decrease in the skin resistance. Several speakers had spoken of the undoubted influence of toxins, but it was not necessary to assume that these were necessarily pressor substances. A toxin such as alcohol or histamine, which was a normal constituent of the intestine, although a capillary dilator and capable of bringing about shock if absorbed in large quantities, brought about constriction of arteries reflexly, as did haemorrhage. Here, then, was another example of striving on the part of the vasomotor centre, but in this instance to maintain arterial pressure in spite of capillary dilatation, and which tended to soak up the blood and allow the animal to bleed, as it were, into its own capillaries. As he had pointed out in a recent paper, there was actually a pressor reflex, by way of the vagi, called into operation. These toxic cases were, then, not so essentially different from the simple nervous strain cases as at first sight might appear. This reflex action might readily be overdone, and might be sup-

plemented by direct action of substances—for example, histamine, which, although a capillary dilator, had a definite constrictor action, as shown by Dale, on all smooth muscle. They knew that all reflexes, if continued, tended to become more active. He considered that the often rapid recovery in individuals suffering from hyperpiesis, and the intermittency which was often observed, supported the conception that the condition was due to muscular contraction. Lord Dawson appeared to have summed up the matter when he stated that hyperpiesis was in its first stage a physiological mechanism "gone mad." From physiological evidence the mechanism which was upset was that which was normally responsible for the raising of blood pressure in anticipation of exercise or the maintaining of it in blood loss. At first the condition might be temporary, but later, when degeneration or extensive hypertrophy set in, the high blood pressure would become permanent.

A Lecture

ON

RESPIRATION IN ANAESTHESIA:

CONTROL BY CARBON DIOXIDE.*

BY

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To understand, to predict, to control: these are the objects of all scientific investigation. The last and greatest is control; but unless we have first attained an understanding of the nature and working of basic phenomena, prediction is inaccurate or impossible, and control is incomplete and unreliable. Such, I take it, is always the relation of applied science to pure science.

Anaesthesia is one of the most beneficent of the applications of science, and one of the greatest achievements of modern medicine. Perhaps if we took all other drugs and weighed them in the scales of usefulness against the anaesthetics, the balance would incline in favour of the anaesthetics. We should expect, therefore, that the fundamental phenomena of anaesthesia would have been very thoroughly explored, and that much inventive ingenuity would have been applied to the utilization of fundamental principles. In fact, however, the art of anaesthesia as we have it to-day is founded on little more fundamental knowledge than that certain substances produce unconsciousness; and until quite recent years anaesthetists have been content with an extreme crudity of technique. It is probable that 90 per cent., perhaps even 99 per cent., of all anaesthetics in the world are still administered by dripping the liquid anaesthetic on to a towel or into a cone or on a few layers of gauze; the anaesthetist trusts to the heat of the atmosphere to volatilize the liquid into a gaseous form.

It is one of the first principles of anaesthesia that it is only when the liquid anaesthetic is vaporized and inhaled in gaseous form that it can be absorbed from the lungs into the blood and produce its desired effects. It is another first principle that the depth of anaesthesia should be maintained as nearly uniform as possible; and yet another principle that this depth should be attained as quickly as possible, and that the first stage, the stage of excitement, should be made as short as possible. But, in fact, the fulfilment of these requirements is made as difficult as possible by the crudity of the method of volatilization employed. The conditions are those of an essentially unstable equilibrium. Stable equilibrium would require, in respect to anaesthesia, that the condition should be such as would automatically tend to increase the concentration of ether inhaled whenever the patient tends to come out; and, contrariwise, to decrease the concentration whenever the patient is sunk too deeply under the influence of the drug. In fact, however, as soon as the patient emerges

