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LECTURES

ON THE

EXPERIMENTAL INVESTIGATION OF THE ACTION OF MEDICINES.

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V.—RESPIRATION.

Respiration in Unicellular Organisms; in the Cells composing higher Organisms.—Distinction between Respiration in an Amœba and a Fixed Cell.—Internal Respiration.—External Respiration.—Internal Respiration may be diminished or arrested by Diminution or Arrest of the Circulation generally or locally.—Pathology of Fatty Degeneration, by lessening or destroying the power of Hæmoglobin to act as an Oxygen-carrier. (a) Action of Carbonic Oxide; (b) Action of Nitrites; Action of Phosphorus.—Examination of the effect of Drugs on Hæmoglobin.—Colour.—Spectrum-reducing Agents.—Absorption of Oxygen.—Action of Carbonic Oxide.—Ozonising Power of Blood.—Formation of Acid in Blood.—External Respiration.—Respiratory Movements.—Respiratory Nervous Centre; Excitants to this Centre.—Venosity of Blood.—Dyspnœa.—Apnœa: two opposite meanings of this term.—Effect of Temperature on this Centre.—Effect of Drugs: Tartar Emetic, Chloral, Opium.

THERE is a great deal of truth in the oft-repeated comparison between an animal body and a steam-engine. In both, the motion which is their characteristic function is kept up by combustion, and for combustion there is necessary a free supply of fuel and a free supply of oxygen. Simple organisms, such as the amœba, which consists of a single cell or minute mass of protoplasm only, derive their oxygen, as well as their nutriment, from the fluid in which they swim, and the individual cells which compose the tissues of the higher animals are nourished in much the same way. As Bernard strikingly puts it, "we do not live in air" any more than a number of amœbæ swimming about in a glass of water live in air. The cells of which our bodies are composed live, like the amœbæ, in a fluid—the intercellular fluid or lymph in which they are bathed; and our skin may be compared to the glass in which the amœbæ and the water in which they swim are contained. There is, however, a very great difference between the amœba and the cells composing the bodies of the higher animals, for it can swim about freely, whereas they are for the most part fixed. The amœba can thus obtain fresh supplies of nutriment and oxygen by moving through the water in which it lives, while in higher organisms the fluid moves over the cells. This fluid, or lymph, is the liquor sanguinis, which passes out of the capillaries and supplies all the tissues with nutriment and oxygen, at the same time that it removes from the system carbonic acid and the products of tissue-waste.

The interchange of oxygen and carbonic acid between the tissues and the blood is termed *internal respiration*.

But this interchange would soon remove all the oxygen from the blood and load it with carbonic acid, unless it had some means of absorbing oxygen and giving off carbonic acid to the atmosphere. This is effected in the lungs, and the interchange of gases between the blood and external air is termed *external respiration*.

The blood, therefore, acts as an oxygen-carrier between the blood and the tissues. A certain amount of the oxygen taken up by the blood is simply dissolved in it; but the amount of this is not sufficient to supply the wants of the tissues, and the greater part of the oxygen which they require is carried to them by means of the hæmoglobin, or colour-

ing matter of the blood. This substance forms a loose compound with oxygen in the lungs, and gives it off to the tissues when it reaches the capillaries, and on again passing through the lungs it takes up a fresh supply. The carbonic acid which is formed in the tissues by their oxidation is taken up by the blood in the capillaries and given off in the lungs; but it seems to be carried from the tissues to the lungs, not by the hæmoglobin, but by some one or other of the salts in the blood. Both internal and external respiration are essential for the maintenance of life, and it may be destroyed by putting a stop to either one or other of them.

