A Lecture ON ACCLIMATIZATION TO HIGH ALTITUDES.

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THE great physiological difficulties met with at very high altitudes in the Mount Everest expeditions, and so far conquered, have recently drawn much attention to acclimatization to high altitudes; but apart from this the phenomena of acclimatization, whether to high altitudes or to other unusual conditions of environment, are of the deepest biological interest and significance. In my book on *Respiration*, published two years ago, I discussed this subject piecemeal, but I wish to take this opportunity of reviewing it as a whole in the light of the additional facts revealed by the Mount Everest expeditions and the recent Anglo-American expedition to the Andes.

It was proved quite clearly by Paul Bert nearly fifty years ago that the abnormal symptoms experienced at very low atmospheric pressures, such as those existing at high altitudes, are due entirely to the low partial pressure of the oxygen in the air and consequent abnormally low partial pressure of the oxygen supplied to the tissues by the blood. It took about thirty years before the significance of his experiments and reasoning was generally understood by physiologists; but I think I need hardly go back upon this. He was also well aware that considerable acclimatization to low atmospheric pressure occurs; but as to the manner in which this acclimatization is brought about, or the extent to which it could be carried, his knowledge was limited.

Effects of Low Atmospheric Pressure on Unacclimatized Persons.

The effects of a temporary exposure to low barometric pressure can be studied conveniently in a steel chamber such as that originally employed for this purpose by Paul Bert. The air of the chamber is exhausted by means of a pump, and the pressure inside regulated by varying the amount of air which is allowed to leak in through a tap. We can also study these effects during ascents in balloons or aeroplanes, or after comparatively rapid ascents, whether on foot or otherwise, to high mountain altitudes.

On going within a few hours to a barometric pressure corresponding to an altitude of as little as five or six thousand feet we first begin to notice that any considerable exertion, such as walking uphill, is accompanied by unusual panting and increase of pulse rate. At three or four thousand feet higher this effect is much more marked, and is commonly accompanied by other more serious effects, showing themselves after a time even during rest. One of these effects is what is known as mountain sickness. Its chief symptoms are nausea, vomiting, and headache, though several hours of exposure are needed before they appear. With greater altitudes or depressions of barometric pressure these effects become more and more marked, and show themselves in more and more persons. More or less of blueness of the lips can also be observed, and various abnormal mental symptoms. Breathing also tends in many persons to become periodic, and sleep to be disturbed. When a pressure of only half an atmosphere is reached, corresponding to a height of about 18,000 feet, the acuity of vision and hearing begin to be distinctly affected, as well as the power of remembering the events which are happening and forming a clear judgement about them. This loss of sensory and mental power becomes more and more marked as the barometric pressure is further reduced, until at about 25,000 feet or less a condition of complete helplessness, accompanied by very marked blueness of the lips, is commonly produced after a quite short exposure. Power over the limbs, beginning with the legs, fails; the

pulse and respirations become rapid but feeble; consciousness is lost; and the condition is one of impending death from failure in the depth of respiration.

Influence of Acclimatization.

These symptoms are wiped out completely if, by substituting oxygen for nitrogen in the rarefied air breathed, the fall in the partial pressure of oxygen in the air is prevented; but they can also be prevented or got rid of to a large extent by acclimatization. Persons who ascend gradually, day after day, to heights of 20,000 feet or more will probably never experience mountain sickness or any of the other more formidable effects of great altitudes; and persons who have gone rapidly to great heights and stayed there for several days will recover from the more formidable effects, provided they have not gone too high for acclimatization to occur before their death. The Mount Everest achievement of this year has shown that persons can even reach the height of 28,000 feet without mountain sickness.

Causes of Low Oxygen Pressure in the Arterial Blood.

In order to follow the means by which acclimatization is brought about we must first understand the means by which an abnormally low partial pressure of oxygen is produced in the tissues, and particularly those of the central nervous system. Paul Bert and others showed that whereas with a normal pressure of oxygen in the inspired air the arterial blood is bright scarlet and its haemoglobin almost completely saturated with oxygen during rest, it becomes more or less blue, with the haemoglobin imperfectly saturated, when the oxygen pressure of the inspired air is very low. This is due to the oxygen pressure in the arterial blood being no longer sufficient to permit combination of oxygen to a normal extent with the haemoglobin, since oxyhaemoglobin is easily dissociable. Thus the blood reaching the tissues has an abnormally low oxygen pressure. It may, and does, still contain abundance of dissociable oxygen to cover all the normal consumption of oxygen by the tissues; but the pressure of this oxygen is too low, and the observed symptoms are evidently due to the low oxygen pressure, and not to mere insufficiency in the amount of oxygen in the blood.

