A COMPARISON BETWEEN SOME PHYSIOLOGICAL AND PATHOLOGICAL CONDITIONS.

THE OLIVER-SHARPEY LECTURES, DELIVERED BEFORE THE ROYAL COLLEGE OF PHYSICIANS OF LONDON.

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LECTURE II.

(Abstract.)

RENAL OXYGEN WANT AT HIGH ALTITUDES AND IN THE WARDS.

At the conclusion of my first lecture I pointed out that the scientific value of the two comparisons, which formed the subject of the lecture, depended upon the identity or otherwise of the causes which gave rise to them. Further, I mentioned that we were still in the dark as to these underlying causes. The comparison of which I wish to treat to-day differs from those, since not only the physiological and pathological aspects of the comparison can be discussed, but a common cause can be suggested. I wish to put before you: (1) The physiological adaptations which take place in rarefied atmospheres; (2) a similar complex of phenomena which may be seen in the wards, and (3) to suggest that in both cases the root of the condition is to be found in the fact that the kidney cell lacks its usual facility for obtaining oxygen.

Oxygen Want Generally.

I must preface my discussion of these subjects by some remarks upon the general subject of oxygen want.

The whole or part of the body may suffer from oxygen want as a result of any one of a number of causes.

These causes group themselves under two main headings, just as the causes of want of money in the pocket may be classified according to the side of the ledger on which they are to be found. Impecuniosity may result from too lavish expenditure or too slender income, and is, of course, intensified when the two take place simultaneously. Oxygen want may similarly be the result of excessive demand or insufficient supply.

Scheme of causes of bodily oxygen want.

The most obvious and frequent cause of oxygen want is muscular exercise; its most immediate effect is the flooding of the system with carbonic acid. Gradually the carbonic acid in the blood gets replaced to some extent by lactic acid, so that there is an actual diminution of the pressure of carbonic acid, though the combined effect of the two acids—carbonic and lactic—is sufficient to make the blood less alkaline than before; or, in other words, to increase its hydrogen ion concentration. This change in the acid direction causes breathlessness. Probably essentially the same changes in the blood take place from muscular oxygen want caused in any other way. Thus we may take lactic acid in the blood and urine in excessive quantities as the index of this condition.

The Reaction of the Blood at High Altitudes.

The observations of which I am about to speak were carried out in two localities—the island of Teneriffe and the mountain of Monte Rosa; in the former case the sea-level control observations were made at Orotava, and these were checked at Cambridge, Oxford, and Berlin; whilst in the latter case the party did control experiments in the ancient and historic University of Pisa, and checked these at Carlingford. I cannot let slip this opportunity of expressing my thanks to Professors Panwitz and Zuntz for the remarkable facilities and unfailing goodness which they showed us in Teneriffe and Berlin;

for the like courtesy extended to us by Professor Aducco and Dr. (now Professor) Camis at Pisa; and by Professor Agazzotti in the Monte Rosa laboratories.

The changes which we sought to investigate in these regions may be classified as follows:

- The alteration in carbonic acid in the air cells of the lung.
- The extent and nature of the increase of fixed acids in the blood.
- The change in reaction of the blood, consequent on a combination of changes (a) and (b). Our observations may be summed up as follows:

(a) We confirmed the observations of previous observers¹ who had found a lowering of the alveolar carbonic acid, which, of course, is an index of a similar lowering of the carbonic acid pressure in the arterial blood, with which the alveolar air is in approximate equilibrium.

(b) We confirmed the observations of previous observers² who found in the blood an increase of fixed acids relatively to bases, and to this we added evidence of a negative but important nature with regard to the character of the acids in question.

The most careful observations made by Dr. Ryffel, of Guy's Hospital, who was detailed to carry out this part of the work, failed to show evidence of increased lactic acid commensurate with the total increase of fixed acid radicles. Both the blood and the urine were investigated at an altitude of 10,000 ft. and also at 15,000 ft., and at both situations was this the case; though the rise in lactic acid at the latter station was appreciable. Nor was he more successful in obtaining evidence of any other acid abnormal in kind—for example, β -oxybutyric or diacetic.

