A Lecture

ON THE

SYMPTOMS, CAUSES, AND PREVENTION
OF ANOXAEMIA(INSUFFICIENT SUPPLY OF OXYGEN TO THE TISSUES),
AND THE VALUE OF OXYGEN IN ITS TREATMENT.*

BY

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In this lecture I propose to review briefly what is known with regard to the physiology of anoxaemia, and the means by which it may be prevented. Our knowledge on this subject is as yet imperfect, but has quite recently developed very rapidly; and the development, as I shall try to show, has the closest bearing on a number of everyday problems in practical medicine.

DEFINITION.

Anoxaemia may be defined as a condition in which the rate of supply of oxygen to the tissues by the blood in the systemic capillaries is insufficient for the normal carrying on of life. Its existence is shown by the abnormal symptoms produced, and by the fact that these symptoms are annulled by increasing the rate at which oxygen is supplied.

Clinically the condition is very common. It is a very dangerous complication in pneumonia and in bronchopneumonia, especially the very fatal pneumonia of influenza. It occurs in bronchitis and in asthma, and is constantly in existence in many chronic cardiac cases and in congenital heart disease. It is the cause also of Cheyne-Stokes breathing.

I need hardly remind you that the place of oxygen in the life of a warm-blooded animal is altogether peculiar, since the body has practically no storage capacity for oxygen, but depends from moment to moment for its supply from the air. If we cut off this supply loss of consciousness is only a matter of seconds, and death of minutes. As Paul Bert was the first to point out, the immediate cause of death is practically always anoxaemia. But death is not the mere stoppage of a machine; it is also total ruin of the supposed machinery. Similarly—and this is a lesson which I wish to emphasize as strongly as I can—partial anoxaemia means not a mere slowing down of life, but progressive and perhaps irreparable damage to living structure.

MAINTENANCE OF NORMAL SUPPLY OF OXYGEN
TO THE TISSUES.

To grasp the causes of anoxaemia it is necessary to understand quantitatively the means by which the rate at which oxygen is given off from the blood towards the tissues is normally kept sufficient. As is well known, the available oxygen present in the blood is in two forms. A small part (about 1/50th in normal human arterial blood) is present in free solution in the blood. By far the greater part is combined with haemoglobin as an easily dissociated compound, oxyhaemoglobin, which dissociates, and so

yields free oxygen, as the oxygen in free solution is used up. Human arterial blood is almost (about 95 per cent.) saturated with oxygen. The readiness with which oxygen is supplied towards the tissues depends on the partial pressure, or diffusion pressure,† of the oxygen in free solution. Thus it is the oxygen in free solution, and not the total available oxygen in the blood, that is of immediate importance. In proportion as oxygen is taken up from the blood in the systemic capillaries the amount of oxygen in free solution, and consequently its diffusion pressure, tends to fall, but is, under normal conditions, kept from falling too low by oxygen flowing out from the oxyhaemoglobin in the red corpuscles. Fig. 1 (after Christiansen, Douglas, and Haldane) is a curve showing the percentage to which the oxyhaemoglobin in human blood is dissociated with varying partial pressure, or diffusion pressure, of the free oxygen present. The peculiar form of the curve with its evident physiological significance was discovered by Bohr of Copenhagen, while Barcroft and his pupils showed that the peculiarity depends upon the salts present in the red corpuscles.

CAUSES OF ANOXAEMIA.

Anoxaemia, or excessive fall of the diffusion pressure of oxygen in the systemic capillaries, is due to one or more of the following causes:

1. Defective saturation of the arterial blood with oxygen.
2. Slowing of the circulation, so that an excessive proportion of oxygen is used up in the systemic capillaries.
3. Defective proportion of available haemoglobin in the blood.
4. Alteration of the dissociation curve of oxyhaemoglobin, so that it gives off oxygen less readily.

Of these causes the last has hitherto hardly been recognized, but is of great importance, as

will be shown. I shall first discuss briefly these four causes and their mutual relations.

1. Defective Saturation of the Arterial Blood with
Oxygen.

This depends on one or other of two circumstances. Of these, one is that the partial pressure of oxygen in the lung alveoli may be insufficient to produce normal saturation of the haemoglobin with oxygen. A glance at Fig. 1 will show that if either the percentage of oxygen in the alveolar air, or the barometric pressure, falls sufficiently, defective saturation of the arterial haemoglobin must result unless active secretion of oxygen inwards by the alveolar epithelium redresses the balance. The other is that, owing to swelling, exudation, or other abnormality in or around the alveolar walls, oxygen cannot diffuse inwards quickly enough to saturate the blood during the limited time which it takes to pass through the alveolar capillaries. When the air supply is completely cut off from alveoli, they of necessity collapse, owing to diffusion of nitrogen out of them; and it appears that in this case, or if they are completely filled by exudation, the pulmonary circulation through them practically ceases, so that they do not pass onwards any considerable proportion of venous blood. For this reason, apparently, the

† In a recent paper on the extension of the gas laws to liquids (*Biochemical Journal*, xii, p. 488, 1918) I have endeavoured to define diffusion pressure and point out its fundamental significance in physiology.

* Delivered at the Physiological Laboratory, Guy's Hospital, June 26th, 1919.

arterial blood may remain of a bright red colour, in spite of extensive consolidation or collapse of the lungs.

2. Slowing of the Circulation.

The effects of anoxaemia due to slowing of the circulation are seen in ordinary fainting from sudden diminution of the heart's action, or from rapid loss of blood. In the latter case the supply of blood to the right side of the heart fails, so that not sufficient blood reaches the left side to maintain the arterial blood pressure. The blood supply to the right side of the heart may also fail from other causes, such as excessive filling of vessels in some part of the body, or rapid loss of blood plasma. The heart itself may also fail from various causes, primary or secondary. In any case the certain result is anoxaemia, with all its urgent dangers.