The most natural explanation of the low oxygen pressure in the arterial blood is that the oxygen pressure in the lung alveoli is correspondingly low, and that, since the passage of oxygen inwards depends, presumably, on simple diffusion, the arterial blood cannot be saturated to a higher oxygen pressure than that of the alveolar air. This reasoning, however, takes no account of acclimatization or of the fact that between the alveolar air and blood there is a thin layer of living protoplasm which might upset the reasoning altogether by actively driving oxygen inwards into the blood. The suspicion that this may be the case originated with Ludwig, and was transmitted by him to his pupil Christian Bohr of Copenhagen, and thence to a pupil of the latter—myself. It is pretty clear that Ludwig's idea was suggested by the experiments of Moreau, a French physiologist, on the physiology of active secretion of oxygen by the living wall of the swim-bladder. I have in my library Ludwig's own copy of one of Moreau's papers. Moreau's work was inspired by the remarkable discovery made at the beginning of last century by Biot, Pasteur's early master, that the swim-bladder may contain almost pure oxygen. In a deep-sea fish the pressure of oxygen may be five hundred times that in the surrounding sea-water. The secreting epithelial cells are thick and cubical, while the epithelial cells of the lung alveoli are extremely thin; but for secretory activity to be of great importance in the lungs it would only be necessary for the secreting cells to overcome an oxygen pressure of less than a four-thousandth of that overcome by the cells of the swim-bladder. In considering acclimatization to high altitudes I shall first discuss the evidence for and against active secretion of oxygen inwards, and its relation to acclimatization.

We must first distinguish the oxygen secretion controversy from another one relating to gaseous exchange in the lungs, and also emanating from Ludwig. He suspected that the process of oxygenation of blood in the lungs may help to expel carbon dioxide, and one of his pupils published experiments which gave some support to this idea.

With the help of the aerotonometer devised by Pflüger, evidence was, however, brought forward by the latter's pupils which seemed to negative Ludwig's idea. Bohr failed also to substantiate it. Finally, however, Christiansen, Douglas, and I, with the help of far better methods of blood-gas analysis, showed clearly, about eleven years ago, that Ludwig was right; and our results are now everywhere accepted, particularly as they explained how the aerotonometer experiments of Pflüger's pupils had been fallacious.¹

Experiments with Aerotonometers.

It was Bohr who first, in 1891, brought forward definite experimental evidence in favour of the oxygen secretion theory.² He used an improved form of the Pflüger aerotonometer. The arterial blood, which was rendered incoagulable by the injection of peptone or leech extract, was allowed to flow for a short time alternately in and out of two glass vessels connected together above, and containing a gas mixture with which the blood came into contact, so that free diffusion could occur between the blood and gas mixture before the blood returned to the animal. It was found that although the pressure of oxygen in the gas mixture usually fell below that of the alveolar air, it occasionally rose distinctly higher. Bohr regarded these results as showing that active secretion of oxygen may occur in the lungs.

The investigation was then taken up by Fredericq.³ Using a slightly simpler form of aerotonometer, permitting less interference with the animal's circulation, he found that, when sufficient time was given for complete diffusion equilibrium to occur between the gas mixture and arterial blood, the oxygen pressure in the gas of the aerotonometer was, in his experiments, always very considerably below that of the alveolar air. He therefore concluded that there is no real evidence for oxygen secretion, and that the apparent positive results of Bohr were due to experimental error. The results of Fredericq's experiments are definite and unmistakable, and they were fully confirmed by later experiments made by Krogh with a still better apparatus.⁴ They certainly showed no evidence of oxygen secretion; but they had a further significance, which to my mind has emerged more and more clearly as our knowledge of respiration and the blood gases has increased. That significance is that neither the aerotonometer method nor the corresponding method of analysing the gases of arterial blood and calculating the oxygen pressure from the results is reliable in testing the theory of oxygen secretion.

On examining Fredericq's results we find that they give two values, one being the pressure of carbon dioxide, and the other of oxygen, in the arterial blood. For carbon dioxide the value corresponds to an excess of about 3 per cent. of carbon dioxide in air, while for oxygen it corresponds to a deficiency of about 8 per cent. If we assume, as we can do with practical certainty, that the pressure of carbon dioxide corresponded to the percentage of carbon dioxide in the alveolar air, it is quite impossible that the deficiency of oxygen can also have corresponded to the deficiency of oxygen in the alveolar air. The respiratory quotient would be a quite impossibly low one, particularly in some of the experiments. We thus seem at first sight driven to conclude, as Fredericq did, that even when an animal is at rest, and breathing pure air at ordinary pressure, the oxygen pressure in the blood and alveolar air may be far from coming into diffusion equilibrium with one another. But if this is so even during rest, what would happen during muscular exertion, when more than ten times as much oxygen has to be taken up from the alveolar air? The arterial blood would certainly be of a deep blue colour, which is not the case; and a simple calculation shows that the absorption of the amount of oxygen which is actually absorbed during muscular work at a high altitude would be quite impossible.