(c) As regards the ultimate change in the reaction of the blood, it is the balance of (a) and (b), the loss of CO_2 tending to make the blood more alkaline, the gain in fixed acids tending to make it more acid. The resultant is a trifling change in the acid direction, but sufficient to account for the degree of breathlessness which takes place.

Quite recently a parallel series of observations has been published by Hasselbalch and Lindhard.⁴ This is doubly valuable. (1) The experiments were done in Copenhagen, the mountain having been brought to that city in shape of a chamber in which the observer could live in a rarefied atmosphere which exerted any desired pressure of oxygen, thus showing that the changes observed by us were not caused by any accessory factor in the Alps, but were certainly due to low oxygen pressure. (2) By the very beautiful electrical methods which have been introduced by Hasselbalch, he came to precisely the same quantitative change in the reaction of the blood which we had observed by methods of a widely different character. The leading facts, therefore, do not rest on the work of any one observer or any one type of technique.

Having arrived, therefore, at a statement of the principal changes wrought in the blood by oxygen want not aggravated by exercise we are forced to ask, How are these brought about? Here again there is fortunately considerable unanimity. At the time of our Monte Rosa expedition a party consisting of Haldane, Douglas, Henderson, and Schneider were at Pike's Peak (14,000 ft.); their researches were primarily concerned with the respiratory exchange; they, however, verified the principal observations which I had made at Teneriffe and arrived at the same opinion as regards the cause, which we formulated at Col d'Oleu, namely, that the change in reaction of the blood was the work of the kidney. This view is founded partly on the exactness with which the kidney maintains the reaction of the blood under normal circumstances and partly on the absence of acids, such as lactic acid, which would be present if the system was being flooded by the products of oxygen want of other organs such as the muscles. We conceive, therefore, that at 10,000 ft. altitude, and even as low as 7,000 ft., the kidney, by a process of excretion of bases or retention of acids, reacts to oxygen want by increasing the hydrogen ion concentration of the blood.

The advantages which the body derives from this

⁴ The detailed account of these experiments will be found in the *Phil. Trans. of Royal Society*, B, 206, p. 49. A less technical statement of them is given in *The Respiratory Function of the Blood*, Cambridge University Press, 1914, in which an account is also given of the methods employed and the principles on which these methods are based.

change are clear: the fall of carbonic acid in the pulmonary air cells means a relatively greater quantity of oxygen than would otherwise be the case. The change amounts to perhaps 12 mm. pressure. At the top of "the Peak" the adjustment which I have discussed means the difference between 48 and 60 mm. oxygen pressure in the air cells, and this is a great asset. Not only does oxygen enter the lung more easily, but it leaves the blood more quickly when the red corpuscles reach the kidney or any other destination. The whole process is, therefore, a true physiological adaptation. It is "making the best of a bad business." The body is not in so strong a position as it normally is at the usual barometric pressure, but it is in a stronger one than it would otherwise be at a pressure of 450 mm.

A PATHOLOGICAL TYPE OF DYSPNOEA.

My introduction to the pathological cases which I wish to bring to your notice was of the following kind: My friend, now also my colleague, Dr. Thomas Lewis, wrote to me of certain cases which he had from time to time. As he described them to me, their leading symptom was their breathlessness; this, however, was unaccompanied by vascular or pulmonary lesions adequate to explain completely the degree of dyspnoea present. In the most characteristic cases there is no cyanosis, whilst in others the cyanosis is relatively slight.* In two words, Dr. Lewis, finding no sufficient evidence of an actual lesion, asked whether I could find evidence of what I have already termed an adequate "chemical lesion."

I am presenting this matter to you in this way because I do not wish to involve myself at the outset in some such term as uraemic dyspnoea or cardiac or renal asthma. First let me deal with the facts, then I will say what I can about the phrases.