1. Internal respiration may be completely stopped by preventing supplies of fresh blood from reaching the tissues. The stoppage may be general or local. General stoppage of internal respiration is produced by arresting the circulation in the whole body, by stopping the action of the heart, or obstructing the flow of blood through the large vascular trunks which are connected with it. Internal respiration may be arrested locally in any part of the body by compressing or tying either its arteries or veins. Thus, if the arteries going to the head be tied, so that no fresh blood can reach it, or the veins coming from it be ligatured, so that the deoxygenated blood cannot leave it, the blood which is present in the capillaries of the brain loses all its oxygen and becomes charged with carbonic acid. The nervous centres are thus effectually suffocated, although the lungs may be working vigorously, and the blood in the rest of the body may be richly arterialised. That the loss of function which follows stoppage of circulation in a part is due to the want of the oxygen carried to it by the blood, rather than to the want of nutriment, is well shown by the experiment of Kronecker, who found that contractility could be restored to the excised gastrocnemius muscle of a frog, after exhaustion by repeated contractions, by passing through its vessels a solution of permanganate of potash, which supplied oxygen to the interior of the muscle, but conveyed to it no nutrient matter.

When the circulation is diminished but not completely arrested, as, for example, by weakening the heart, or by contracting without obliterating the lumen of the blood-vessels, or when the oxidising power of the blood is impaired, internal respiration will be diminished, but not stopped.

The tissues, or at any rate the albuminous tissues, in all probability do not undergo combustion directly; *i. e.*, the albumen does not combine at once with oxygen. It is first split up by the action of a ferment into nitrogenous substances, which, after being oxidised, form urea and non-nitrogenous substances, such as fat, and probably also glycogen. When internal respiration is imperfect, the nitrogenous substances may not be oxidised, and appear in the urine instead of being converted into urea. The non-nitrogenous substances may also continue unoxidised, and, instead of being converted into carbonic acid, remain in the tissues as fat, giving rise to fatty infiltration or fatty degeneration. This is seen in the heart when the size of the coronary arteries is diminished by atheroma. The supply of blood being insufficient to keep up perfect combustion in the muscular fibres, the non-nitrogenous products of decomposition accumulate and cause the heart to become fatty.

When there is little hæmoglobin in the blood, as in anæmia, internal respiration is diminished, and there may frequently be noticed a tendency to the deposit of fat in anæmic girls. The peasantry in some parts of Germany are acquainted with this fact, and bleed their cows so as to induce an artificial anæmia whenever they wish to fatten them.

2. Internal respiration may be arrested by the action of substances which deprive hæmoglobin of its power to take up and give off oxygen easily, and thus render it useless as an oxygen-carrier. *a.* Certain gases—for example, carbonic oxide and nitric oxide—do this by driving out the oxygen from its combination with hæmoglobin, and forming compounds with it themselves. These compounds resemble those with oxygen, but are more stable, and are not decomposed during the passage of the blood through the capillaries, nor by the action of reducing agents added to the blood, as oxyhæmoglobin is. *b.* The oxygen-carrying power of hæmoglobin has been shown by Dr. Arthur Gamgee to be also destroyed by nitrites, but in a different way. Instead of driving out the oxygen from its combination with hæmoglobin,

the nitrites combine with the oxyhæmoglobin, and as it were lock up the oxygen in it, so that the oxygen no longer separates from the hæmoglobin when the compound is placed in a vacuum, nor can it be driven out by the action of carbonic oxide. At the same time, the blood which has been acted on by nitrites is deprived of its power of absorbing any more oxygen. But, although the nitrites lock up the oxygen in oxyhæmoglobin so firmly that it cannot be driven out by carbonic oxide, they do not prevent its removal by reducing agents. These first break up the nitrite compound, and then deoxidise the hæmoglobin; and, when this is next exposed to air, it takes up oxygen in the normal way. On this account, the action of nitrites in impeding or arresting internal respiration is only transitory; for, when the blood on which they have acted once becomes deoxidised during its passage through the capillaries, it is restored to its normal condition. The action of carbonic oxide, on the contrary, is permanent, the blood with which it has combined remaining unaltered during its circulation either through the body or the lungs; and, if the greatest part of the hæmoglobin have been acted upon, life can only be saved by the transfusion of fresh blood into the vessels, although, in slighter cases, a fatal issue may be averted by the diligent use of artificial respiration. Internal respiration is also diminished by phosphorus; and the fatty degeneration produced by this substance has been shown by Voit and Bauer to be partly due to this action. It is not due to this alone, however, for the phosphorus has a double action: 1. It causes the albuminous tissues to split up more rapidly; 2. It lessens the combustion of the products of decomposition. The increased rapidity of albuminous decomposition causes more urea to appear in the urine; and, if the nitrogenous compounds be not sufficiently oxidised, leucin and tyrosine may appear instead of urea. Fat is also formed from albumen more rapidly, as well as more slowly oxidised, than in the normal condition.