It is thus perfectly evident that in these experiments some cause was preventing the gas pressures in the arterial blood passing through the aerotonometer from representing the degree of equilibrium which is reached between the oxygen pressures in the alveolar air and blood passing through the alveoli, so that neither the aerotonometer method nor the corresponding method of inferring the

oxygen pressure in the arterial blood from the degree of saturation with oxygen of the haemoglobin in it could possibly give reliable measurements relating to the question of oxygen secretion. We thought for long that this cause was most probably that during the period which elapses between saturation of the blood in the lungs and its passage through the aerotonometer, or into the blood-gas apparatus, a certain amount of oxygen enters into stable chemical combination. The real cause was, however, revealed quite clearly by the investigations published in 1919 by Meakins, Priestley, and myself on the effects of shallow breathing, and by the light which our results threw on the composition of arterial blood.⁵

Uneven Composition of the Alveolar Air.

We found that when the breathing is shallow, even if it is very rapid, and even if the oxygen percentage in the mixed alveolar air is above normal owing to great increase in the amount of air breathed with the rapid respirations, unmistakable symptoms of oxygen shortage are produced, and are promptly relieved by raising the oxygen percentage in the inspired air. The evident explanation of these facts is that the air in the different alveoli, instead of being uniform in composition as had formerly been assumed, varies in composition at different parts of the lungs. A sample of alveolar air, taken by the ordinary method introduced by Priestley and myself, represents, therefore, only the mean composition of the air in the deep alveoli. In some alveoli the oxygen percentage must be much lower than the mean and the carbon dioxide percentage higher, and conversely in other alveoli. With shallow breathing this irregularity is much exaggerated, owing to the uneven manner in which different parts of the lungs expand, as was pointed out by Sir Arthur Keith.

Owing to the different shapes of the dissociation curves of the oxyhaemoglobin and the bicarbonate, in the forms of which the oxygen and carbon dioxide in the blood are respectively combined, the irregularity will affect quite differently the partial pressures of carbon dioxide and oxygen in the mixed arterial blood. This can be seen at a glance on looking at the two curves, which are reproduced side by side in our paper. The carbon dioxide pressure in the mixed arterial blood will depend simply on the average carbon dioxide pressure in the alveolar air, since the effects on the blood of excesses of carbon dioxide in some alveoli are neutralized by those of the deficiencies in others. But a deficiency of oxygen brings the blood down the steeper part of the dissociation curve, while an excess brings it along the flatter part. The inevitable result is that the pressure of oxygen in the mixed arterial blood is lower, and may be far lower, than that of the mixed alveolar air. This effect will also, it can be seen, be much exaggerated in its effect on the percentage saturation of the mixed arterial blood with oxygen if the mean oxygen pressure in the alveolar air is low, as at high altitudes. An experiment of Krogh's on an animal breathing a low percentage of oxygen shows this clearly. We have thus a simple explanation of why, before acclimatization occurs, there is far more cyanosis than could otherwise be accounted for.

It is an entire mistake to suppose that this want of correspondence occurs only during shallow breathing, though it is much exaggerated by shallow breathing. Whether we use aerotonometers or the method of inferring the oxygen pressure of the arterial blood from the degree of saturation of the haemoglobin in it, as shown by blood-gas analysis, the result always is that under normal resting conditions the oxygen pressure of arterial blood is below that of the mixed alveolar air. In my own case, for instance, blood-gas analysis showed an oxygen pressure about 14 per cent. below that of the alveolar air. Perhaps no experiments bring the facts home to us more clearly than observations on the effects of holding the breath. If we distend the lungs with a deep breath of air, and then hold the breath as long as we can, we find, by repeating the experiment with air enriched with oxygen, that it is not merely excess of carbon dioxide, but also, as Leonard Hill and Flack first found, want of oxygen that has limited the time during which the breath can be held. With the enriched air the breath can be held far longer. Douglas and I found that the curtain-

ment still existed, although the mixed alveolar air at the breaking point contained more oxygen than normal, while Davies and Meakins proved by analyses of the arterial blood that at the breaking point the oxygen pressure in the arterial blood is far below that of the mixed alveolar air.

The Carbon Monoxide Method of Investigation.

The fact that it is quite impossible to obtain reliable results as to the presence or absence of oxygen secretion by the aeronometer method, or by analysing the arterial blood, led me to introduce a quite different method of experiment. This method depends on the fact that oxygen and carbon monoxide compete with one another in accordance with a perfectly sharp and definite physical law when they both strive to enter into combination with the haemoglobin of the blood. The equilibrium which is reached depends on the relative pressures of the two gases, so that if we know (1) the percentage saturation of the blood with carbon monoxide when equilibrium is reached, and (2) the pressure of carbon monoxide, we can infer the pressure of oxygen. It is evident that by this method we can infer the mean pressure of oxygen, not in the mixed arterial blood, but in the unmixed blood leaving the lung alveoli. This is the method used, first by Lorrain Smith and myself; later, in an extremely careful series of experiments, by Douglas and myself with greatly improved technique⁶; and later still in the Anglo-American expedition to Pike's Peak by Douglas, Yandell Henderson, Schneider, and myself, for the investigation of acclimatization to high altitudes.⁷ For further details of the method I must refer to the original papers, or to my book on *Respiration*. I need only give here the results which were reached.

Experiments at Normal Atmospheric Pressures.