So far as the results are concerned, I need not go into very minute particulars; they would be a repetition of the picture I have already drawn. In the graver cases, of course, all the symptoms were much exaggerated. I will simply say, therefore, that the dyspnoea was often very urgent, and in some patients—but not in all—it was of the Cheyne-Stokes type; that the blood showed an appreciable addition of fixed acid; that this was accompanied by a fall in alveolar CO₂ pressure. But the fall in carbonic acid was not equivalent to the rise in fixed acids, and therefore the blood in the body became less alkaline in reaction.

I can best illustrate the point by a single case, that of M. P. I choose this case not because it was a grave one—quite the contrary—but because the patient got better; I will not say well. The grave cases proved fatal. This one, however, recovered sufficiently for the symptoms to pass off and therefore we had the opportunity of testing the condition of this patient both with and without the symptoms.

CASE 1.—M. P., aged 61, was seen on May 23rd, 1913, and showed the following symptoms: The heart was enlarged; no murmurs. The arteries were thickened. The urine contained albumin; no casts. Respiration was irregular, rate 30 to 40; there was orthopnoea; not much distress; nocturnal attacks. There was very slight cyanosis. Alveolar CO₂: 35 mm. The degree of acidosis in the blood was equivalent to 0.02 per cent. lactic acid. Quantity of oxygen with which 1 c.cm. of blood unites when exposed to 31 mm. O₂ pressure, and CO₂ as in the body: 0.094 c.cm.†

A month later (June 24th) the respiration was regular—rate 24; there was no orthopnoea, and the patient could walk without dyspnoea. There were no nocturnal attacks. There was still very slight cyanosis. There was no acidosis in the blood. Quantity of oxygen with which 1 c.cm. of blood unites when exposed to 31 mm. O₂ pressure, and CO₂ as in the body: 0.109 c.cm.†

As between May 23rd and 24th the blood in the former case was abnormally acid in reaction, there was increase in fixed acids, lowering of alveolar CO₂, and dyspnoea.

The contrast between this case and one of pure cardiac origin is shown in the following table. In the cardiac case there are high CO₂ pressure, no increase of fixed acids, and a slightly abnormal departure in reaction in the acid direction:

	Case I. M.P.	Case II.
Age	61	29
Heart	Enlarged; no murmurs	Much enlarged; mitral stenosis
Respiration	30 to 40	33
Urine	Albumin; no casts	Albumin; no casts
Cyanosis	Very slight	Deep
Alveolar CO ₂	35 mm.	43 mm.
Degree of acidosis in blood	= 0.02 per cent. lactic acid	Nil
Reaction of blood to CO ₂ at "proper" concentration	1 c.cm. blood at 31 mm. O ₂ unites with 0.091 c.cm. O ₂	1 c.cm. blood at 31 mm. O ₂ unites with 0.097 c.cm. O ₂

So far the chemical analogy between the cases of dyspnoea of unascertained origin and those of the mountain dweller is complete, but the analogy does not end at this point, for a systematic effort was made to discover the nature of the acid or acids involved. These tests again yielded negative results, there being no excess of lactic, diacetic, or β-oxybutyric acids present, and nothing to indicate excessive amino-acids in the blood. These matters formed the subject of investigation by Drs. Ryffel and Wolf, whilst the urea in the blood was tested in different ways by Dr. C. G. L. Wolf and Dr. Cotton. Only in the later phases of some cases was the amount of urea in the blood abnormally high, and then also lactic acid was sometimes in excess. I should here point out that definitely uraemic cases (in the sense of having excessive urea in the blood) were studied independently at Guy's Hospital by Ryffel and Poulton, their work linking up to our own at that point.

Since the "chemical lesion" in Lewis's cases was precisely the same in kind as the "physiological adaptation" to high altitudes, the question may reasonably be asked: Is not the underlying cause the same in both cases? If it be granted that the one is the result of oxygen want in the kidney cell, cannot the other be explained in the same way? *A priori* there is no difficulty in supposing that such was the case, for in all the cases which reached the *post-mortem* room there was this in common—considerable quantities of interstitial material existed. In other words, a barrier appeared between the blood vessels and the kidney cells. This interstitial substance often showed signs of containing many white corpuscles, which, like all nucleated structures, would tend to take their share of oxygen as it passed. Such a screen of material would decrease the rate at which oxygen could diffuse to the cells from the blood vessels, and would probably mean a lower pressure or concentration of oxygen in the cells, and would, from their point of view, be equivalent of too low a pressure of oxygen in the blood.

