giddiness might be so pronounced as to compel him to stop work and to go home in a cab. Rest led to disappearance of these symptoms.

The pulse was 60, and the arterial pressure was 110 mm. On lying down the pulse was definitely fuller than when sitting. The vessels were soft. The heart at the apex was in the mammary line; the sounds were fairly good and closed. The abdomen presented no abnormality; to regulate the bowels a penta was taken regularly. The urine presented no abnormal characters.

In this patient the headache and giddiness were primarily cerebral, and were to be regarded as the result of disordered cerebral circulation, due to too close mental application, or to emotional influences. There could be no doubt that there was an imperative call for complete mental rest, away from the patient's ordinary environment. Here, again, on the hypothesis of local cerebral angioplasm being the cause of the phenomena, the danger was not that in one of these attacks cerebral haemorrhage would occur, but that the angiospasm might be so pronounced and of sufficient duration to lead to cerebral softening in the more purely mental areas of the brain.

A Lecture

ON

OXYGEN WANT AND THE MEANS OF ITS RELIEF.

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THE important advances made within recent years in the physiology of the respiration have furnished us, amongst other things, with more precise conceptions as to the rôle of the blood gases, the nature and production of oxygen want, the adaptations provided by the body for the relief of this want, and their assistance by art. To the laborious investigations of Haldane and his collaborators in particular we owe in great measure the light which has been shed on this subject, albeit many difficult problems still await solution. Now, oxygen want constitutes in itself a true disease of the respiration; therefore in this lecture it is not proposed to discuss the gross results of prolonged want of oxygen such as are found in the heart, the nervous system, the alimentary system, and the kidneys, but to confine attention to the respiration factors proper.

The Gases of the Blood.

The governing factor in the respiration is the carbon dioxide of the arterial blood. As observed by Haldane, the respiratory centre is probably as sensitive to carbon dioxide as the retina is to rays of light. Its activity is entirely dependent upon it, and should the tension of this gas fall below a certain point apnoea will result. When Head made his observations it was supposed that the vagi not only regulated the rhythm, but to a considerable extent also activated the centre. A vagus apnoea was supposed to result from summation of stimuli. But there appears to be little room for this theory nowadays. The tension or partial pressure of the carbon dioxide in the blood and alveolar air is maintained constant under normal conditions (Haldane and Priestley); the slightest increase exciting the respiratory centre and the excess of gas being given off by the increased breathing. It is now considered that what the centre really responds to is the hydrogen ion concentration. So sensitive is this reaction that a rise of 0.22 per cent. in the alveolar carbon dioxide percentage—that is, of 1.6 mm. in the pressure (the normal pressure being about 40 mm.)—will raise the breathing by 100 per cent. This corresponds to a difference in the hydrogen ion concentration so minute as to be beyond detection. Now, any acid other than carbonic, if added to the blood, increases the hydrogen ions in proportionate amount, and the effect of these, added to the hydrogen ions of the carbonic acid already present, is to excite the centre and cause hyperpnoea. To put this differently, the added acid lowers the threshold of excitation of the centre to carbon dioxide, so that it reacts to a correspondingly lower tension of the gas. This factor is of the greatest

importance and constantly comes into play in the physiology and pathology of the respiration. It is due to defective oxidation in the tissues.

Let us recognize that the respiration is essentially carried on in the tissues. The lungs, the circulation, and the kidneys are receiving, transmitting, and adjusting agents. It is the gas exchanges in the tissues which determine those in the lungs. In either case they are not necessarily carried out according to the law of the diffusion of gases. The endothelial lymph cells, the endothelium of the capillaries, and the epithelium of the lungs have secretory and selective functions. Normally they permit diffusion to take place in accordance with the gas laws, but under abnormal or exceptional conditions they exercise their powers of selection and secretion. The experiments of Bohr in 1891, attributing this function to the pulmonary epithelium, has been amply supported by recent research. Strassburg also found that the tension of carbon dioxide may be lower in the lymph spaces than in the venous blood. This secretory action, as in the case of the swim-bladder of fishes, may be largely dependent on the integrity of the pertaining nerves.