We first investigated, partly on man and partly on mice, what happens under perfectly normal conditions at ordinary atmospheric pressure during rest. The experiments showed unmistakably that very exact diffusion equilibrium is reached between the oxygen in the alveolar air and that in the blood. This is what one would expect on purely physical grounds; and the experiments showed clearly the fallacy in the experiments of Fredericq, Krogh, and others who have inferred from experiments with the aeronometer, or from analyses of arterial blood, that sensible diffusion equilibrium does not occur. The result is what one would expect on physiological grounds: for oxygen secretion, if it occurred, would be of singularly little use, since it could increase but little the normal saturation of the arterial blood with oxygen.

We then examined in mice what occurs in fairly prolonged exposure to the oxygen shortage of carbon monoxide poisoning. The result was that as the oxygen shortage increased the mean oxygen pressure in the blood leaving the alveoli gradually rose high above that of the alveolar air and even the inspired air. With oxygen shortage produced rapidly in man by lowering the percentage of oxygen in the inspired air the oxygen pressure in the blood leaving the alveoli rose only very slightly above that in the alveolar air. This is in good agreement with the fact that acclimatization to the low oxygen pressure in the air at a high altitude requires a considerable time.

Our next step was to examine what happens during muscular exertion. It is during muscular exertion that we should expect to find oxygen secretion coming into play. The reason for this inference is that during hard muscular exertion shortage of oxygen occurs very readily, and this shortage, in so far as it affects the breathing, must be due to deficient saturation of the arterial blood with oxygen. The breathing during hard muscular exertion becomes usually of the type produced, not by mere excess of carbon dioxide, but by a combination of this with shortage of oxygen. In other words, the rate of breathing and volume of air breathed increase out of proportion to the rise of carbon dioxide in the alveolar air, and finally the percentage of carbon dioxide in the alveolar air falls below normal. We have also now direct evidence, first obtained by Harrop, that with hard enough work there is a great fall in the oxygen pressure of the arterial blood. Further indirect evidence is furnished by the fact that

the doing of very hard work is greatly facilitated by air in which the percentage or pressure of oxygen is raised.

The physiological function of oxygen secretion (if it occurs) during muscular work is presumably to prevent or diminish the fall which would otherwise occur in the oxygen pressure of the arterial blood. Hence it is not to be expected that an actual rise above that of the alveolar air will occur readily during muscular work when active secretion occurs. On the other hand, it is evident from our observations of oxygen secretion in connexion with carbon monoxide poisoning that the stimulus to oxygen secretion originates in the tissues, not in the lungs, and is probably due to some substance carried to the lungs, or possibly the central nervous system, from tissues which are short of oxygen. Hence we thought that the best chance of producing an actual rise of oxygen pressure in the blood leaving the alveoli would be to do exhausting work with only one arm, so as to furnish the stimulus to secretion without at the same time so raising the consumption of oxygen in the body as to occasion, apart from secretion, any appreciable fall in the oxygen pressure of the arterial blood. Our expectations were justified, and we found a very considerable rise in the mean oxygen pressure of the blood leaving the alveoli over that of the alveolar air. This occurred in every experiment, and was quite unmistakable. It seems probable that the occasional positive result in Bohr's experiments depended on stimuli arising from interference with the circulation in his method of experiment.

If the response to want of oxygen by oxygen secretion in the lungs is a normal response we should expect to find that it becomes more ready and powerful with use, just as other functions are improved by use. Evidence on this point has been furnished by a series of observations made by Professor Briggs of Edinburgh.⁸ While experimenting with mine-rescue apparatus, during the use of which air greatly enriched with oxygen is breathed, he found that men who are in good muscular training receive hardly any benefit from the enriched air during comparatively hard muscular work. Men who are not in training receive, on the other hand, great benefit—a fact which is well known to me from personal experience. The difference can be measured easily by analyses of the expired air or alveolar air, and these are evidently a good test of physical training. It thus seems evident that a man in good physical training can prevent shortage of oxygen in his arterial blood; and active secretion of oxygen is the only known means of doing this.

Experiments on Pike's Peak.

The final experiments were made during our stay of some weeks on the summit of Pike's Peak at a height of 14,000 ft. The results were again quite definite. The mean oxygen pressure of the blood leaving the alveoli was found to be, after, but not before, acclimatization had occurred, at least 50 per cent. higher than in the alveolar air, and only a little lower than at sea level. Let us see what this result did, and did not, mean. It meant that the mean oxygen pressure of the blood leaving the lung alveoli was 50 per cent. higher than in the alveolar air, but certainly not that the mixed arterial blood as we find it in an artery or in blood taken from an artery had almost a normal oxygen pressure or saturation with oxygen. The whole of the phenomena of acclimatization are dependent on the continued stimulus of oxygen shortage in the blood, as we said again and again in the Pike's Peak report.