In order to ascertain whether the hæmoglobin of the blood has been altered by the action of a drug: 1. If it be poisonous, examine the blood from the arteries and veins of an animal which has been poisoned by it, and note whether its colour is normal in both sets of vessels or not. 2. Dilute a portion of this blood with water, examine it with the spectroscope, and see what spectrum it presents. Shake it with air, and observe if the bands of oxyhæmoglobin alone are present, and if they are of their normal intensity and in their normal place. Take another portion of the diluted blood and add to it a deoxidising solution, such as sulphide of ammonium or Stokes's fluid,* and see if the spectrum of reduced hæmoglobin appears. 3. Take two portions of normal blood, or of a solution of hæmoglobin, and add to one of them the drug to be tested, or pass it through, if it be a gas. Note, as before, whether any change is produced in the colour or spectrum, or in its behaviour to oxygen or reducing agents. 4. Take two equal portions of diluted blood or solution of hæmoglobin in small test-tubes, shake them with air till they are thoroughly oxygenated, and add to one of them the drug to be tested. Then add to each an equal quantity of deoxidising solution. Let the test-tubes be full, and cork them so as to exclude the solutions from contact with air. Note the length of time which elapses before the spectrum of oxyhæmoglobin disappears and is replaced by that of reduced hæmoglobin in each. 5. Take two equal portions of normal blood, and act on one of them with the drug. Bring them into contact with equal portions of oxygen or air, and let them remain so for some time. Then ascertain how much oxygen has been absorbed and how much carbonic acid has been evolved by each, by seeing whether any alteration has taken place in the volume of the gas, and by analysing it in order to determine its composition. 6. Act on a portion of normal blood with the drug; arterialise it completely, and then determine the amount of each gas which it contains by extracting them by means of warmth and a vacuum, and analysing the mixture thus obtained. 7. Oxygenate a portion of blood thoroughly, act on it by the drug, and then ascertain whether the oxygen can be driven out by carbonic oxide. To describe the methods of gas-analysis would occupy more space than can be devoted to it here; and I must, therefore, refer to Bunsen's or Frankland's text-books on the subject, or to Sanderson's *Handbook for the Physiological Laboratory*; for an excellent example of the mode of ascertaining the action of a drug on the blood, to Dr. Gamgee's paper on the Action of Nitrites in the *Philosophical Transactions of the Royal Society* for 1858, p. 589-625; and to Dr. Harley's paper on the Action of Alkaloids, etc., in the *Transactions* for 1864, p. 687.

The object of adding the drug to the blood before arterialising, as in 6, and after arterialising, as in 7, is to discover whether it prevents the blood from taking up oxygen in the former experiment, or of giving it off in the latter. Normal blood has the power to produce ozone, or to

