is seen when young growing cells are partially asphyxiated. The tubercle bacilli in a tubercle are in a situation where they are in a minimum concentration of oxygen. First of all they are in relationship to the lymphatic system, where outside them the oxygen supply is at its poorest; and then, in addition, they are separated from the lymph by a non-vascular area which increases in size as the tubercle grows. This is a favourable condition of growth, and when the tubercle breaks down the live bacteria are discharged to find new points at which to start more tubercle formation.

The well recognized treatment of tuberculous joints by the hyperaemic method of Bier is interesting from this point of view: the increased capillary pressure leads to increased lymph flow, and so does artificially for the joint what mitral stenosis does for the lung. The beneficial results upon lupus of the Finsen light treatment are also commonly ascribed to the local hyperaemia induced in the affected area. If this be so, it is an additional argument in favour of the view that increased oxygenation of the surrounding lymph is the beneficial agent, for the increased blood supply and blood pressure in the capillaries will lead to increased lymph flow, and hence to increased oxygenation of the affected area.

The treatment of phthisis by open-air methods and by high altitudes is also in accord with this view, upon which the effect obtained would in both cases be due to a common cause—namely, the more efficient ventilation of the lung, and, as a result, increase mechanically of the lymph flow, especially at the apices.

If this view be the correct one, the resistance to blood flow in the systemic circuit, and especially in the capillary portion of the peripheral circulation, ought to be kept low, so as to secure an easy return of the blood to the lungs. While, at the same time, the stimulating effect of the cool air in increasing pulmonary ventilation should be preserved to the utmost, and too much demand upon oxygen in the tissues by excessive work should be avoided. In other words, the patients should rest, or sleep, quite warmly in cool air, in that recumbent position which demands least oxygen for maintenance.

Cold in itself applied to the whole body will not be a benefit but an evil, since it will give no superior oxygen value at that part of the vascular system where it is demanded. This point is experimentally proved by a series of experiments which have recently been carried out by J. G. Thompson, M.B., Ch.B., and the author in collaboration.

Through the kindness of Sir Ronald Ross we were allowed the use of a large cold chamber supplied to

the Tropical School of this university by the generosity of Sir Edwin Durning-Lawrence, Bart. In this chamber we exposed a number of guinea-pigs which had been inoculated with tuberculosis to a temperature of 0° C. to -5° C., while another set were kept in air at ordinary temperatures, and a third set in an atmosphere enriched by oxygen. It was found that the tuberculous lesions developed most rapidly of all in the animals kept in the cold chamber. At that time we were anticipating the opposite result, but there is no doubt whatever in our minds as to the results of the experiments—namely, that keeping in a cold atmosphere does not by itself alone inhibit the growth of the tubercle bacillus, but rather the reverse.

What is, then, the mode of action of the fresh air treatment? There is nothing different in the chemistry of the air, and it would appear as if it administered a purely physical stimulus to increased pulmonary ventilation, due to the reflex nervous effects of the draughts of cold air playing upon the face.

The lassitude due to confinement in heated rooms, and its removal by fanning or movement of the air, have been explained in this way by Leonard Hill, who has shown that the accumulation of carbon dioxide in the air of occupied and heated rooms has nothing to do with the matter. The cooling by convection and evaporation from the skin of the face leads to increased respiration, and removes at once the feeling of lassitude and oppression.

It may next be asked in what way does increased pulmonary ventilation affect the tubercle bacillus, and it may be pointed out that it is not purely by increased uptake of oxygen, for, as has been stated above, animals left even in an atmosphere of oxygen in a resting condition have no more oxygen in their blood than when breathing air, and develop tubercle, as Adams has shown, just as rapidly as other animals in ordinary air.

The other effect is increased movement of the lungs, leading to increased lymph flow, and hence increased rate of oxygen access to the actual site of the tubercle.

It is this action which, in our opinion, gives the beneficial action of the fresh air treatment. Without such a stimulus a patient cannot by voluntary effort in any breathing exercises keep up for any length of time an increased ventilation; he becomes apnoeic, and the respiration diminishes automatically. For this reason some experimentation would appear necessary upon the subject of how best to administer the cool air in drafts or puffs over the face so as to keep up the stimulus most effectually and for the longest period, and as to what alternations are of most advantage in such administrations of fresh air.