In the next place let us briefly consider the all-important matter of the tension or partial pressure of the gases of the blood. It is the tension that matters, not the amount. The amount may vary widely, and yet the pressure remain the same. In the case of the carbon dioxide, this regulation is very intricate and only partially understood. Of the total quantity of the gas taken up by the blood, from 36 to 46 volumes are in chemical combination, and only two and a half volumes are in solution in the plasma and corpuscles. It is only this small amount of the free gas in solution that determines the tension, the large quantity in loose chemical combination forming a store, so that as soon as the gas in solution decreases, an equivalent amount is dissociated to take its place, and vice versa, if the gas in solution rises above normal, the excess is taken into chemical combination, until matters are again adjusted by the breathing. This regulation is carried out chiefly through the serum-globulin. When the tension rises the globulin is displaced from its adsorption combination with the alkali (sodium) by the mass action of the gas, and alkali carbonate or bicarbonate is formed; when the tension falls the globulin again enters into possession. As the carbon dioxide tension rises the alkalinity of the plasma also rises. Very high tension, according to Gürber, causes expulsion of some of the hydrochloric acid from the sodium by mass action, with migration of the acid to the corpuscles. When acids other than carbonic—that is, those due to defective oxidation in the tissues—enter the blood, the carbon dioxide is dissociated to a certain extent and pumped out by the breathing. Such acids, however, except under extreme conditions, are taken up by the blood only to a limited extent, as its potential alkalinity is maintained within certain definite and necessary limits. As acid products of catabolism increase, the organism utilizes ammonia (which otherwise would pass to the liver to form urea) to combine with them. Hence the quantity of ammonia present in the urine is an index of the acidity of the blood. Did the organism not possess this means of defence, acid poisoning would quickly supervene in many conditions. On the other hand, as will shortly be seen, the addition of a certain amount of acid to the blood acts in a compensatory or protective fashion.

The partial pressure of carbon dioxide, as has long been recognized, exerts a very important influence on the absorption and dissociation of oxygen; the higher tension of carbon dioxide in the capillaries facilitating the dissociation of oxygen to the tissues, and the fall in tension in the lungs facilitating the absorption of oxygen. On the other hand, it has consistently been held since the experiments of Bohr in 1890, that the absorption and dissociation of carbon dioxide were uninfluenced by the presence of oxygen, and the ready combination of the former gas with methaemoglobin lent support to this belief. Just lately, however, an important communication has been made by Christiansen, Douglas, and Haldane,¹ in which it is contended that saturation of the haemoglobin with oxygen has a very marked effect in diminishing the absorption and increasing the dissociation of carbon dioxide as compared with blood deprived of oxygen. In the light of this statement, the blood gases reciprocally exert exactly similar effects, in accordance with the needs of the body.

Just as in the case of carbon dioxide, the existing tension of oxygen in the blood depends on the small amount held in solution in the plasma, the large reserve in the corpuscles being drawn upon as required. Under ordinary conditions the haemoglobin is practically saturated with oxygen, and any increase brought about by inhaling pure oxygen or compressed air is mainly in the quantity in solution, and this has the advantage of being readily available for the needs of the tissues. Normally the oxygen tension of the arterial blood, like that of the carbon dioxide, is maintained within very narrow limits, the haemoglobin being enabled to take up all its required oxygen at a considerably lower atmospheric pressure than exists at the ordinary level.

The Voluntary Production of Oxygen Want.

The oxygen of the blood gets used up very quickly under conditions of sudden and severe exertion, or when the breath is held. It was found by Hill² that the previous inhalation of oxygen under these circumstances made a great difference. This was due in the case of exertion to the lessened formation of lactic acid in the tissues, while the power of holding the breath longer is susceptible of explanation in the new observation referred to—namely, the heightened oxygen tension in the pulmonary blood expelling the carbon dioxide into the alveoli. These observations show certain effects of want of oxygen in the tissues and in the lungs. Again, by making a number of deep voluntary respirations many persons can create a miniature Cheyne-Stokes type of breathing, as was shown by Douglas and Haldane.³ But, if abundance of oxygen be added to the air inhaled, the breathing, after a longer apnoeic pause, begins and proceeds normally. From this much may be learnt. The initial forced breathing pumps the carbon dioxide well out of the blood. If no oxygen be inhaled, the breathing, nevertheless, begins when the alveolar carbon dioxide tension is still comparatively low, and the tension of the gas in the centre much below the stimulating value. The authors explain this by assuming that lactic acid forms in the centre itself, lowering its threshold of excitation to carbon dioxide, as there is no time for lactic acid to be produced in the general circulation. As soon as the breathing begins this acid is oxidized, more carbon dioxide is pumped out, and apnoea again sets in, the cycle continuing until the carbon dioxide in the blood has risen to the critical value. Now, if plenty of oxygen be first given, it prevents the formation of lactic acid in the centre, and with the production of a high alveolar percentage of carbon dioxide the breathing is longer delayed, and then proceeds *regularly*. We herein see the effect of want of oxygen on the respiratory centre. That lactic acid is the unoxidized substance produced in this case is hypothetical, and it is more correct to say that the excitation of the centre is due to the effects of want of oxygen, either direct or indirect, increasing its hydrogen ion concentration.