withdraw it from substances which contain it, and transfer it to others which are easily oxidised. Arterial respiration may be modified, and the process of oxidation diminished, by the action of certain substances which deprive blood of this power. The usual test for ozone is fresh tincture of guaiac (1 part guaiac to 6 of alcohol), which is oxidised by it with extreme rapidity. It shows the progress of the oxidising process with great distinctness by the blue colour which it assumes. A few drops of tincture of guaiac are put upon a piece of porous paper, allowed to become almost quite dry, and a drop of blood or solution of hæmoglobin is then placed on it. In a few minutes, the drop becomes surrounded by a blue ring from the formation of ozone and the oxidation of the guaiac in its neighbourhood. The formation of ozone is independent of the oxygen contained in the hæmoglobin; and carbonic oxide-hæmoglobin will produce it as well as oxyhæmoglobin, provided air be present. When the hæmoglobin itself contains oxygen in the form of oxyhæmoglobin, the presence of air is not necessary to the reaction. The oxidation of guaiac by means of blood alone is, however, not nearly so easily observed as when another substance containing ozone is added to it, such as peroxide of hydrogen or oil of turpentine which has been kept for some time. The hæmoglobin takes the ozone from these substances, and yields it up again to the guaiac.

The method adopted by Briz, in order to test the influence of drugs on this ozonising power of hæmoglobin, is to take a mixture of tincture of guaiac with a few drops of ozonised oil of turpentine, and divide it into two parts. A few drops of a solution of the drug to be tested is added to one of them, and a few drops of solution of hæmoglobin then dropped into both. If the drug increase the oxidising power of the hæmoglobin, the solution containing it will become blue more quickly than the other, but more slowly if the oxidising power be diminished.

Another process more simple than that of analysing the gases of the blood has been used by him and his scholars Zuntz and Schulte, in their observations on the effect of drugs on oxidation, in the blood. This process is based on the fact, noticed by Zuntz, that, immediately after blood has been drawn from the body, an acid begins to form in it, so that its normal alkalinity goes on decreasing. The formation of acid is most abundant during the first few minutes after the blood has been drawn, and before coagulation has taken place, so that Zuntz considers it a vital phenomenon; but it continues, though in a less degree, till putrefaction commences. They take the rapidity with which acid is formed as an index of the rapidity with which oxidation takes place in the blood; and, when they find that the addition of a drug to the blood has diminished the formation of acid in it, they consider that the drug has diminished oxidation in the same proportion. The following method is the one which they employ. Three equal portions of the same blood, of fifty cubic *centimètres* each, are measured out. The alkalinity of the first portion is then determined at once. To a second portion, the drug to be tested is added. The solution of the drug must be neutral; or, if it be acid, the amount of its acidity must be determined and allowed for in the final calculations. To the third portion, nothing is added. The second and third portions are then kept for one or two hours at a temperature of about 40° C. They are then allowed to cool, and the alkalinity of both portions is determined. If acid have been formed in either of these portions during this time, the alkalinity will of course be less than that of the first portion, and the amount of acid formed is estimated by the diminution which the alkalinity has undergone. The alkalinity is ascertained by noting what quantity of a standard solution of phosphoric acid must be added to the blood before it begins to give a red colour to blue litmus paper. But, if phosphoric acid were used alone, the red colouring matter of the blood would be apt to stain the litmus-paper, and it would be almost impossible to say when the reddening was due to it, and when to free acid. In order to prevent this, a quantity of chloride of sodium is added to the acid. The salt prevents the corpuscles from being dissolved, and the hæmoglobin from disturbing the reaction. The acid and salt are gradually added to the blood, and the reaction tested from time to time by putting a drop of the blood on a piece of fine satin-paper coloured with litmus. The paper should be first moistened with a tolerably strong salt solution, the drop of blood allowed to remain on it for a few seconds, and then wiped off with blotting-paper. The point of saturation is held by Schulte, who has also employed this process, to be reached whenever the blue litmus-paper becomes distinctly reddened, even though the red colour should disappear again immediately. This transient reddening is due to carbonic acid; and Schulte prefers it to the first permanent reddening, because it can be more easily observed. This does not give the absolute amount of alkalinity; but all that is wanted is the comparative alkalinity of the three portions, and this is got accurately enough if they be all treated in the same manner as regards temperature, shaking, etc. In this way, Zuntz, Scharrenbreich, and Schulte, find that quinine lessens oxidation in the

* Stokes's fluid consists of a solution of protosulphate of iron, to which is added a sufficient quantity of tartaric acid to prevent precipitation, and then as much ammonia as will render it decidedly alkaline.

blood, and Binz finds that it does the same in a solution of hæmoglobin.