3. Defective Proportion of Available Haemoglobin.

Anoxaemia due to a defective proportion of available haemoglobin in the blood is seen in extreme cases of primary or secondary "anaemia,"* or in the action of poisons which, like carbon monoxide, nitrites, or arseniuretted hydrogen, combine with, chemically alter, or destroy haemoglobin or red corpuscles. Owing to the defective reserve of combined oxygen in the blood, the partial pressure of free oxygen in the systemic capillaries falls excessively, so that anoxaemia is produced.

4. Alteration of the Dissociation Curve of Oxyhaemoglobin.

It was discovered by Bohr of Copenhagen and his pupils that when the partial pressure of CO_2 in blood is altered the dissociation curve for oxygen is also altered. The general nature of this alteration is shown in Fig. 2, after Bohr. It will be seen that as the partial pressure of CO_2 is diminished the dissociation curve of oxyhaemoglobin moves to the left. In other words, the haemoglobin holds on more tightly to the oxygen. Barcroft has shown that other acids in minute quantities have the same effect as carbonic acid.

It is thus in virtue of its acid properties that carbonic acid alters the properties of haemoglobin. Now we can diminish the normal proportion of carbonic acid in the arterial blood by over-ventilating the lungs, as when breathing is voluntarily forced. It will be seen at once that the effect of this must be to make the haemoglobin in the systemic capillaries hold on more tightly than usual to the oxygen. In this way we can produce anoxaemia with the blood of a normal red colour. Forced breathing produces a train of symptoms which are very similar to those produced by a pure anoxaemia, such as that due to reduced atmospheric pressure. It was also discovered by Hill and Flack that when the forced breathing is performed, not with air but with pure oxygen, these symptoms are greatly diminished. As when pure oxygen is breathed the proportion of free oxygen in the blood is much increased, the inference seems plain, in the light of Bohr's discovery, that by forced breathing we actually produce anoxaemia. This is one of Nature's many ironies, and has a far-reaching significance in connexion with our subject.

THE EFFECT ON THE RESPIRATORY CENTRE.

When the respiratory centre is short of oxygen it instantly responds with increased activity, and the corresponding increased breathing brings more oxygen to the lungs. Now when along with deficiency of oxygen there is excess of CO_2 in the lungs, as is usually the case, the increased breathing brings relief in the normal way. But when there is no excess of CO_2 the increased breathing washes out an abnormal proportion of CO_2 from the blood.

* By anaemia is here meant deficiency in the percentage of haemoglobin in the blood. This is often associated with a great increase in the volume of the blood, as Lorrain Smith showed.

and, owing to this, produces a secondary anoxaemia. The result is that there is little relief to the primary anoxaemia. Hence a simple anoxaemia of this sort cannot be annulled by mere increased breathing. Similarly, if anoxaemia is due to some cause not associated with increased pressure of CO_2 , it cannot be annulled by simply increasing the rate of circulation; for the increased circulation, just like the increased breathing, removes CO_2 as quickly as it brings more oxygen.

These considerations explain why it is that in many cases there is very little increase in either the breathing or the circulation during dangerous anoxaemia. For example, we can understand, from a teleological standpoint, why there should be so little increase in the circulation rate or breathing at very high altitudes or during CO poisoning, and why there should be so little real increase in the lung ventilation in uncomplicated circulatory anoxaemia.

SYMPTOMS PRODUCED BY ANOXAEMIA.

The symptoms of anoxaemia, and the response generally of the body towards it, must now be considered.

When anoxaemia is produced by lowering *rapidly* either the percentage of oxygen in the inspired air, or the atmospheric pressure, the first definite symptom is usually an increase in the breathing; but unless the anoxaemia is great the breathing soon quiets down again more or less.

If the anoxaemia has been *gradually* produced and is not excessive, the increase in breathing is not noticeable, though a definite increase can be recognized from the diminished partial pressure of CO_2 in the alveolar air.

Under normal conditions the activity of the respiratory centre, as Priestley and I discovered, is regulated with astounding exactness by the partial pressure of CO_2 in the alveolar air; and evidence has since then gradually accumulated that it is simply in virtue of its acid properties that the carbonic acid carried from the lungs to the respiratory centre acts on that centre.

It is thus variations in the hydrogen-ion concentration of the blood that normally determine the degree of activity of the centre. Moreover, these variations are for the most part so extraordinarily minute as to be undetectable by the existing methods, whether electrometrical or chemical.†

The significance of this latter fact has not hitherto been realized by medical writers, nor the serious sources of error involved in methods used for comparing the hydrogen-ion concentrations in samples of blood of varying composition. As a result, there is at present a chaos of confused opinions which I cannot stop here to criticize. It is clear, nevertheless, that the hydrogen-ion concentration of the blood is regulated with almost incredible delicacy, and that the respiratory centre does the comparatively rough and immediate work necessitated by rapid variations in CO_2 production within the body, while the kidneys, liver, and probably other parts, do the finer but far slower work.

When want of oxygen comes in as an additional stimulus to the respiratory centre, the result is that if no excess of CO_2 accompanies the want of oxygen, more CO_2 than usual is washed out of the arterial blood. Hence the hydrogen-ion stimulus to the centre becomes latent, and a state of "alkalosis" is produced in the blood. The action of the centre, therefore, quiets down again as soon as time has been given for washing down to a lower level the relatively large quantity of CO_2 contained in the blood and body fluids; and the net final result in increasing the breathing is comparatively small, as Poulton and I showed in 1908. Moreover, the anoxaemia is, for the reasons already given, not much relieved, and certain amounts of both anoxaemia and alkalosis remain.

† Campbell, Douglas, Haldane, and Hobson, *Journ. of Physiol.*, *lvi*, p. 316, 1914.

FIG. 2.—Curves representing the percentage saturation of haemoglobin with oxygen at different partial pressures of oxygen and CO_2 . Dog's blood at 38°C . Ordinates = percentage saturation with oxygen; abscissae = partial pressures of oxygen in millimetres of mercury.