The Production of Oxygen Want in Disease.

But when there is a general and continuous want of oxygen, the acid products of catabolism which escape oxidation in the tissues are constantly being absorbed into the circulation, and excreted by the kidneys. In this way the respiratory centre is excited in a more or less regular and permanent fashion, and it is only when there is defect of the local circulation in the centre, often due to individual peculiarities, that we encounter Cheyne-Stokes respiration. In the diseases of the lungs and in obstructed conditions of the circulation it is after this manner that want of oxygen causes the hyperpnoea or dyspnoea. Now it is particularly to be noted that in the great majority of such cases coming under observation the carbon dioxide tension is low, and it is only when the breathing is exceptionally obstructed, as for instance in acute asthma or extensive stasis of blood in the lungs from any cause, that we find the hyperpnoea or dyspnoea to result from increased carbon dioxide tension. The reason for this is that the hyperpnoea in the great majority of cases can practically always get rid of the carbon dioxide, even though it cannot, as a rule, supply the requisite oxygen to the tissues. If want of oxygen is made rapidly, the hyperpnoea is excessive, but when it occurs very gradually, the carbon dioxide is pumped out slowly and

the patient may be cyanosed from the amount of reduced haemoglobin in his arterial blood, with but little observable hyperpnoea. Different persons react differently, however, as the respiratory centre possesses, as mentioned, individual differences in regard to the circulation. In any case the important point to remember is that the carbon dioxide may be pumped out of the blood without producing a corresponding increase in the absorption of oxygen. During this time the respiratory quotient is raised, but Pembrey and Cook⁴ found that after a hyperpnoea had continued for hours, as in cardiac disease, a quotient as low as 0.63 may be obtained—in other words, the carbon dioxide is first pumped out and then kept low by the breathing. A severe and prolonged hyperpnoea while the body is at rest may reduce the carbon dioxide to an extent dangerous to life and must be guarded against.

Nature's Adaptations to Oxygen Want.

But it is the increased pulmonary ventilation, associated with a low carbon dioxide tension, and due to the acidosis, on which the patient's life depends. And here we encounter the remarkable adaptations which constitute Nature's means of relief for want of oxygen. Clinically we often obtain evidence of these, as when patients highly cyanosed manage to get on very comfortably. In some of these cases such evident compensations as hypertrophy of the heart and alterations in the distribution of the blood are found. The adaptations which are evoked by the stimulus of acid products of catabolism consist mainly in—(1) Excitation of the respiratory centre, causing increased pulmonary ventilation; (2) excitation of the heart-rate; (3) increase in the haemoglobin and red corpuscles, with alteration in volume of the blood; (4) energetic oxygen secretion by the pulmonary epithelium; (5) shifting of the dissociation curve of oxyhaemoglobin to the right; and (6), in some cases at least, modification of the alkali regulation of the blood by the kidneys. The common aim of all these factors is to increase the arterial oxygen tension and maintain oxidation in the tissues.