External respiration, or the interchange of gases between the blood and the atmosphere, takes place whenever they come into sufficiently close relation with one another, as they do in the capillaries of the skin, intestinal canal, or lungs. In the frog, respiration is carried on by the skin to such an extent, that it can live for a considerable time after the lungs have been excised; but in mammalia respiration is carried on almost entirely by these organs, and any interference with their function quickly puts an end to the life of the animal. In order that the blood which circulates through the body may get rid of its carbonic acid and take up oxygen sufficient for the wants of the tissues, fresh portions of it must constantly be brought into contact with the air, and therefore it must constantly circulate through the pulmonary capillaries. But the air in the lungs would soon become saturated with carbonic acid and deprived of its oxygen by the blood which comes into contact with it, and all farther diffusion would be arrested, unless it also were constantly renewed. This is effected by the respiratory movements. These consist in the alternate enlargement and diminution of the thoracic cavity, after the fashion of a pair of bellows, by the motion of its walls and of the diaphragm. These movements are kept up in a rhythmical manner by a nervous centre, situated in the medulla oblongata and upper part of the spinal cord, which sends off periodic motor impulses to the diaphragm and inspiratory muscles. When the breathing is quiet, expiration is usually a passive act performed by the elasticity of the lungs and ribs, and by the weight of the thoracic walls. But when it becomes excited, active expiratory muscles are brought into action, and they receive their motor impulses from the respiratory centre alternately with those of inspiration. It is probable, though not certain, that the respiratory centre is not a mere reflex apparatus, which simply transmits impressions which it receives from sensory nerves to motor ones; for its activity continues, although its connections with sensory nerves be almost entirely destroyed. The periodic impulses which it imparts to the motor nerves of the respiratory muscles are not due to its being periodically excited by impressions from afferent nerves, but to its being constantly excited by the venosity of the blood circulating in it; while some resistance within itself prevents the excitation from being constantly transmitted to motor nerves, and only allows it to be so at periodical intervals.

The venosity of the blood consists in the absence of oxygen and the presence of carbonic acid, and it is not certain whether or not both of these act as excitants to the respiratory centre; but it seems not improbable that the presence of carbonic acid is the excitant, while the amount of oxygen simply alters the excitability of the centre. According to this view, when there is much oxygen in the blood, the excitability of the centre will be slight, and little affected by any irritant applied to it, whether this be carbonic acid or anything else. When the amount of oxygen in the blood is small, the centre will be very excitable and easily affected by any irritant. In venous blood, there is both little oxygen and much carbonic acid, so the centre is both rendered more sensitive, and is more strongly excited by the acid. The more venous the blood, the greater is the excitation of the respiratory centre, and the more active the respiratory movements. When other interfering circumstances are excluded, it would appear that greater excitement of the respiratory centre causes the respirations to become quicker, and, at the same time, deeper. This excited respiration is termed dyspnoea, and it occurs when the blood becomes venous in the respiratory centre. As the venosity increases, the ordinary muscles of respiration are no longer employed alone, but the expiratory and accessory muscles are called into play; and, lastly, all the muscles of the body are affected by clonic convulsive movements, called asphyxial convulsions.

When the blood which circulates in the respiratory centre is not at all venous but is perfectly arterialed, as it is when artificial respiration is vigorously performed, the centre is both rendered less sensitive, and the irritant, viz., the carbonic acid, is at the same time diminished or removed, the centre is not excited at all, and respiratory movements cease.

This condition, in which no desire for respiration is felt, and respiratory movements cease, is termed "apnoea" by German writers, and it must be carefully distinguished from the "apnoea" of English authors, which is simply extremely great dyspnoea; so great, that the blood is hardly aerated at all.