to any extent, the volume of his breathing increases, and under the drop method more of the anaesthetic is blown away by each expiration. Thus the anaesthesia tends to be still further decreased. Contrariwise, when the patient is deeply anaesthetized, the volume of breathing grows less, and the tendency is for a more concentrated vapour to be inhaled. The latter tendency is met by the watchful anaesthetist decreasing the rate at which the anaesthetic is dripped upon the mask. But it is far more difficult to meet the situation when the patient is excited and struggling. Sometimes, during recurring periods of excitement, it seems as if the more liquid that is poured upon the mask the more it becomes chilled and frosted; the less the volatilization therefore, and the greater the difficulty of getting the patient under again. By such recurring periods of excitement, alternating with periods of unduly profound anaesthetic coma, the vitality of the patient is depleted to an extent equalled only by a severe haemorrhage. The risk of failure of respiration or circulation is increased, and a prolonged period of post-anaesthetic prostration and slow recovery is rendered inevitable. There is probably also an increased liability to a subsequent pneumonia.

I am aware that this picture is somewhat highly coloured, although I insist not too highly. I rather expect that one or more skilful and conservative anaesthetists will take up the cudgels and reply: "Nothing of that sort occurs as I conduct anaesthesia." In my own country, at least, such remarks as I have here made have called forth this rejoinder. But my answer is ready: The fact that these conditions do not occur in your cases is due, my dear sir, or madam, to the great skill which you have acquired as the result of natural aptitude and unflagging care, and not to the inherent adaptation of a mask and dripping bottle to the production of a uniform or easily controllable mixture of vapour in air.

Perhaps I ought to confess here that I am not an anaesthetist by profession, but merely a physiologist with a special interest in respiration and in gases and other volatile substances, including the anaesthetics, of course, which enter the body through respiration. For twenty years I specialized in bad anaesthesia by the drop method. Out of a hundred or more cases a year I saw a mortality early in anaesthesia running usually around 30 per cent., and sometimes higher. I was then teaching physiology, and I felt that medical students could not have a more valuable experience than to have undergone the trouble and anxiety of an anaesthetist with a bad case, and that even to have had a "death on the table" was very instructive for them. Of course, I reprimanded them and sent them away in disgrace whenever a fatality occurred, saying to them: "It is not allowable for you to report, 'I have killed that patient; give me another.'" Let me explain, however, that the patients in question were cats, or occasionally dogs, which were intended for experiments on blood pressure. It seemed to me that it was well worth while for these future medical men to have an experiment delayed and to have to buy another animal, for the sake

* Delivered under the auspices of the Dental Board of the United Kingdom.

of seeing how disastrously the vital mechanism may be affected by badly administered anaesthesia.

While those young men thus learned the elements of anaesthesia I utilized the opportunity to study anaesthetists. I am convinced that they made no errors that are not inherent in the drop method, or that are not made to some extent by all who use it. They merely made these errors much more frequently, more acutely, and on subjects which, being smaller and more excitable than human patients, are more readily and more obviously affected deleteriously.

Importance of Control of Breathing.

What, then, is it that an unskilful anaesthetist does? Or, contrariwise, what are the errors which the skilled anaesthetist instinctively avoids? To put the matter in a single short statement, which I shall spend the remainder of this hour in elaborating, the whole difference between good and evil in anaesthesia lies in this: the capable anaesthetist with suitable apparatus and technique controls respiration to his purpose, or adapts his administration to the patient's respiration. The incapable anaesthetist, on the contrary, is constantly struggling with a respiration over which he has neither intelligent nor instinctive control; he is like the nervous driver of a horse, or, if he is more up to date, of a motor car which alternately runs away with him and stalls. What I shall here say applies particularly to the use and effects of ether, for chloroform, formerly extensively used in America, has, I am glad to say, been almost entirely discarded.

Respiration is a function of great variability. Its rate may vary from four or five times a minute to twenty or thirty or more. The volume of air breathed may vary from 5 litres a minute to 30 or 50 or more. It is unfortunate that respiration is usually thought of in terms of rate. The really important quantity is the volume of air breathed in a minute. This is particularly true with relation to anaesthesia, for the quantity of the drug that the patient receives is the product of the volume of air breathed and of the concentration of the vapour mixed with the inhaled air. Let us say no more of the rate of breathing therefore; but let us fix our attention on the volume a minute.