We thought at the time when the report was written that the shortage was almost entirely due to increased oxidation in the blood during the period which elapsed between its leaving the lungs and reaching the tissues; for we did not then know of the irregularity of the composition of the air in the lung alveoli and the consequences of this which I have already pointed out. With a lowered partial pressure of oxygen in the inspired air these consequences must, of course, be far more marked, as already remarked; and this accounts for the very marked blueness of unacclimatized persons on Pike's Peak. Meakins, Priestley, and I found that in neurasthenic cases suffering from the nervous disturbance of respiration, which makes the breathing

abnormally shallow and rapid (so-called "D.A.H." or "disordered action of the heart"), even a slight diminution of atmospheric pressure, such as produced no appreciable reaction whatever in normal persons, produced the most urgent symptoms when these patients were tested in a steel chamber.

In the persons carefully observed on Pike's Peak—at least in the cases of Douglas, Yandell Henderson, and myself—the shortage of oxygen in the arterial blood was so slight after acclimatization that we could observe no diminution at all in the normal redness of the lips, though we were all very distinctly blue in the lips during the day or two which elapsed before acclimatization, when we were still suffering from mountain sickness. In the many persons who came up temporarily by train, on donkeys, or on foot, the blueness was also nearly always well marked, and sometimes not only extreme, but accompanied by clouding, or even complete temporary loss of consciousness. In unacclimatized persons who were walking up along the railway track and who were not in physical training the cyanosis during the exertion became extreme, and rests were necessary every few steps.

It is well known to mountaineers that persons who are in good training are much less susceptible to mountain sickness than others. In the light of Briggs's observations and their interpretation we can now understand this readily, for persons in good training are also ready to secrete oxygen.

Increased Percentage of Haemoglobin at High Altitudes.

I must now pass on to the discussion of other factors in acclimatization. The best, and longest, known of these is increase in the percentage of haemoglobin in the blood. This must help in the following manner. With a higher percentage of haemoglobin in the blood there must be, other things being equal, a larger store of dissociable oxygen in the arterial blood. This is of no direct help in combating the symptoms, which, as we have already seen, are due to deficiency in the partial pressure of the oxygen; but it must help indirectly in the following manner. With a given disappearance of free oxygen in the tissues the pressure of oxygen will not fall so low if there is an increased proportion of haemoglobin in the blood. In this indirect way the mean pressure of oxygen will be kept higher, and it is the pressure of oxygen round the living tissues, and not merely in the arterial blood, that matters.

The extent and the rapidity with which the haemoglobin percentage in the blood increases in different individuals are very variable; and the more essential physiological changes during acclimatization may be almost complete before there is much increase in the haemoglobin. The mean percentage of haemoglobin, however, increases quite regularly with fall in barometric pressure, as was shown by Miss FitzGerald. The importance of increase in the haemoglobin percentage was formerly much exaggerated, at a time when the other more decisive factors in acclimatization were not yet understood; but in the long run, and at very high altitudes, increase of haemoglobin is probably of considerable indirect importance.

Increased Breathing at High Altitudes.

I now come to a factor which is certainly of very great importance. Those not familiar with the physiology of respiration and circulation might easily imagine that in order to combat the effects of defective saturation of the arterial blood with oxygen what is chiefly necessary is merely to increase the amount of air breathed, for by this means the pressure of oxygen in the alveolar air and arterial blood can be raised considerably. It is evident also that in persons under greatly reduced atmospheric pressure, whether they are acclimatized or not, the breathing is much increased; and mere increase in breathing is thus apt to be taken as a sign of acclimatization. But we know now how amazingly delicate is the normal regulation of the hydrogen-ion concentration of the blood, and that this regulation is at once upset with serious effects if, by unnaturally increased breathing, too much carbon dioxide is washed out of the blood. Under the stimulus of want of oxygen the breathing tends to be increased;

but this, by washing out carbon dioxide, makes the blood and whole body more alkaline—in other words, produces a state of alkalosis; and since the normal regulator of respiration is increase or diminution in the hydrogen-ion concentration round the respiratory centre or centres, the increase in breathing from the direct action of want of oxygen is limited, though just at first, before the alkalosis has developed fully, it may be very considerable. The alkalosis also tends to diminish the circulation rate and thus prevent relief which might otherwise be brought by an increase in the circulation rate and consequent rise of oxygen pressure in the tissues.

Although during acclimatization the oxygen pressure of the arterial blood is rising, as already explained, the breathing continues for many days to increase, as shown by the continued fall in the pressure of carbon dioxide in the alveolar air. This increase in breathing cannot, therefore, be due merely to want of oxygen. We followed it closely on Pike's Peak, and in our report attributed it to the gradual development of an acidosis owing to a special action of want of oxygen in stimulating the kidneys to excrete alkali. We had not then realized the alkalosis produced by the slightly increased breathing owing to the stimulus of want of oxygen.