The same effects are seen at work in the treatment of phthisis by high altitudes, where the oxygen supply is considerably less than at sea-level. Here the patient is compelled vigorously to ventilate the lungs in order to obtain sufficient oxygen, especially if any light exercise be taken. It is certainly not in this case an enrichment of oxygen. But the changed conditions are such as to give more oxygen locally where it is wanted—namely, in the lymphatic spaces of the lungs where the tubercle bacillus is situated. The over-ventilation alternately distending and collapsing the lung tissues sends a rapid stream of lymph along bearing more oxygen in solution past the tubercles. At a high altitude the cooler air also plays its part in inducing increased ventilation of the lung, and the two effects work together.

If this view be the correct one, the things to be aimed at in treating phthisis are such as will secure increased oxygenation at the site of the tuberculous lesion. This is obtainable by hyperaemia of the affected area and increased lymph flow at that part. In regard to the vascular circuit as a whole, the resistance should be so affected, if possible, that the pressure is increased in the pulmonary capillaries before the alveolar areas are reached, and the systemic circuit should be vaso-dilated, so as to send the blood to the pulmonary region as highly oxygenated as possible. Next, the ventilation in the lung should be increased as much as possible so as to cause a mechanical lymph flow. The body of the patient should be kept warm, and the face, if possible, subjected to rhythmic applications of cool air at such a rate as to stimulate respiration. Exercise should be indulged in to that extent to which it will somewhat stimulate ventilation without loading up the system with unoxidized products by making too great a demand

upon oxidation, and this exercise possibly might best be in the open air, alternated with the cold air applications.

REFERENCES.

- ¹ *Bio-chemical Journal*, vol. iv, 1909, p. 177; vol. v, 1910, p. 181.
² *Ibid.*, vol. vi, 1910, pt. 11. ³ *Proc. Roy. Soc., B*, vol. lxxxv, 1912, p. 56.

EXPERIENCE OF THE DIORADIN TREATMENT.

A REPORT UPON TEN PATIENTS WHO RECEIVED THE TREATMENT.

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DIORADIN is a combination of chemical substances introduced for the treatment of tuberculous affections by Dr. Szendeffy, of Budapest.

An announcement of its alleged marvellous efficacy was made in the English lay press in May, 1911. Some allusions to its composition were made in the *BRITISH MEDICAL JOURNAL* at that time.

At the beginning of August Dr. Bernheim came to England. Dr. Bernheim is President of the French Department for the dealing with human tuberculosis and Chief Physician of the French antituberculosis dispensaries, and he came with credentials from the English Ambassador in Paris.

I had the pleasure of a long interview with Dr. Bernheim, and he very kindly provided me with a supply of the dioradin sufficient for the systematic treatment of ten patients.

He assured me that, though he had given several thousands of injections, he had never seen any ill effects, and he was enthusiastic with regard to the beneficial results. In these circumstances I felt that it was my duty to test the method of treatment.

Dioradin is said to contain peptonized iodine, menthol, ethereal solution of radium barium chloride, and almond oil.

It has been said that peptonized iodine is a compound unknown to chemists. Dr. Bernheim explained that the substance indicated is what we term iodo-albumose. Menthol is a stearoptene; it is somewhat loosely described by Dr. Szendeffy as a terpene, but terpenes and stearoptenes are not far apart chemically, both being derived from essential oils. The critic in the *BRITISH MEDICAL JOURNAL* said that he could not find any terpenes on analysis of dioradin, but recognized the presence of menthol. Radium barium chloride is soluble in ether, and is added in solution. The excipient is almond oil.

Dioradin is an oily fluid, smelling strongly of menthol, with a suggestion of iodoform. Dr. Bernheim told me, however, that iodoform was not present. Dr. Melville found at the Brompton Hospital that dioradin has some radio-activity.

Dioradin is administered by intramuscular injection with aseptic precautions. The dose is 1 c.cm., given daily for thirty days, followed by fifteen more injections on alternate days. If necessary, a further course may be given after a period of rest.

The contraindications to the use of the preparation are said to be disease of the heart or kidneys, but no record of ill results from its use in such cases is given in Dr. Bernheim's report. Symptoms of iodism and diarrhoea call for cessation of treatment, but again the report does not include any examples of these complications, and Dr. Bernheim told me that he had not met with any.

The cases were selected for the treatment with great care, and represented common types of the disease. In all the diagnosis of tuberculous infection was certain; in the 9 cases of pulmonary tuberculosis tubercle bacilli had been found in the sputum, and in the case of tuberculous peritonitis and epididymitis the clinical characters leave no room for doubt as to the diagnosis.

In none of the cases has any ill effect, either general or local, followed the injections. Several patients said that they could taste the injections for some time afterwards, and in one or two cases there was a slight increase of cough after a few days.