The significance and relations of the volume of air that a man breathes were first clearly grasped and explained by Haldane.¹ The interpretation which he gave of this matter has been one of the most important contributions that modern physiology has made to the science and art of medicine. It has been the foundation of the developments in many important clinical fields, among others that of anaesthesia. It has been particularly appreciated, and its originator honoured, in America. In fact, in delivering this lecture, I come as one of Haldane's disciples to preach an application of his doctrine in the land of the prophet of modern science who is its author.

The principle is simple. Carbon dioxide is produced in the body by the same process by which oxygen is consumed. The supply of oxygen has relatively little immediate influence upon respiration. The administration of pure oxygen gas never acts as a stimulant. Carbon dioxide, on the contrary, is the normal stimulant and regulator of breathing. The amount, or, more exactly, the pressure, of carbon dioxide in the air in the lungs, and thus in the arterial blood flowing from the lungs, acts upon the respiratory centre so precisely that in normal life the volume of air breathed is kept in almost exact proportion to the amount of carbon dioxide. Even during the tenfold variation of carbon dioxide production during bodily rest and in vigorous muscular work, the proportion of respiration to the amount of its gaseous stimulus is maintained. In other words, the lungs are automatically ventilated so that the air which they contain has, under all normal conditions, a content of a little more than 5 per cent. of carbon dioxide. This concentration of carbon dioxide is also one of the prime factors in the acid-base balance of the blood and tissues. It is itself the chief acid in this balance, and it controls indirectly, but effectively, the amount of the alkali in use in the blood.

Suppose now that a nervous patient is anaesthetized.

His anxiety has caused overbreathing and an abnormal depletion of the carbon dioxide in his lungs and blood, the condition of acapnia, and other disturbances of function. Suppose that the first stage of anaesthesia is prolonged, a stage in which the exciting effect of an insufficient concentration of anaesthetic in the blood often causes excessive breathing and further depletion of the body's normal store of carbon dioxide. I am speaking now particularly of ether administered by the drop method. Finally a sufficient amount of the drug is administered to produce full anaesthesia. The sensitiveness of the respiratory centre is thereby reduced to normal; or, if the anaesthesia is profound, it is reduced far below normal. Respiration may then fail temporarily; and it is to be noted that this failure is not merely the result of what the anaesthetist has done in the minute preceding. It is rather the resultant of all that the patient has been through up to this time. The excessive breathing has reduced the carbon dioxide and has thus decreased the normal stimulus for respiration. It has finally caused an excessive inhalation of the anaesthetic vapour, and thus reduced the sensitiveness of the respiratory centre much below normal. There is therefore a simultaneous decrease both of the stimulus and of the sensitivity of the centre. Respiration inevitably stops, and with it ceases the supply of oxygen to the blood, and so to the brain. Thus to acapnia is added anoxaemia. If respiration is restored, the anoxaemia leads to another period of excessive breathing, and so to an intensification of acapnia—a vicious circle of increasing velocity.

The Control of Anaesthesia.

The practical problems of anaesthesia are uniformity of administration, rapid induction and termination, prevention of acapnia and anoxaemia, and preservation of the patient's vitality generally. These problems have been attacked with marked success in America during the past decade. Our anaesthetists have asserted the importance of their work and have brought our surgeons to realize, as they formerly did not, that the anaesthetist plays a part, for good or ill, in the outcome of every major operation, second only to that of the surgeon himself. From being a matter of dead routine, anaesthesia has become a field of active study and progress. The national and local associations of anaesthetists hold meetings and publish discussions and researches which testify to the live interest and vigorous development in their field. But the particular aspect of this growth to which I wish to call attention is the invention of apparatus for administering the various forms and combinations of anaesthetics.