The true facts were revealed in an investigation carried out in steel chambers in London by Kellas, Kennaway, and myself shortly after the war.⁹ We found that during the want of oxygen which is immediately produced by exposure to low atmospheric pressure the urine becomes alkaline or much less acid and the amount of ammonia in the urine diminishes greatly, just as in any ordinary alkalosis produced by forced breathing or ingestion of alkali. In other words, the kidneys and formation of ammonia in the body were reacting normally to an alkalosis. The increase in breathing during the process of acclimatization is thus due, not to an acidosis, but to the gradual compensation in a normal manner of an alkalosis produced by the slightly increased breathing caused directly by want of oxygen. As the alkalosis becomes compensated the full effect on the breathing of the slight oxygen-want is unmasked more and more, even though the oxygen-want itself is continuously diminishing as acclimatization advances. In this connexion I should like to point out that the regulation of the reaction in the body is an active physiological process, and not, as the confused accounts in many textbooks and papers seem to represent, a mere result of the physico-chemical buffering in body fluids, blood corpuscles, etc.

We can thus see why it is that with acclimatization at higher and higher altitudes the breathing during rest is more and more increased, just as in a true acidosis. On Pike's Peak the increase was only about 50 per cent.; but on the higher slopes of Mount Everest it would be at least 100 per cent. Graphs constructed by Miss FitzGerald from her observations in connexion with the Pike's Peak expedition in various villages or towns of the Rocky Mountains and elsewhere show the mean decreases in alveolar carbon dioxide pressure and oxygen pressure at different altitudes, together with the increases in haemoglobin percentage. These graphs, which are reproduced in my book on *Respiration*, give us a clear idea of the probable increase in the breathing and haemoglobin during the Mount Everest expedition. But for the tragic death of Dr. Kellas from, as appears to have been the case, want of oxygen owing to failure of acclimatization during illness, we should by this time have had far fuller information on the increase of breathing and haemoglobin at great altitudes.

An increase of 100 per cent. in the breathing during rest is noticeable enough, but not uncomfortable. But when the breathing during muscular exertion, such as walking or climbing, is also, as must happen in persons acclimatized at high altitudes, increased by at least 100 per cent., the distress caused becomes very great, and at once limits the exertion. I have for long been familiar with this in connexion with observations of the effects of carbon dioxide in mines and submarines, and on divers. Owing to a recent discovery by my son, we can now reproduce this phenomenon by causing acidosis in a healthy person breathing ordinary air at sea level.¹⁰ I confess that when he first produced

the acidosis on himself I was almost ashamed to walk with him at a leisurely pace along the streets of Oxford, for he was panting so hard as to attract everyone's attention.

We found on Pike's Peak that some part of the greatly increased breathing on considerable exertion was due to the immediate effects of want of oxygen; but comparatively little. Air enriched with oxygen would not give more than very partial relief to the breathing in a person acclimatized to a high altitude; and the benefit might be more than neutralized by the inconvenience caused by the weight of the apparatus. In the case of a person not acclimatized, however, the relief to all the symptoms would be complete if the oxygen was sufficient. He would breathe during exertion just as easily as at sea level; but if he were not acclimatized, and the apparatus failed at an altitude of about 25,000 ft. or even less, he would certainly perish. The cause of death would be a fatal combination of oxygen-want and alkalosis; and the immediate cause would, to judge from our observations in steel chambers, be failure in the depth of breathing.

Acquired Toleration of the Tissues to Low Oxygen Pressure.

I now come to a fourth factor in acclimatization. This factor, as it seems to me, has been revealed by the recent Anglo-American expedition to a high altitude in Peru under Mr. Barcroft's leadership.¹¹ The Peru expedition differed from that to Pike's Peak owing to the fact that observations could be made on persons who were natives of the place, or who had been acclimatized for long periods. Owing to improved technique, analyses could now also be made of the gases in arterial blood. The new factor is that persons who have been long acclimatized become able to exist normally with a considerably lowered pressure of oxygen in the arterial blood. Apparently the tissues themselves become acclimatized to the lowered oxygen pressure, and this, of course, diminishes the stimulus to secretion. At any rate, numerous individuals were found who were living healthily with their lips and skins of an abnormally bluish tinge, and who became very distinctly pinker when they were moved to a lower altitude or breathed air enriched with oxygen. The haemoglobin of their arterial blood was found to be only about 83 per cent. saturated with oxygen, whereas such a low saturation, if it were produced rapidly, as in patients with certain acute lung affections, would be indicative of danger to life.

We are familiar clinically with what appears to be a similar phenomenon, and I have referred to it in my book on *Respiration*. We see persons with chronic emphysema, or certain chronic heart affections, going about and leading a fairly normal life with their lips and skin more or less blue; and there is no doubt that in many of these cases the blueness depends on imperfect saturation of the arterial blood with oxygen, and that the patients in question have become acclimatized to it. This fact has for long obscured the deadly significance of any appreciable degree of arterial cyanosis in ordinary patients who are not gradually acclimatized, and the urgent need, so strongly emphasized recently by Meakins, of combating the cyanosis by continuous enrichment of the inspired air with oxygen, or by any other means.