Perhaps the principal criticism which may be brought against my theory is that it is too comprehensive. Are there not numerous other conditions which cause want of oxygen in the kidney? Do they produce the symptoms of which I have been speaking?

The following table gives a rough idea of some of the ways in which the kidney cell may conceivably suffer from oxygen want:

If the terminal branches of this tree be labelled 1-5, the question arises, Do all five causes of oxygen want produce this particular chemical lesion? This matter has only partially been investigated. The type of case which has been investigated most completely from this point of view is pneumonia.⁵ Here, for some time after the crisis, the symptoms which I have described are present. They abate gradually. Pneumonia, like exposure to rarefied air, falls into position 3. Moreover, positions 3 and 5 agree in that the failure essentially lies in the fact that the oxygen

* The reader is referred to Dr. Lewis's own description, *Heart*, vol. v, p. 45; also *Lectures on the Heart*, by Thomas Lewis, published by Hoeber, New York, 1915, p. 81.

† The normal quantity is 0.106-0.118 c.cm.; in proportion as the figure is below this the blood is abnormally acid.

reaches the cell at too low a pressure, and in this they perhaps differ to some extent from the, as yet, uninvestigated causes of oxygen want 1, 2, and 4.

CONCLUSION.

Let me now redeem my promise to say a word about nomenclature. If my argument proves anything, it proves that there is a type of dyspnoea to which the adjective "renal" may justly be applied. It is renal because this stimulus to the respiratory centre is the direct result of oxygen want in the kidney, the intermediary between the one and the other being the reaction of the blood. The degree of dyspnoea which will be produced by a given accomplishment on the part of the kidney will depend upon the irritability of the respiratory centre—for this, according to the admirable work both of Dr. Poulton⁶ in this country and of Dr. Peabody⁷ in America, seems capable of fluctuation in renal cases.

On the side of treatment there would seem to be a theoretical case for the consideration of oxygen, at all events when the patient is in great distress. That is to say, the distress might be alleviated whilst the patient was breathing the gas. The limitations of such treatment, however, are as great as the limitations of our present methods for the administration of the gas.

Such, then, is the last of my three comparisons; if, as I hope, it may contain something that is useful, a justification in practice would be found for the view on which the comparison is based—the view that in the "adaptations" of the body to special sets of circumstances there lies the germ of certain "chemical lesions," the view that the pathological is sometimes rather the exaggeration of the physiological than its antithesis.

REFERENCES.

¹ For literature see Haldane, Douglas Henderson, and Schneider, *Phil. Trans.*, B, vol. cccii, p. 510. ² For literature see Barcroft, Camus, Mathison Roberts, and Riffel, *Phil. Trans.*, B, vol. ccvi, p. 49. ³ Campbell, Douglas, Haldane, and Hobson, *Journal of Physiology*, xvi, p. 316. ⁴ *Biochem. Zeitschr.* ⁵ *Quarterly Journal of Medicine*, vol. viii, p. 97. ⁶ *Quarterly Journal of Medicine*, 1914. ⁷ *Archives of International Medicine*, August, 1914, pp. 236-262.

An Address

ON

WOUND INFECTIONS;

AND ON

SOME NEW METHODS FOR THE STUDY OF THE
VARIOUS FACTORS WHICH COME INTO CON-
SIDERATION IN THEIR TREATMENT.

DELIVERED BEFORE THE ROYAL SOCIETY OF MEDICINE
ON MARCH 30TH.

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(Concluded from p. 723.)

TREATMENT BY VACCINE THERAPY.

I EMPHASIZED at the outset of this discourse that Treatment by Vaccine Therapy could take rank only as ancillary to Treatment by Physiological Methods. In *treatment by physiological methods* we take the antibacterial agencies of the patient just as they are, and do our best to bring them into more effective application on the infective microbes. In *vaccine therapy* we seek to reinforce those agencies. We endeavour to increase the bacteriotropic power of the blood, and to modify the chemiotropic sensibility of the leucocytes. And, now that we have come to appreciate its importance, we should seek to increase also the antitryptic power of the blood fluids.