The activity of the respiratory movements and the amount of air respired in a given time, depend on the degree of excitement of the respiratory centre. As we have just seen, this excitement depends on two factors; 1. The excitability of the centre; and 2. The amount of irritation applied to it. In general, the venosity of the blood determines both factors, and it is not the venosity of the blood in the general circulation which does this, but only of that blood which courses

through the vessels of the medulla. This was shown by Hering, who passed a stream of arterialed blood through the vessels of the head while venous blood was circulating in those of the body. The respiratory movements then ceased exactly in the same way as if the whole blood in the body had been perfectly oxygenated. When he reversed these conditions, and passed arterialed blood through the body and venous blood through the head, asphyxial convulsions took place. This shows that the degree of activity of the respiratory centre in the medulla oblongata depends on the greater or less venosity of the blood circulating through it, and not on an irritating action exerted by venous blood on the ends of afferent nerves in the lungs, or other viscera.

The excitability of the respiratory centre may be greatly modified; 1. By the temperature of blood in it; 2. By the action of drugs upon it. When the blood becomes warmer, the excitability of the respiratory centre is greatly increased; the movements of respiration become much more vigorous, and it is no longer possible, by the most active artificial respiration, to produce a state of apnoea. Certain drugs, as tartar emetic, or apomorphia, when injected into the veins, also prevent the production of apnoea, but whether they do so by increasing the excitability of the centre, or by acting as irritants to it, is uncertain.

Other drugs, such as chloral, greatly diminish the excitability of the respiratory centre, so that the respirations become fewer, notwithstanding the increase of carbonic acid in the blood to which their diminution gives rise, and if the dose be large they may stop altogether. Apnoea may also be produced by means of artificial respiration with great ease after their administration, and it may last so long, that one is sometimes inclined to think that the animal is not going to breathe again at all.

FOUR CASES OF AFFECTION OF THE VERMIFORM APPENDAGE, WITH FATAL ISSUE.

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THESE cases are brought forward, not as offering any thing very new, but as illustrative of affections of the vermiform appendage, which are not very uncommon, but which, perhaps, are not sufficiently borne in mind in ordinary practice. The cases are, themselves, so illustrative, that their description involves almost all that need be said of the conditions involved.

CASE I. Concretion in the Vermiform Appendage, consisting of Inspissated Faecal Matter. Inflammation of the Appendage, resulting in General Peritonitis.—This was the case of a middle-aged man, who, while apparently in perfect health, was attacked by symptoms resembling those of ileus, and which were at first supposed to be due to some internal incarceration of the bowel, or to strangulated hernia. A surgeon was consulted with a view to the latter question; the bowels were, however, freely moved by enemata, but without relief to the symptoms, and the patient died on the fourth day. On opening the abdomen, there were evidences of very acute recent peritonitis. The intestines were everywhere glued together with soft lymph, and the great omentum was adherent by its lower margin to the folds of intestine at the brim of the pelvis. The lymph was everywhere soft, but towards the right iliac region it was much softer than elsewhere, and there was here even fluid pus. On removing the lymph and pus, the vermiform appendage was found lying on the surface of the colon, in the form of a turgid black coiled up mass. It was much dilated, and most intensely congested, so as to have an almost gangrenous appearance. In the dilated appendage, which was congested through its entire thickness, a solid body about the size and shape of a cherry-stone was discovered. This foreign body was about the consistence of half-dry clay, and had a similar brownish yellow colour. On being cut into, this body, which, from its appearance, evidently consisted of dried faecal matter, was seen to be stratified. The dilated portion of the appendage, in which the body was lying, did not appear to communicate with the peritoneal cavity—at least, no perforation could be discovered. The mucous membrane of the intestines was perfectly normal, and the calibre in no part obstructed.

In this case, it appears as if the small mass of inspissated faecal matter had found its way into the vermiform appendage—possibly when of small size, as the stratification seems to indicate that it was of gradual growth, and the successive layers may have been added after its passage into the appendage. The mass acted as a foreign body, producing an intense inflammation of the appendage, which passed from its mucous to its serous surface, and thence to the general