We observed no such cases among acclimatized persons in the Pike's Peak expedition; but this was probably due to the very limited number of persons observed, and the fact that the duration of acclimatization had been so short, or the acclimatization so perfect. Had we been able to analyse the arterial blood we should certainly, however, have found a distinct diminution in the normal saturation with oxygen, and a corresponding considerable diminution in the arterial oxygen pressure; for had this not existed the whole of the phenomena would have been quite unintelligible, as already pointed out. In the case of Meakins there was, after acclimatization in the Peru expedition, a diminution of 4 per cent. in the arterial saturation, and this small difference is just about what we should have expected from the Pike's Peak results.

The Inferences of Mr. Barcroft and Professor Krogh.

In his report on the expedition Mr. Barcroft draws what seems to me to be the amazing inference that the blood-gas

analyses indicated that no active secretion of oxygen exists. I have already given the evidence that it is practically impossible to decide this question directly by means of either aerotonometers or blood-gas apparatus, together with a summary of the evidence, both direct and indirect, in favour of the secretion theory. It seems to me that without a shadow of doubt this theory still holds the field completely, though I am sorry to have to differ so emphatically from Mr. Barcroft, to whom physiology owes so much. The secretion theory rests not merely on the direct evidence furnished by the carbon monoxide method, but also on a mass of indirect evidence, part of which I have summarized. The blood-gas analyses on members of the Peru expedition seem to me, when these analyses are interpreted in the light of existing knowledge, to afford very strong evidence in favour of the secretion theory; but it is much to be regretted that the carbon monoxide method was not employed. The details of the analyses bear out, up to the very hilt, the conclusions of the Pike's Peak expedition. The only observations which at first sight seem to bear out the diffusion theory are the results of determinations by a modified aerotonometer method of the oxygen pressure of arterial blood at sea levels. These results are, however, quite inconsistent with the aerotonometer results for animals, and were, I am confident, erroneous for reasons which can be surmised easily.

Not only Mr. Barcroft, but also Professor Krogh of Copenhagen has opposed the secretion theory. The time at my disposal prevents me from dealing with the later experimental method relied on by Professor Krogh for determining the rates of diffusion of gases into the blood. This method seems to me fallacious; but the point may be waived for the present. What is essential is that if these measurements are even very approximately correct, the aerotonometer results of Fredericq and Krogh are hopelessly inconsistent with the theory that the oxygen pressure of the mixed arterial blood represents the mean oxygen pressure of blood leaving the lung alveoli. While I admire so much of Professor Krogh's work, I think he suffered the misfortune of putting his money on the wrong horse when he definitely opposed the oxygen secretion theory of his former chief, Professor Christian Bohr.

The Mount Everest Expedition of this Year.

In the Mount Everest expedition of this year Colonel Norton and Dr. Somervell climbed without oxygen to a height of 28,100 feet, and had slept well at 27,000 feet. But for an affection of Dr. Somervell's throat and the limited time for return they could have gone higher; and Colonel Norton actually did climb some distance further, up an extremely difficult and dangerous slope. He reports that although the panting on exertion was, of course, very great, he had none of the mental symptoms of serious lack of oxygen. He considers that so far as the physiological difficulties are concerned it is quite possible to get to the top without oxygen, and he doubts whether the advantages of an oxygen apparatus such as that used are sufficient to outweigh the disadvantages.

At 28,100 feet the resting alveolar oxygen pressure would, to judge from Miss FitzGerald's graph, be only about 26 millimetres. Arterial blood such as that of the observers on Pike's Peak could, even during complete rest, only be about half-saturated with oxygen at this pressure, apart from secretion of oxygen; and the persons to whom it belonged would be black in the face. If considerable alkalosis existed the blood would be more highly saturated; but the alkalosis would, in its bad effects, counteract the good effects of the increased saturation. It seems to me that with the publication of the Mount Everest results the opposition to the oxygen secretion theory of acclimatization is in, if possible, a still more hopeless position than before.

In the Pike's Peak report the authors (Douglas, Yandell Henderson, Schneider, and myself) expressed the conclusion that though it would be hopeless for an unacclimatized person to reach the top of Mount Everest, even by aeroplane or balloon, without the use of oxygen, there was no known physiological reason why an acclimatized person should not succeed in climbing it. At this point I should like to refer to an unfortunate misunderstanding which

crept into a paper (in the *Geographical Journal*, vol. ix, p. 410, 1922) by the late Mr. Mallory. He mentioned that he had been told by the Professor of English Literature at Oxford that the physiologists had proved in a pressure-reducing chamber that it was impossible to climb to the top of Mount Everest without oxygen. There was evidently some misunderstanding about this statement. The experiments referred to were possibly those made on unacclimatized persons by Kellas, Kennaway, and myself. The Oxford physiologists who have concerned themselves with the subject have never regarded the ascent of Mount Everest as impossible, on physiological grounds, without oxygen, or supposed for a moment that any experiments hitherto made in steel chambers indicated such an impossibility; but it is quite evident that the less complete the acclimatization, the more benefit will be obtained from oxygen. In this connexion it would be interesting to try whether acclimatization at the highest camps could not be hastened by administering small doses of an acid salt or of ammonium chloride, so as to get rid of the alkalosis more rapidly than in the natural slow way.

The Acclimatization Phenomena as a Whole.