Let us try to see how the case for vaccines and vaccine therapy stands—keeping always before us the great practical issue as to how much clinical benefit can in the particular case be secured for the patient, and arranging for the purposes of our survey the multifold applications of vaccines under six subheadings.

1. *Prophylactic Employment of Vaccines.*—This is not only from the theoretical point of view the best of all

methods of employing vaccines, but it is also the method which gives in practice the maximum of advantage. We have only to look to the results obtained by prophylactic vaccination against small-pox, cholera, plague, and typhoid fever.

2. *Employment of Vaccines in the Treatment of Localized Bacterial Inroads.*—Next to prophylactic inoculations, this gives the best results. And the results, in the respect that they are almost immediately manifest to the eye, are even more dramatic than those of any preventive inoculation. Perhaps the most rapid and convincing results are those obtained by small doses of streptococcic vaccine in lymphangitis and erysipelas; by staphylococcic vaccine in furunculosis, when the boil is just beginning to develop; and by minimal doses of tuberculin in phlyctenular affections of the conjunctiva.

3. *Employment of Vaccines in Dealing with Unopened Abscesses and other Localized Infections where the Microbes cannot be Reached from the Blood Stream.*—Vaccines are here, so far as appears to clinical inspection, quite inoperative.

4. *Employment of Vaccines in the Treatment of Localized Infections Associated with Heavy Autoinoculations.*—The scientific application of vaccines in these cases is extremely difficult and laborious; and the results which are obtained—and those obtained in the treatment of developed phthisis by tuberculin supply a good example—are not very convincing.

5. *Employment of Vaccines in the Treatment of Undrained Wounds Infected by Sero-saprophytes.*—There is not yet a sufficient body of experience to decide the question as to whether benefit can be obtained from vaccines in these cases. The question will be further discussed below in connexion with the wound infections of the war.

6. *Employment of Vaccines in the Treatment of Septicæmic Infections, and in particular Streptococcic Septicæmias.*—Up to the present—except perhaps in certain series of experiments relating to typhoid fever—vaccines have on the whole given very disappointing results. But it will be obvious to consideration, that as we advance through the whole series of applications—from prophylactic application to the employment of vaccines in septicæmias, the conditions are becoming progressively more difficult; so that success in treatment of septicæmias, if it is ever achieved, will be the very final achievement of vaccine therapy.

We have now prepared the ground for considering what has been obtained by the use of vaccines in the treatment of wound infections in this war.

I have in connexion with this heard the opinion of a very distinguished French surgeon—pronounced after watching the effect of vaccines upon, I should think, undrained wounds and septicæmic infections—that they had never done any good. I shall, by my general survey above, at least have put you on your guard against generalizing from one class of cases to all other cases. Let us now take each class of case separately, and ask ourselves whether in this vaccines have rendered any service. I think we shall then see that things work out everywhere in accordance with scientific law.

1. Prophylactic Inoculations of "Antisepsis Vaccines."

—If prophylactic inoculations of this kind have not been undertaken in our army, it has not been because a supply of antisepsis vaccines has not been at hand; but because the idea of undertaking such inoculations has not appealed to the individual medical officers who have given first aid to the wounded. And if any prophylactic inoculations have been undertaken, this can have been only on a very small scale; and the fact has not transpired. To be considered therefore here is only the question as to what we should on *a priori* grounds be justified in expecting from prophylactic inoculations against wound infections, undertaken upon the wounded. The answer is, I think, not doubtful. We might justifiably hope in a proportion of cases to sterilize the upper reaches of the wound, which would be less heavily implanted; and perhaps in isolated cases—those in which we have a comparatively light sowing of microbes—to sterilize the whole wound. Moreover, if we could employ vaccines in combination with *physiological drainage* (I mean by that: free outpouring of lymph obtained by the use of a lymphagogic solution) we might, I think, hope to stave off infection in