These apparatus enable the anaesthetist to administer nitrous oxide, ether, ethylene, sometimes even acetylene, and other new anaesthetics, in any sequence or combination, with oxygen pure or combined with any percentage of carbon dioxide. It is particularly noteworthy that such provision is made for volatilizing ether that it is administered as a vapour. There is also in nearly all such apparatus a rebreathing bag or bags, and various valves and other devices for estimating the volume of the flow of the gases in and out of the bag, and also the volume of the patient's breathing. Some of these apparatus are, indeed, quite unnecessarily or even appallingly complex, but they give the anaesthetist a far greater control over conditions than he has ever had before. Nearly every prominent anaesthetist has a special apparatus which he has devised; and the clinical journals are full of advertisements of these devices, thus testifying to the extent to which their use has already grown.

Only the main features common to most of these apparatus and approved by almost universal experience concern us here. The primary features, in my opinion, are the rebreathing bag and such accessories as a cylinder of compressed oxygen, another of carbon dioxide, pure or diluted with oxygen, and the valves for their control. As regards this bag, experience has shown, in confirmation of theory, that nothing contributes so much to uniformity of anaesthesia as properly adjusted rebreathing. Our lungs are themselves a rebreathing apparatus, especially fitted to prevent fresh atmospheric air from coming in contact with the blood as it flows through the pulmonary vessels,

Suppose that the lungs had only the capacity of the breath and were emptied by each expiration; then at each inspiration the gaseous contents of the lungs would be virtually atmospheric air, and the blood would be momentarily greatly over-aerated. Similarly by the end of each expiration the air in the lungs would be so vitiated that the blood would be inadequately aerated. The faces of our friends would go blue and pink a dozen times a minute. Instead of this truly alarming spectacle, Nature has arranged that the lungs constantly contain 3 to 5 litres or more of air, of which only about a tenth is thrown off at each respiratory tide. This fraction is replaced by the same quantity of fresh air, which is immediately mixed with the stationary air. Accordingly, in the successive phases of each breath, the composition of the air in the lungs normally varies so little that the oxygen and carbon dioxide rise and fall by only two or three tenths of 1 per cent.

By following Nature in this regard, anaesthetists have found that the addition of a rebreathing bag of 4 or 5 litres to the volume of the stationary air of the lungs is advantageous. The total contents of lungs and bags are thus about 8 litres, and the variations in the composition of the air are reduced to half what they would be in the lungs alone. This is true even when a volume equal to the whole volume of the tidal air escapes from the bag at each expiration, and is replaced by fresh air or oxygen. The equalizing and conserving effects are even more marked when the volume discharged and replaced is less than the tidal volume by a third, a half, or even two-thirds.

This is the main point in the now well established principle of enlarging the stationary air of the lungs by the addition of a rebreathing bag. It requires, however, that oxygen from a cylinder attached to the apparatus shall be fed into the bag instead of merely atmospheric air. In order to be managed in the best manner, the apparatus must have a sufficiently accurate device for measuring the flow of oxygen, so that the anaesthetist knows within a small fraction of a litre how much oxygen he is feeding in each minute. The apparatus should also afford at a glance a quite approximate indication of the volume of the breath, and thus, from the volume and rate, a close estimate of the respiratory volume a minute. Furthermore, there must be, and on all the apparatus that I have seen lately there is, some arrangement for volatilizing ether, so that the anaesthetist can feed the vapour to the mask over the patient's face, or into the rebreathing bag, instead of handling merely a liquid, which may or may not volatilize completely and immediately. Such a device is essentially similar to the carburettor in which petrol is volatilized in an automobile—a fact full of practical suggestion for those with a turn for invention or adaptation.

Use of Carbon Dioxide with Anaesthesia.

Finally, there is a feature in an increasing number of these apparatus, and in the technique employed by an increasing number of the most skilful and intelligent anaesthetists, to which I wish especially to direct attention. It is a cylinder of a mixture of oxygen and carbon dioxide. The amount of carbon dioxide, the percentage added to oxygen, is still variable. On physiological grounds and in order to play safe, I first recommended about 5 per cent. of carbon dioxide in 93 to 95 per cent. of oxygen.² But one anaesthetist after another has used stronger and stronger mixtures with increasing advantage, until now some of the most competent tell me that 25 per cent. carbon dioxide in 75 per cent. oxygen is the mixture which affords them the most perfect control of respiration. Of course, it is not used straight, but is added to air or to oxygen from another cylinder. It then allows any degree of stimulation, and in fact it enables the anaesthetist to exercise an absolute control of the patient's breathing. Thus at the initiation of anaesthesia before nitrous oxide, or ethylene, or ether vapour is turned on, full deep breathing may be induced. Then the anaesthetic is added, and full anaesthesia is induced almost instantaneously. The stage of excitement is virtually eliminated. During anaesthesia the breathing can be allowed to decrease as it does under the full effects of ether and ethylene, or it can be increased by throwing into the breathing bag a moderate amount of the carbon