When we regard as a whole the phenomena of acclimatization to a low atmospheric pressure we see at once that when acclimatization is complete the organism is still in a physiologically different state from what it was before exposure to the low pressure. The breathing is greatly increased; the concentration of the blood in haemoglobin and red corpuscles is also increased, as well as the blood volume; the blood plasma is altered in composition; the blood-forming bone-marrow is increased; and if we could detect them we should probably find histological changes in the lung epithelium. All these changes, and probably many more which are not yet discovered, centre, quite evidently, round what may metaphorically be called an attempt to keep the oxygen pressure, and simultaneously the hydrogen-ion concentration, about and within the living tissues constant. But the attempt is not completely successful: a slight deficiency in both oxygen pressure and hydrogen-ion concentration remains over, and doubtless becomes more appreciable the greater the altitude. This deficiency is necessary as the stimulus for maintaining the state of adaptation. The primary stimulus is the deficiency in oxygen pressure, and the hydrogen-ion deficiency is secondary to this. If we ask why the hydrogen-ion deficiency at least should not be fully compensated, the probable answer is that this would involve such a loss of sodium, and perhaps potassium, as is resisted.

Although from its very nature the process of acclimatization cannot be theoretically complete, yet it has the unmistakable effect of keeping the oxygen pressure within the body approximately constant without more than slight disturbance of other important factors in environment. The carrying out of this involves both functional and structural changes. These changes are intelligible and predictable on the assumption that life tends to assert and maintain structure, activity, and environment in a normal and definitely co-ordinated manner. Without this assumption biology is to my mind nothing but a jumble of disconnected and unintelligible observations. It was a true physiological sense that led Ludwig and Bohr to suspect the existence of oxygen secretion by the lungs, and that led Claude Bernard to his great generalization about the active maintenance of the constancy of the internal environment. The everyday reactions of living organisms to change in environment seem to me not in any way different in kind from the reactions during acclimatization to higher altitudes, and I cannot myself see that physiology is ever likely to get anywhere worth getting to unless it makes the fundamental assumption just referred to.

This assumption differentiates it completely from mere applied physics and chemistry. Biological reality is something which our present physical and chemical conceptions fail to represent and can never come near representing until they have been profoundly modified. This modification may come in the future, but meanwhile biology must regard itself as an independent science. It is also an exact science, since it is everywhere dealing with and revealing

exact regulation and co-ordination. Nothing gives us, perhaps, a clearer and more comprehensive idea of this regulation than thorough study of the phenomena of acclimatization to higher altitudes. That study must, however, be based on exact quantitative results and coherent reasoning; and if in this paper I have had to point out incoherency in the reasoning of scientific friends who in other directions have made most valuable contributions to physiology, I hope that both you and they will understand that any other course would be inconsistent with scientific honesty on my part.

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The Vicary Lecture

ON

RICHARD OWEN AS CONSERVATOR.

GIVEN IN THE THEATRE OF

THE ROYAL COLLEGE OF SURGEONS OF ENGLAND,
NOVEMBER 12TH, 1924,

BY

SIR ARTHUR KEITH, M.D., F.R.S.,
CONSERVATOR OF THE MUSEUM.

(Abstract.)

In the Vicary Lecture of last year* I gave an account of the dramatic proceedings which culminated in the confession by Sir Everard Home that he had burnt the Hunterian manuscripts. These proceedings were enacted in this College during the summer of 1824—just a century ago. The Board of Curators, six members of the Council of the College, to whom the management of the museum was delegated, then met to consider afresh the problem of describing and cataloguing John Hunter's specimens—some 17,000 in number. The Board sent for its conservator, William Clift, and told him to proceed with the preparation of catalogues forthwith.

William Clift.

Let us see how William Clift was situated. He was then 50 years of age; from Hunter's death in 1793 until the summer of 1824 he had, in reality, been servant to Sir Everard Home; all he knew he had picked up for himself; time after time he had made fruitless attempts under Sir Everard Home to carry out the task just imposed upon him. His daily duty of meeting parties at the door of the College and conducting them round the floor-space and galleries of the museum—a single great room, which had been built for the display of Hunter's treasures—was altogether a joyful task for him. But when it came to stepping into John Hunter's shoes and explaining and interpreting to all the world the harvest of the greatest medical genius of the eighteenth century—a much abler man than the faithful, modest William Clift might well have shrunk back. He set to work in his old way, pen in hand, and in his fairest script copied from such Hunterian documents as he had saved, and from other sources, such extracts as threw light on the collections under his charge. The Board met from time to time and examined these extracts, but by the end of 1826 it had become apparent to John Abernethy, surgeon to St. Bartholomew's Hospital, and at this time President of the College, the truest and most helpful friend William Clift ever had, that further skilled assistance must be given if a catalogue were to be forthcoming.

* See BRITISH MEDICAL JOURNAL, 1923, vol. ii, p. 1127. The sources from which I have drawn information for this lecture are the same as given there, with the addition in the present instance of *The Life of Richard Owen*, by the Rev. Richard Owen, 1834.