"ALKALOSIS."

For the existence of the anoxaemia we have other evidence, to which I shall refer presently; but what direct evidence have we for the alkalosis? Clear physiological evidence has been furnished in the course of a quite recent investigation by Dr. Kellas, Dr. Kennaway, and myself (at present in course of publication) on the effects of very low atmospheric pressure in the steel chamber at the Lister Institute. Dr. Kennaway's analyses of the urine showed that the excretion of acid at once falls to a very low figure at the low atmospheric pressure, while the excretion of ammonia diminishes also, as Hasselbalch and Lindhard had, indeed, already found. These diminutions indicate that the blood is abnormally alkaline during the anoxaemia, and that the kidneys and liver are doing their best to redress the balance, just as they would under normal conditions. If the blood is the least bit too alkaline the kidneys excrete alkali; if it is the least bit too acid they excrete acid. Moreover, if the blood is the least bit too acid the liver produces ammonia instead of urea. Another reaction to too great acidity is that the breathing is increased, which washes out carbonic acid.

In this connexion I have to confess to joint responsibility for originating an erroneous interpretation. On first noticing in 1908 that, after experiments at low pressures in the steel chamber, the alveolar CO_2 pressure remained low for a time after the subject had returned to normal atmospheric pressure Boycott and I drew the not unnatural conclusion that owing to the anoxaemia lactic acid had been produced in the body, and remained in the blood for some time after the anoxaemia had ceased, and thus helped to stimulate the respiratory centre by producing an acidosis. Douglas and I had already found that after any severe muscular over-exertion there is a similar effect, which we attributed to lactic acid produced in the muscles during the over-exertion, the oxygen supply to them by the blood being totally insufficient to balance the enormously increased oxygen requirements. This interpretation was afterwards verified at Guy's Hospital by Ryffel, who made use of his now well known and very beautiful method for estimating lactic acid. But the acidosis of muscular over-work passed off much more quickly than that apparently produced by a pretty long exposure to moderate anoxaemia. The lactic acid was apparently oxidized rapidly, while the apparent acidosis of ordinary anoxaemia was very persistent.

In other respects also the lactic acid theory was unsatisfactory. In the report on the Pike's Peak expedition of 1911 we therefore put forward the conclusion that the acidosis of moderate anoxaemia is a compensatory phenomenon which tends to relieve the anoxaemia by producing increase of the breathing, and is due to a special response of the kidneys and liver, which, as already mentioned, normally regulate the alkalinity of the blood. Meanwhile, Ryffel found that no lactic acid to speak of was present in the blood or urine during exposures to moderate anoxaemia in a steel chamber, or even on the summit of Monte Rosa.

The hypothesis of a special adaptive reaction appears now to be quite unnecessary. The kidneys and liver are apparently reacting during anoxaemia in their normal manner to an alkalosis; and this alkalosis is produced by the increased breathing due to the anoxaemia. The apparent acidosis which develops during anoxaemia is thus not an acidosis in the sense of a shifting to the acid side of the normal physiological balance, but the partial compensation of an alkalosis; and this compensation, as it slowly progresses, makes it possible for the breathing to respond more and more fully to the stimulus ultimately due to anoxaemia, without the compensating disadvantages produced by alkalosis in the manner already described. From the same point of view we can now understand much better why CO_2 acts so effectively in staying off anoxaemia. This effect is not merely due to increase of the breathing. It is seen strikingly, for instance, in CO poisoning under conditions where mere increase of the breathing could give no relief to the anoxaemia.

TREATMENT OF THE (SUPPOSED) ACIDOSIS OF ANOXAEMIA.

At this point I should like to say that it seems to me a gross mistake to treat the supposed acidosis of anoxaemia

due to gas poisoning, "shock," and other conditions by the administration of alkalis. The body is calling for both oxygen and acid. I should also like to enter my protest against the unintelligible physical chemistry and physiology of the common assumption that because the "alkaline reserve" of the blood is found to be diminished an acidosis is necessarily present.* The greater the anoxaemia, the greater is the permanent increase of breathing, and the greater also must be the alkalosis produced. At very low atmospheric pressures, for instance, the permanent increase in lung ventilation is quite noticeable subjectively.

"PERIODIC" BREATHING.

I must now refer to another respiratory phenomenon shown by many, but not all, persons as a response to anoxaemia. The breathing becomes, or is very apt to become, periodic, as in ordinary clinical Cheyne-Stokes breathing. A relation between Cheyne-Stokes breathing and anoxaemia was first discovered in the wards of Guy's Hospital by Pembrey and Allen in 1905.† They showed that Cheyne-Stokes breathing could be abolished by giving oxygen, as well as by adding CO_2 to the inspired air, or diminishing its oxygen percentage. Douglas and I then found that periodic breathing is easily produced in normal persons after forced breathing or in other ways. We also showed that its production depends upon the fact that when want of oxygen acts on the breathing, the action and cessation of the stimulus occur much more sharply than when CO_2 is the stimulus. Thus the respiratory governor becomes too sensitive, just like the governor of an engine when there is no fly-wheel or an insufficient load, and begins to "hunt," the oxygen supply to the centre becoming, when the anoxaemia is not too considerable, alternately so small as to cause urgent breathing, and so great as, in the absence of the CO_2 which has been washed out, to produce apnoea.

Periodic breathing is thus always a symptom of anoxaemia, and is most easily produced by moderate anoxaemia, as at a fairly high altitude. When the anoxaemia is great the breathing becomes regular again, since even during the hyperpnoea the breathing cannot relieve anoxaemia. It is also easy to see why CO_2 stops the periodicity. The reason why the periods tend to be shorter in healthy persons than in ordinary clinical Cheyne-Stokes breathing will appear later. We can understand why want of oxygen should act far more promptly than the increase of hydrogen-ion concentration through which CO_2 acts on the centre. The blood and body as a whole are full of "buffer substances" which make changes of hydrogen-ion concentration a comparatively slow matter; but for changes of oxygen concentration there are no corresponding buffer substances between the blood and the tissues. In this connexion I should like to make another recantation—of the suggestion, namely, that want of oxygen acts by causing liberation of lactic acid within the living substance of the respiratory centre and thereby producing a hydrogen-ion stimulus.