As regards the modification of the alkali content of the blood by the kidneys, this suggestion was made in the Pike's Peak research by Douglas, Haldane, Henderson, and Schneider,⁵ in consequence of the fact that the alveolar carbon dioxide tension was as low, or even lower, after the initial lactic acid excess had disappeared from the blood. The persistence of diminished alkalinity of the blood (which was necessary to maintain the oxygen pressure) is referred to a lowering (caused by the catabolic stimulus) of the threshold of alkalinity for the kidneys, corresponding, in fact, to what occurs in the respiratory centre in relation to carbon dioxide. It is evident that the part played by the kidneys in the respiration is of the most vital importance. It is needless to point out that the various products of the digestive activity and the general metabolism in so far as they affect the composition of the blood are regulated by the kidneys, as the great variations in the alkali, acid, and nitrogen content of the urine prove. The blood is normally maintained by the kidneys at a more or less fixed composition and at a fixed potential alkalinity. It has been shown by Schittenhelm and Katzenstein⁶ that the ratio of ammonia in normal urine to the total nitrogen remains constant within narrow limits.

Defective Oxidation from Tissue Poisoning.

Now want of oxygen, provided one is breathing a fairly normal atmosphere, must always be due to a defect in the lungs or the circulation. But reference may here be made to a group of cases in which, with dyspnoea, there is not, strictly speaking, want of oxygen, but a condition of defective oxidation in the tissues either of a primary kind or else associated with renal disease. The acidosis in this case doubtless lowers to a greater or less degree the oxygen capacity of the haemoglobin (meionexy), but if, as frequently happens, the alveolar carbon dioxide tension is at the same time very low, the meionexy is not such as to necessitate the amount of hyperpnoea or dyspnoea sometimes found, and which may be in excess of the requirements. The excitement of the respiratory centre may be overdone. This is the more evident when it is considered that in the severe acidosis of diabetic coma, where the ammonia supply fails, and β -hydroxybutyric and acetoacetic acids utilize as far as possible the alkali of the

blood, it was nevertheless shown by Pembrey⁷ and his collaborators that the low tension of carbon dioxide was not due to failure of carrying power on the part of the blood, but to lessened production of the gas in the tissues. In accordance with this is the observation of Abderhalden⁸ that in such cases there is diminished tissue oxidation, as various products of the hydrolysis of albumin (amino acids) are found in the urine. This diminished tissue oxidation is therefore due to failure of the oxidizing ferments to utilize the oxygen offered them, a condition the reverse of that found in true oxygen want. One cannot help believing that differences to a corresponding degree are to be found in the acid metabolites themselves. In cases of renal dyspnoea, examination of the blood and urine by Ryffel⁹ failed to indicate the acid body. It was not lactic acid, nor was the meionexy connected with the high percentage of urea in the blood. Now this type of dyspnoea may doubtless complicate a dyspnoea from true oxygen want, as that of cardiac disease, but in view of the foregoing considerations it would obviously be incorrect, as lately suggested by Lewis,¹⁰ to place both the cardiac and renal types in a single group.

Some idea may now be gained of the extent and variety of the respiration changes which must necessarily be associated with the various diseases, and of which at present we know little or nothing. Not only each disease, but each separate case possesses its own features, the seat of failure being now here and now there, and the compensations in like manner varying.

Scope of the Investigation.

The cause of the oxygen want being discovered, inquiry is made as to how the machinery for its relief is working. To be sure, severe oxygen want may be caused by a massive pleural effusion or other mechanical condition, artificially removable, to which further reference need not be made. The clinical examination of the various organs is carried out, and the points of obstruction noted. Then comes the investigation of the alveolar air and blood gases, and the various nitrogens, more especially the relation of the ammonia to the total nitrogen of the urine. The investigation may be extended almost indefinitely so far as work on the blood is concerned, but, ordinarily, the oxygen and carbon dioxide content* and the oxygen capacity are sufficient. By means of Barcroft's apparatus all this can be accomplished with 1 c.cm. (or less) of blood. If it be desired to calculate the total respiratory exchange and the volume of air breathed, the "bag" method of Douglas is easy and convenient,¹¹ care being taken, however, to make due allowance for the dead space. For the general kidney efficiency the phenolsulphonaphthalein test of Rowntree and Geraghty may be used. For the blood nitrogens the method of Folin and Denis is accurate, and requires but little blood.