dioxide-oxygen mixture. Finally, at the termination of the anaesthesia, the supply of anaesthetic is shut off, the breathing bag is emptied or disconnected, and by mixing some of the carbon dioxide-oxygen with the air which the patient inhales vigorous breathing is stimulated for a few minutes, and the anaesthetic is quickly ventilated out of the patient's blood. Consciousness returns with extraordinary rapidity, although enough of the anaesthetic still remains in out-of-the-way parts of the body to induce the patient to sink into a condition approximating normal sleep, after removal from the operating table to his bed.

The principal advantages of modern anaesthetic apparatus over the mask and dropping bottle are, then, as follows: (1) Ether is fully vaporized before it is administered. This is advantageous, not only for the reasons already stated, but also because the deleterious cooling effect of ether, when vaporized close to the patient's face, is thus eliminated. (2) The use of rebreathing apparatus affords a far more uniform concentration of the anaesthetic vapour than is attainable in any other way. The contents of the bag should be so enriched with oxygen that its supply and concentration are always equivalent, or more than equivalent, to that in atmospheric air. The rate at which the contents of the bag are renewed is then adjusted to keep the pressure of carbon dioxide at that concentration which will afford the amount of respiration desired. (3) The use of carbon dioxide mixed with air or with oxygen furnishes the anaesthetist with the means of dominating respiration and of using this function for the purposes of rapid induction, smooth administration, and rapid termination of anaesthesia. He is no longer under the necessity of struggling with unruly breathing, while the vitality of the patient melts away under his hands. Nothing in my observation is more striking than the differences in the appearances of patients anaesthetized in two different ways. Those of one group were etherized by the open drop method in the usual fashion, and were then left to hours of subnormal breathing, cyanosis, nausea, acapnia, and anoxaemia. In contrast to these conditions are the rapidity of the return of normal functions in patients who have had uniform anaesthesia, rapid elimination of the anaesthetic, and a restoration of their store of carbon dioxide sufficient to ensure normal breathing, and therefore a normal oxygenation of the blood, during the hour following anaesthesia.

Other Uses of Carbon Dioxide.

The use of carbon dioxide as a means of controlling respiration is not confined to the field of anaesthesia. It applies equally well to other scarcely less important problems. Several anaesthetists of my acquaintance have told me of their success in overcoming the asphyxia of the newborn by a brief inhalation from a cylinder of mixed oxygen and carbon dioxide. The last case that I learned of was that of a baby which persistently refused to breathe spontaneously until its lungs were inflated a few times with 25 per cent. carbon dioxide and 75 per cent. oxygen. Then it started breathing on its own account. In fact, it could not very well do otherwise, if it had any respiratory centre at all. At the last report, some days later, it was breathing as if it intended to continue for a full life term of three-score years and ten.

Another very practical use to which the inhalation of carbon dioxide has been put is in the treatment of alcoholic intoxication. This is a matter both of benefit to the patient and of a very large saving of expense in a large city hospital. Alcohol of all varieties is volatile. Common experience and the sense of smell teach us that even in quiet breathing some of it may be exhaled in the breath. Ethyl alcohol is burned in the body to a certain extent; but methyl alcohol, which now is contained in some cheap liquors, at least in America, is not burned. It is very slowly excreted, and if it accumulates in the body it is extremely poisonous, causing optic atrophy and thus many cases of permanent blindness. Such patients may occupy hospital beds and be a source of expense for weeks. On the other hand, it is found that by means of simple and inexpensive apparatus for administering carbon dioxide mixed with air, which is also very cheap, even a comatose alcoholic may be made to ventilate the alcohol out of his blood through

his lungs in the course of an hour or so. He can then be discharged from the hospital sober and well the next morning.