RESPONSE OF THE CIRCULATION TO ANOXAEMIA.

The response of the circulation to anoxaemia appears to be on the whole similar to the response of respiration; but we know so little as yet of the physiology, as distinguished from the physics, of the circulation, that I can say very little definitely on the subject.

When anoxaemia is rapidly produced there is at first a marked increase of pulse rate and some increase of blood pressure; but, as in the case of respiration, this increase soon moderates, though the pulse rate remains above normal, and the more the greater the anoxaemia. The causes acting on the circulation seem to be, in the main, similar to those acting on the respiration, though they are less easily accessible to accurate observation and measurement.

The colour of the lips, tongue, and face gives us some indication of the degree of anoxaemia. If anoxaemia is produced rapidly, or produced in such a way that CO_2 is not removed in excess from the blood, there is a blue flush of the lips and face—the typical "blue" cyanosis. If, on the other hand, the anoxaemia is produced gradually and in such a way that CO_2 is removed in excess from the

* Some very important experiments published a year ago by Yandell Henderson and Haggard illustrate in a striking manner the fallacy of this assumption, as I recently pointed out in a short article on acidosis in *Nature*, May, 1st, 1919.

† *Journ. of Physiol.*, xxxii, Proc. Physiol. Soc. p. xviii, 1905.

blood the cyanosis is usually less evident, and of a duller colour, tending if the anoxaemia is very extreme to a leaden colour. Nevertheless, among different individuals there is marked variation in the relation of the colour to the general symptoms. In myself, for instance, the general symptoms are very marked by the time that the lips show distinct blueness, whereas in some other persons there is more blueness with only very slight general symptoms. In others, again, both the blueness and the general symptoms are more marked than in myself when the same air is breathed in a steel chamber at a low pressure. The shifting of the dissociation curve of oxyhaemoglobin will explain the fact that a man may be suffering considerably from anoxaemia although his lips are of a fairly good colour. To explain the differences in different individuals it would probably be necessary to know more than we yet do about how the circulation regulates itself in different persons in response to anoxaemia and alkalosis.

EFFECTS OF ANOXAEMIA ON THE NERVOUS SYSTEM.

The effects of anoxaemia on the nervous system are characteristic. A rapidly produced anoxaemia causes, of course, temporary disturbance; but when the onset is gradual there is little or no discomfort, and for this reason anoxaemia is an insidious and therefore dangerous condition, as is well seen in CO poisoning or in ascents to very high altitudes in aeroplanes or balloons. The senses become dulled without persons being aware of it, and if the anoxaemia is suddenly relieved by administration of oxygen or other means the correspondingly sudden increase in powers of vision and hearing is an intense surprise. Powers of memory are greatly affected, and are finally almost annulled, so that persons who have never lost consciousness can nevertheless remember nothing of what has happened. Powers of sane judgement are much impaired, and anoxaemic persons become subject to fixed ideas which afterwards appear to them quite irrational, and to unrestrained emotional outbursts. I could occupy a whole lecture with anecdotes of the vagaries of my own friends and acquaintances, and myself, under the influence of anoxaemia.

ACCLIMATIZATION TO ANOXAEMIA.

When a cause of anoxaemia is persistent there can be only one or other of two terminations. Either the person becomes adapted or acclimatized to a greater or less extent, or he becomes progressively worse. Let us first glance briefly at acclimatization. To one side of this I have in reality already alluded. The alkalosis of anoxaemia is gradually dealt with by the kidneys and liver; but several days are usually needed for this, and quite clearly the process can never result in a complete restoration to the previous normal; otherwise there would be no stimulus to the maintenance of the new condition. When, however, the alkalosis has been sufficiently diminished it has also become possible so to increase the breathing that the oxygen saturation of the blood, otherwise imperfect, can be largely increased without compensating ill effects from shifting of the dissociation curve of oxyhaemoglobin. In a precisely similar manner the alkalosis and correspondingly increased anoxaemia would be more or less compensated in a case where the anoxaemia was due to a lasting deficiency in the circulation, or to a rapid diminution in the proportion of available haemoglobin, though in the former case the blood in the systemic capillaries would remain abnormally blue. There would seem here to be an indication for the administration of acid in suitable form and amount, with a view to hastening the adaptation.

The second side of adaptation consists in an increase in the facility with which the alveolar epithelium responds to the stimuli which originate in anoxaemia of the tissues. It responds by active secretion of oxygen inwards. I know that many physiologists still remain sceptical as to oxygen secretion in the lungs, and I shall not attempt in this lecture to go into the subject fully. It seems to me, however, that the direct quantitative evidence in favour of oxygen secretion is absolutely unshaken, while the indirect evidence is now practically overwhelming. But I hope to have another opportunity before long of examining this old controversy in the light of the new evidence.

The third side of adaptation is an increase in the percentage of haemoglobin. This is well seen at high

altitudes and in chronic—particularly congenital—heart disorder. With the increased charge of combined oxygen in the blood the rate of fall in the diffusion pressure of free oxygen in the capillaries is, of course, diminished, and in this way anoxaemia is mitigated. Whether the tissues of a warm-blooded animal can adapt themselves to live with a lower diffusion pressure of oxygen than usual is an interesting question on which we have as yet no clear evidence.

The adaptive responses to anoxaemia have hitherto been studied only in connexion with acclimatization to high altitudes, but I am convinced that they are of great significance in practical medicine. It is particularly important to realize that they require time, and that measures which afford a patient the requisite time may save his life.