Peabody,¹² working lately on the lines above indicated, in a series of cases of pneumonia obtained some interesting results. He took the gas content of the peripheral venous blood and quantitated the nitrogen and ammonia of the urine. He also investigated the action of the pneumococcus on the blood. The carbon dioxide content was always diminished in the febrile period, except in two cases, and the oxygen content was well within normal limits in the various stages of the disease in by far the largest number of uncomplicated cases. The fluctuations in the carbon dioxide were in inverse proportion to the output of ammonia in the urine and bore no relation to the chlorides. High nitrogen and ammonia excretion were found with low carbon dioxide tension not only during the fever but sometimes also after the crisis. Their relations, however, could be modified by the administration of sodium bicarbonate. Two cases showed, along with cyanosis, a relatively high carbon dioxide and a low oxygen content, due to the block in the lungs; but in a third case these features persisted even when the lungs were clear, due either to failure of the epithelium, slowing of the circulation, or a change in the chemical constitution of the blood. In all cases where the pneumococcus had entered the blood the oxygen content was much diminished, and experiments made *in vitro* proved that the pneumococcus

acted, not in utilizing the oxygen, but in changing the constitution of the haemoglobin molecule, rendering its combination with oxygen difficult. *In vitro* there was formation of methaemoglobin. It is obvious that the treatment would vary considerably if guided to some extent by these indications.

The Principles of Treatment.

The experiments of Lorrain Smith¹³ proved that long-continued inhalation of oxygen under pressure induces a pneumonia in animals by causing injury to the alveolar epithelium. But when given in physiological doses oxygen acts as a restorative and tonic to the epithelium. In the Pike's Peak investigation stress is laid on the dangers attending fatigue of the epithelial cells, consequent on the long-continued stimulus by metabolites. The authors refer to the high mortality of pneumonia at high altitudes, which they believe might be avoided by treatment with oxygen or by carbon dioxide added to the air. "Such chambers," they remark, might be used in treatment at ordinary levels provided there was "intelligent knowledge of the physiological conditions." This "knowledge" enables us to assist the treatment in a rational and therefore successful manner. We do not give digitalis in every case of heart disease, nor should we give oxygen simply because a patient has hyperpnoea or even cyanosis, as neither symptom may be due to want of oxygen. Now we recognize the direct and indirect methods of oxidizing the blood, the first by inhaling the gas, and the latter by improving the circulation and the ventilating capacity of the lungs. When the disease is acute and attended by a hyperpnoea which is not maintaining the normal oxygen pressure, oxygen by inhalation should be given. With evident cardiac weakness the gas should be alcoholized after the method described by Willcox and Collingwood.¹⁴ Should there be much stasis of blood in the lungs venesection may be indicated in suitable cases, so as to get the oxygen into circulation. Whether the gas be given pure or diluted with air will depend on the severity of the symptoms, and in many cases it may be given for short periods of about five minutes, and repeated at intervals where necessary. But prolonged administration may be needful. The good effects of the inhalation are not limited to increasing the oxygen carried by the blood. There is evidence that it enables the pulmonary epithelium to consume the circulating metabolic products, to some extent at least. In cases with Cheyne-Stokes breathing, or when the carbon dioxide content is very low, the best results may be obtained by adding a measured percentage of carbon dioxide to the oxygen, or to oxygen mixed with air, or to pure air, as the observations of Pembrey have shown. This has the additional advantage of increasing the dissociation of oxygen to the tissues.

The high importance of the kidney in these cases has been mentioned. Hence the far-reaching effects of diet in metabolism and excretion. Otto Folin has shown how by a low nitrogenous diet it is possible to reduce greatly the urea and non-protein nitrogen in the blood. Again, as carbohydrates contain sufficient oxygen to oxidize their hydrogen, a vegetable diet is the most saving of oxygen.

In the large class of cases, more or less chronic, exhibiting oxygen want, the inhalation of oxygen is resorted to only should urgent symptoms supervene. The really effective treatment is that which increases the oxygen in circulation by means devised to improve the circulation in the lungs, their nutrition and ventilating capacity; and which in suitable cases induce a certain degree of Bier's hyperaemia treatment—for example, by rarefied air. The contraindications are a tendency to haemorrhage, advanced arterial degeneration, and hyperpnoea when the patient is at rest. Here, as in the more acute cases, when guided by physiology, we are to some extent at least no longer groping in the dark, and alongside the methods of treatment otherwise sanctioned, indications of a precise and luminous character may be placed and considered.

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* Usually this gives a fairly correct idea of the pressure. Clinically, the tension of the carbonic dioxide cannot be made directly, but may be estimated from the alveolar tension, while that of the oxygen is difficult. The carbon monoxide method is available.