IMPERFECT ADJUSTMENT: MOUNTAIN SICKNESS.

Let us now look at the other mode of termination. Whenever a comparatively slight anoxaemia, such as that produced when a person not in good physical training goes to a height of about 10,000 ft., or stays in air containing more than about 0.02 per cent. of CO, is continued for several hours, the common result is nausea, headache, and general depression. This "mountain sickness" may only come on after the anoxaemia has ceased, but is unmistakable evidence of temporary damage, however slight, affecting the nervous system. Different persons are susceptible in very different degrees to mountain sickness. The usual ending of mountain sickness is that acclimatization gets the upper hand and complete recovery ensues; but sometimes the fight is long, or even dangerous.

FAILURE OF ADJUSTMENT: PROGRESSIVE DAMAGE TO TISSUES.

When the anoxaemia is more severe, the evidence of progressive damage becomes more and more marked, so that even when the cause of anoxaemia is completely removed grave symptoms may remain. Thus, in severe CO poisoning, when the patient has remained unconscious for several hours, it is always a matter of doubt whether recovery will take place, or how many days, weeks, or months it will require. The CO diffuses off comparatively quickly through the lungs as soon as the patient is in pure air; within two or three hours very little CO is left in the blood. But the damage has been done—damage in the central nervous system, and very probably also in the heart and various other organs. It is often only by the most careful nursing and attention to every symptom indicating nervous and other forms of breakdown in different directions that such a patient can be saved.

IMPORTANCE OF ACTIVE TREATMENT.

I shall not attempt to describe or analyse in detail the general picture of the progressive damage from serious and prolonged anoxaemia; but I wish to emphasize very strongly the existence of this damage, and the consequent need for cutting anoxaemia short or preventing it if this is at all possible. Perhaps no cases have presented a more impressive picture of the dangers of anoxaemia and the advantages of preventing it than the cases of poisoning by lung-irritant gas during the war.

THE BREAKDOWN OF THE RESPIRATORY CENTRE.

To one all-important aspect of the general breakdown during anoxaemia I should like to direct special attention. This is the breakdown of the respiratory centre. A forthcoming paper by Davis, Priestley, and myself deals fully with this subject, and it was also partially dealt with by Meakins, Priestley, and myself in a paper which has just appeared in the *Journal of Physiology*. The whole of this work was undertaken under the auspices of the Medical Research Committee. The result on which we lay emphasis is that when anoxaemia exists the centre very readily shows signs of the same sort of exhaustion as is caused by excessive resistance to breathing. That is to say, the breathing becomes progressively shallower and more frequent, just as happens so commonly in a dying man.

Now it has been generally assumed—by myself among others—that so long as a sufficient total quantity of air reaches the lung alveoli it does not much matter in itself whether the breathing is deep and slow, or shallow and frequent. A study of cases of chronic neurasthenia, and

particularly those caused by irritant gas poisoning, led Meakins, Priestley, and myself, however, to note that not only were there symptoms of anoxaemia in many of them, but that the breathing, particularly on exertion, was abnormally frequent and shallow. We then investigated the effects of shallow breathing in normal persons, with the help of the apparatus described and figured by Meakins, Priestley, and myself, in the *Journal of Physiology*, 1919, lii, p. 433. The result was that we could easily produce periodic breathing and other symptoms of anoxaemia by so limiting the depth of the breaths that rapid shallow breathing had to be substituted for normal breathing. Moreover, the periodic breathing was in comparatively long and stately periods, just like ordinary clinical Cheyne-Stokes breathing. Yet when samples of alveolar air were taken in the ordinary way the oxygen percentage was somewhat above normal.

THE FAN-LIKE EXPANSION OF THE LUNGS.

To cut a long story short, we were forced to the conclusion that the key to the anoxaemia was furnished by the fact, clearly formulated by Professor Arthur Keith ten years ago,* that in the living body the lungs do not expand evenly and simultaneously at all parts, but open out part by part, somewhat similarly to the opening of the leaves of a lady's fan. When the breathing is shallow only certain of the leaves open, so that only certain parts of the lungs are properly ventilated, though in these parts the ventilation is quite abnormally increased owing to the increased frequency of the breathing. Now this increased ventilation must wash out from the blood a correspondingly increased proportion of CO_2 , but cannot put in any appreciably increased quantity of oxygen, since the haemoglobin would be already almost saturated with oxygen by normal breathing. On the other hand, in the parts of the lungs where the air is left more or less stagnant there will not be nearly enough oxygen to saturate the haemoglobin. The net result will be that the mixed arterial blood will be deficient in oxygen, but will not contain more than the normal proportion of CO_2 . If the proportion of CO_2 were abnormally high the breathing would immediately increase till the balance was at least redressed; and actually the balance will be more than redressed, since the anoxaemia produced by the deficiency in oxygen will itself stimulate the breathing to some extent.

CLINICAL SIGNIFICANCE OF VARIATIONS IN RATE AND DEPTH OF BREATHING.

This discovery has of course thrown an entirely new light in all directions on the physiology and pathology of breathing, and particularly on the clinical significance of variations in the rate and depth of breathing. It has also shown that administration of air enriched with oxygen, or even simply with CO_2 , as recommended by Yandell Henderson, may be of essential service in a great variety of clinical conditions accompanied either by rapid and shallow breathing, or by breathing in which, owing to uneven resistances in the bronchi or other causes, the expansion of the lungs is uneven. For, clearly, it is only necessary to increase the oxygen percentage in the air, or the depth of breathing, in order to get sufficient oxygen into the badly ventilated alveoli; and we actually found that only a small addition of oxygen to the inspired air was needed in order to abolish the symptoms of anoxaemia in our experiments.

A VICIOUS RESPIRATORY CIRCLE.

To return to the exhausted respiratory centre in cases of anoxaemia: it is evident that when the breathing becomes shallow from this exhaustion a dangerous vicious circle tends to be produced, since the anoxaemia makes the breathing shallow though rapid, and the shallow breathing increases the anoxaemia. This is a vicious circle which leads straight towards death, and it now seems probable that one of the most common immediate causes of death is failure of the respiratory centre rather than of the heart. The heart must, of course, always fail in the end if the respiratory centre has failed; but in the case of the heart itself there does not seem to be so great

and immediate a danger from a vicious circle.† Ordinary clinical Cheyne-Stokes breathing, with its stately rhythm owing to the shallow breathing, is usually a sign of advancing failure of the respiratory centre.

OTHER CAUSES OF PARTIAL FAILURE OF THE RESPIRATORY CENTRE.

Partial failure of the respiratory centre, with consequent secondary anoxaemia, has of course many other causes besides primary anoxaemia. Among these causes are toxic substances circulating in the blood, anaesthetics and other poisons, or the various causes of which the effects on the nervous system are classified as fatigue, shock, or neurasthenia. But the vicious circle of anoxaemia is always there to some extent, and may easily become dangerous. In breaking or preventing this vicious circle there is evidently a very wide field for the administration of oxygen.

IMPORTANCE OF BREAKING THE VICIOUS CIRCLE EARLY.

I wish also to emphasize the fact that the sooner the vicious circle is broken the more striking will be the immediate effects. With long-continued anoxaemia a patient's condition tends to become hopeless. One of the most important effects of prolonged or extreme anoxaemia is a temporary partial failure of the respiratory centre, so that oxygen or even artificial respiration may be required for many hours.

With the help of the apparatus already referred to we discovered the fact that restriction of the depth of breathing produces anoxaemia far more readily in the recumbent than the upright position. This explains the existence of the orthopnoea which is so prominent a symptom in many cardiac and respiratory cases. A patient with shallow breathing due to impaired vigour of the respiratory centre cannot lie down because the anoxaemia is at once increased by this, and he must therefore sit up in bed if he is breathing ordinary air.

THE VALUE OF OXYGEN INHALATION.

The effects produced by temporary oxygen administration in some cases have been known for long. The observations on this subject by Pembrey in the wards of Guy's Hospital were particularly striking. As it is now evident, however, that oxygen administration has a far wider and more important field of application in practical medicine than was previously suspected I will refer shortly to methods of administering it. My own attention was directed to the subject by the practical difficulties, with existing methods, of giving oxygen continuously in cases of irritant gas poisoning. It was evidently necessary to cut down all waste, and simplify the mode of administration as far as possible. As regards waste, there seemed to be no necessity for the patient breathing pure oxygen; and in any case the continuous inhalation of pure oxygen was excluded, owing to the fact that even 80 per cent. oxygen was found by Lorrain Smith to produce fatal pneumonia within three or four days. It seemed evident that only as much oxygen ought to be added to the inspired air as would suffice to relieve the anoxaemia. It was also evident that if the oxygen was delivered to the patient in a continuous stream half would be wasted, as it would come to him during expiration.

METHOD OF ADMINISTERING OXYGEN.

I therefore devised an apparatus so arranged that by a simple device the patient inspired through a face-piece the whole of the added oxygen, without waste during expiration, while the proportion of oxygen could easily be cut down or increased, according as was needful. The original form of this apparatus was described in the *BRITISH MEDICAL JOURNAL*, February 10th, 1917, p. 181, after it had already been supplied extensively to the army in France. Its use there for gas cases was initiated, and the best mode of managing it carefully investigated, by Lieut.-Colonel C. G. Douglas of Oxford. Other well known medical officers have also made very valuable

† Owing to the coincidence of anoxaemia with too high a venous pressure and consequent over-distension of the right side of the heart, the heart itself may enter a vicious circle. Even if the anoxaemia is not relieved this vicious circle can often be broken by free bleeding, the beneficial effects of which in many cases of irritant gas poisoning were first pointed out by Irvine and Macaulay of Johannesburg.

* Keith, *Further Advances in Physiology*, p. 182, 1909.

observations on the effects of oxygen inhalation.* The results, particularly in gas cases, were very striking; but unfortunately at that time, as will be seen from my own paper of 1917, the symptoms and significance of a failing respiratory centre were still unknown, so that the wide applications of oxygen in a great variety of medical and surgical cases were not realized. The apparatus was afterwards simplified, with the immediate object of making it both easy to handle and available for front-line and stretcher work, including treatment of "shock" cases. The apparatus in its latest form can now be obtained from the makers, Messrs. Siebe, Gorman and Co., of London.

FIG. 3 shows the arrangement of this apparatus. It consists of (1) a pressure gauge showing how much oxygen is in the cylinder; (2) a reducing valve which reduces the pressure to a small amount which remains constant till the cylinder is exhausted; (3) a graduated tap indicating the flow of oxygen in litres per minute; (4) light thick-walled rubber tubing conveying the oxygen to the patient; (5) a small flexible collecting-bag connected with the face-piece through a non-return mica valve which prevents expired air from entering the bag; (6) a face-piece provided with elastic straps and a rubber pneumatic cushion which can be taken off for disinfection. The patient can inspire and expire freely through an opening in which there is a rubber flap to cause a very slight resistance. During expiration the oxygen collects in the bag, and is sucked into the face-piece at the beginning of inspiration. From the movements of the bag it can be seen at any moment whether the patient is receiving the oxygen. To put the apparatus in action the main valve is opened freely and the tap adjusted to give 2 litres a minute, or whatever greater or less amount suffices. With a delivery of 2 litres a minute a 40-foot cylinder would last nearly ten hours.

To make oxygen really available for ordinary medical work it is essential not only to prevent waste of oxygen but also to cut down as far as possible the weight of oxygen cylinders and the difficulties with stiff or leaky valves and other defects. A nurse must be able to handle the whole apparatus with ease and administer oxygen at once at any hour of the day or night. The question of cutting down the weight of cylinders to the minimum which is perfectly safe is now being investigated and reported on by a committee of the Department for Scientific and Industrial Research. The old regulations necessitating very heavy cylinders appear to be out of date in view of the great advances in steel manufacture. The Air Force succeeded in getting this problem practically solved for war purposes, so that an aeroplane could easily carry a large supply of oxygen; and the light cylinders adopted by the Army Medical Department for stretcher work are of this pattern. The improved patterns of valves and other fittings simplify greatly the handling of the apparatus.

TWO TYPES OF OXYGEN APPARATUS.

For both hospitals and ordinary medical practice it seems to me that two types of oxygen apparatus will be required—one for continuous administration with cylinders as large as a nurse can manage. The other will be a very light apparatus with no mask, to be used in sudden emergencies by simply letting the oxygen blow into the patient's mouth. From the little I have had the chance of seeing I feel pretty certain that failure of the respiratory centre often occurs with dramatic suddenness, usually in the night, and requires to be dealt with by administering

oxygen without the slightest delay. We now know from experiment how quickly the vicious circle of respiratory failure may produce its effect in a normal healthy person. In a person whose respiratory centre is already weakened by the results of infection or other causes the failure may be far more rapid, and the recovery on giving oxygen equally rapid.

OXYGEN CHAMBERS.

An entirely different method of continuous oxygen administration was initiated last year at Cambridge by Mr. Barcroft and Dr. Hunt of Guy's Hospital, and has also been used recently at Stoke-on-Trent. The patient, together with his bed, is kept in an airtight chamber, the air of which is enriched to any desired extent with oxygen; this enriched air is purified and dried continuously by pumping it through suitable absorption vessels. The great advantage of this plan is that the patient is quite unhampered by a face-piece or tube, and can, if necessary, move about freely within the chamber. In this connexion it must also be remembered that in many cases the restorative effects of oxygen will only be very gradual. On the other hand the cost is heavy, and danger from fire has to be most carefully guarded against, for clothes, etc., will burn fiercely in the enriched air. It is also difficult to alter rapidly the percentage of oxygen according to the requirements of the patient.

I hope that chambers of this kind, with, perhaps, simplifications in detail, will be tried soon in a variety of cases. The results hitherto obtained in chronic gas cases, asthma, etc., seem to be most promising; but a great deal of further observation is evidently needed, and has, of course, been interrupted at Cambridge owing to closure of the Military Hospital there. I venture to hope that the whole matter will be actively taken up and carried further at Guy's Hospital, where Dr. Hunt's knowledge and experience would be invaluable. Along with the trials of oxygen there will, I hope, be trials of CO₂.

SOME OTHER USES OF OXYGEN.

On many points connected with the uses of oxygen I have been unable to touch—for instance, the use of oxygen with anaesthetics and for preventing or mitigating "shock" after operations. I have endeavoured, however, to place before you the main known physiological facts as to oxygen administration.

Although imperfect oxygenation of the arterial blood is a far more frequent primary or secondary cause of anoxaemia than was formerly suspected, there are, of course, other causes, as already mentioned. One of these is failure in the supply of blood to the right side of the heart, with consequent fall in arterial blood pressure. To what extent this condition may be secondary to defective oxygenation in the lungs is not as yet clear. In any case the failure in blood supply can be effectively combated by intravenous injection of gum saline solution, as recommended by Bayliss.† The experimental evidence which he has brought forward on this question seems to me conclusive.

Another of the causes that has been mentioned is a defective proportion of available haemoglobin in the blood. To combat this condition the most effective remedy may often be transfusion of blood, carried out with the necessary precautions; but another powerful remedy is the administration of pure, or nearly pure, oxygen. The object of giving the oxygen is to increase very greatly the amount of oxygen in simple physical solution in the arterial blood. As I showed many years ago, an animal can by this means be tided over the emergency while its haemoglobin is for the time thrown out of action by carbon monoxide or by one of the methaemoglobin-forming poisons; and anaemia from loss of blood could doubtless also be combated temporarily in a similar manner till adaptation had time to occur.

CONCLUSION.

In conclusion, let me say that it is cure and not mere temporary palliation of symptoms that should always be kept in view in connexion with the treatment of anoxaemia. The object of breaking the vicious circle of anoxaemia is to give the body time for adaptation or recovery.

Both the physicist and the physiologist or physician deal with "Nature" (*physis*). But it is with Nature as

* See *The Administration of Oxygen in Irritant Gas Poisoning*. Report No. X of the Chemical Warfare Committee. Issued by the Medical Research Committee, 1918. With full illustrations of apparatus and directions for use.

† Bayliss, *Intravenous Injection in Wound Shock*, 1913.

Democritus and Empedocles saw her that the physicist deals, while the physiologist and physician deal, or ought to deal, with that truer and deeper vision of her as she appeared to Hippocrates. On the practical side the physicist aims at guiding and controlling Nature, whereas the physician aims at helping her. The object of this lecture will have been attained if I have succeeded in indicating how we may help in one of her tight places that ever more marvellous "Nature" which the keen intellectual vision of Hippocrates first began to reveal definitely to the world.

WAR LESSONS AS APPLIED TO CIVIL PRACTICE.*

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IN the limited time at our disposal I propose to select a few subjects only which seem to me to have some bearing upon practice in civil life, and which suggest some modification of previous principles and methods of treatment.

Wound Treatment.

With regard to wounds, it will suffice to describe all gunshot wounds as potentially septic wounds. Potentially septic wounds are by no means uncommon in civil life also—for instance, abraded, contused, lacerated, incised, or punctured wounds received by workers on the soil, especially made soil containing manure, bicycle and motor accidents, and street accidents generally, where any of the above types of wounds may be contaminated by mud, dust, or dung, and are often complicated by fracture of bone; bites of animals, hunting accidents, and the like—all such wounds are potentially septic, and, in so far as they are potentially septic, they resemble the wounds of war, and should be treated on the same lines. If we do so treat them, our results should be better than under war conditions, because we can get at them soon, whereas during heavy fighting forty-eight hours, or even more, often elapsed before the casualty clearing station was reached by the wounded soldier.

During the four and a quarter years of actual fighting the treatment of wounds was revolutionized, and the results showed a marvellous improvement as time went on. The researches of the pathologists laid the foundation, upon which the surgeons built new methods, and we must briefly trace the more important of these in order that we may apply the lessons to be learnt from them.

In the early part of the war tetanus was alarmingly frequent. A large and constant supply of antitetanic serum was then organized, and for the last three years every wounded man received 750 units of serum at the dressing station and another 750 in seven days' time. As a result tetanus became rare, and such cases as were seen were of the modified or so-called local type. Now and again by some oversight a man did not get his injection—I saw such a case in France. He arrived late at night, three days after being wounded, at the base hospital, and there was no record on his field card of his having had an injection. He was given 1,500 units early the next morning; but acute tetanus began that evening, and ended fatally on the seventh day.

It is perfectly true that tetanus is a rare disease in this country, but when it does occur, it is so dangerous and so often fatal that we should, I think, as a routine practice always give an injection of serum as soon as possible after the infliction of wounds such as I have described above. And it is the duty of the sanitary authority or of the Government to provide us with this serum. This, however, is only a preliminary to the actual treatment of a potentially septic wound.

The facts in connexion with such a wound are these: On the one hand, the tissues have been laid open by some contaminating agent, the wound surfaces have not only been contused, injured, or in part devitalized by that agent, but they have had implanted on them a bacterial infection, whether *Bacillus tetani*, staphylococci, streptococci, gas-forming anaerobes, *Bacillus coli*, or what not. On the other hand, there is an exudate from the wound surface, consisting primarily of blood and blood serum.

The bacteria thus implanted require for their growth disorganized albumin, such as is afforded by devitalized

tissues, and also the presence of trypsin, which trypsin is formed by the fermentative action of bacteria. If there has been much devitalized tissue, or if there has been much loss of blood, or shock, or there is general debility and malnutrition, the bacteria multiply rapidly and the wound quickly becomes septic. If, on the other hand, there is no devitalized tissue and the vascular supply is uninjured, it comes to be a direct conflict or trial of strength between the invading bacteria and the natural defences of the body fluids.

The weapons of the invading bacteria are three: (1) Their proteolytic action or power of disorganizing the body albumin; (2) their power of producing trypsin by their fermentative action; (3) their power of producing toxins.

The natural defences of the body are in the main two: (1) The antitryptic power of the blood serum; (2) the phagocytic action of the living cells.

So that if the antitryptic action of the blood serum is able to keep pace with and to neutralize the trypsin formed by the bacteria, and the phagocytic action of the body cells is able to destroy them, repair sets in without suppuration—and this, indeed, is what usually takes place in wounds of the face, owing to the free vascularity of the tissues. The defence therefore has the advantage in wounds of the face. If, on the other hand, the trypsin and broken-down albumins increase and leucocytes are killed by the toxins the defence is beaten. There is suppuration and all the local signs of acute sepsis, with unknown dangers ahead in the shape of toxæmia, septicaemia, secondary hæmorrhage, and the like. The vital reaction has failed and the invader has conquered.

To put the case briefly, except in the case of wounds in the face, it may be said to be "a toss up" in potentially septic wounds as to which will win, the invaders or the defence. I submit that the war has taught us how to help the defence so that in the majority of cases it wins, and I further suggest that in civil practice we should adopt the methods which have been so successful in war. To acquiesce in it being "a toss up" is no longer either prudent or justifiable.

The problem, therefore, is how best to aid the defence in the case of a wound which is contaminated, the walls of which are possibly in part devitalized, and which forms, therefore, a very favourable soil for the growth of bacteria.

Since Colonel Sir H. M. W. Gray published his paper on excision of gunshot wounds, in the *Journal of the R.A.M.C.*, vol. xxvi, in 1916, it has been universally acknowledged that excision is the best prophylactic method of avoiding suppuration; it has been recognized, further, that the sooner a wound is excised after the receipt of the injury the more certainly is infection avoided. By excision we remove entirely, or aim at removing entirely, the wound surfaces which are sown with bacteria, as well as all devitalized tissue and shreds which are cut off from their blood supply, leaving a clean wound relatively free from contamination and capable of healthy reaction.

The procedure, in superficial wounds which do not extend beyond the deep fascia, is comparatively simple.

The skin is shaved and swabbed with iodine, or a 5 per cent. solution of picric acid in spirit, and the tissues infiltrated with novocain and adrenalin. The wound itself is then wiped out with a swab soaked in either iodine or the picric acid solution, and dried; the ends of it are clipped up with Lane's or other forceps so as to put the tissues on the stretch, and with a sharp scalpel the wound is excised completely at a distance of one-third to half an inch from the wound surface. Care is taken to prevent the clean new surface from being touched or contaminated by the original wound surface.

In deep wounds total excision may be anatomically impossible, but the skin and more superficial parts can be excised, and injured muscle removed, loose bone fragments picked out, and a careful toilet of the wound made under a general anaesthetic.

If immediate primary suture is not employed—and in the majority of cases this is too risky—the wound is packed with gauze well soaked in flavine; then in forty-eight hours, if the bacteriological findings are favourable, the wound is sutured carefully so as to bring all surfaces into contact and leave no cavities. This is called delayed primary suture.

There are two classes of wounds where primary or immediate suture has been found to be advisable—namely, in wounds of the scalp, and wounds of the knee-joint. In scalp wounds primary suture after excision is employed in order to attain immediate aseptic union, so as to give an aseptic field for any subsequent operation if such should

* Address delivered at annual meeting of Branch, June 26th, 1919.