Still another and even more important use of carbon dioxide as a stimulant for respiration has been developed in connexion with carbon monoxide asphyxia. Such cases occur frequently in every city where the amount of carbon monoxide in the public gas supply is allowed to rise above the minimal amount. They occur also frequently among the men in the city fire brigade, for the smoke from a burning building usually contains considerable amounts of carbon monoxide. Carbon monoxide asphyxia is best known perhaps as the result of explosions and fires in coal mines. In the blood of the victim the haemoglobin is so far combined with carbon monoxide that its capacity to transport oxygen is seriously diminished. As Haldane showed, oxygen will drive the carbon monoxide out again and restore the normality of the blood. But as Haggard and I have shown, in addition, an asphyxiated man breathes so poorly that oxygen is not adequately inhaled when administered. Accordingly we have introduced very widely in America, and to some extent on the continent of Europe also, the use of oxygen to which 5 per cent. of carbon dioxide has been added. This mixture must be administered with a properly devised inhaler, one which allows a very large volume of breathing, in order to produce the best results. The great increase of breathing, which the carbon dioxide in the mixture stimulates, causes the blood in the lungs to be flushed and flooded with oxygen, by which the carbon monoxide is rapidly displaced.³

This matter may seem somewhat apart from anaesthesia. But there is one point in connexion with it which has a special bearing here. It is the fact that persons partially asphyxiated, and left to recover without such treatment, very frequently develop pneumonia. In fact, in the past a considerable percentage of all deaths, primarily due to asphyxia, have been the immediate consequence of a secondary pneumonia. On the other hand, patients who soon after asphyxiation have been treated with the oxygen and carbon dioxide mixture not only recover rapidly from the asphyxia, but are also relieved of the danger of pneumonia. There is considerable ground for the claim that a similar elimination of post-anaesthetic pneumonia is afforded by the use of oxygen and carbon dioxide at the end of each surgical operation.

The Absorption, Distribution, and Elimination of Ether.

So much for the application of the principles of respiration to the clinical side of our subject. Now let us consider some of the results that have come from recent investigations in the laboratory, but which are not yet fully realized by anaesthetists. The work to which I wish particularly to refer was carried out a couple of years ago in my laboratory at Yale University by my associate, Dr. H. W. Haggard.⁴ It dealt with the principles underlying the absorption, distribution, and elimination of ethyl ether. It has, however, a wider application even than this broad field; for the same principles apply to any gas or vapour whatever that may be inhaled and that is taken up by the blood and by the tissues of the body in simple solution. A similar study of the absorption, distribution, and elimination of nitrogen was made some years ago by Haldane, Boycott, and Damant⁵ in connexion with their important investigation on the prevention of compressed-air illness.

The determining characteristic of each gas or vapour is its solubility; for the coefficient of solubility determines the distribution, or equilibrium, between the vapour in the lungs and the solution of the substance in the blood flowing through the lungs. Secondarily, and much more slowly, it determines the concentration in the tissues. The more soluble the substance the more the body will finally take up, but the longer the time required to reach saturation. Both the amount held in the blood and in the tissues at the point of saturation and the rate of absorption are directly proportional to the concentration in the inhaled air. For any one gas or vapour such as ether the time is the same for all concentrations to reach the full saturation corresponding to that concentration, or any given percentage of that saturation. In regard to absolute amounts,

therefore, the initial rate of absorption when a high concentration is inhaled is proportionally greater than when the concentration in the air inspired is low.

The solubility, or coefficient of distribution between blood and air in the lungs, is a factor also in the elimination of a gas or vapour that has been absorbed. It is of fundamental importance both for the induction and for the termination of anaesthesia.

The One Essential Condition for Anaesthesia.

Haggard's experiments have demonstrated that there is at all times equilibrium in respect to ether between the air of the lungs and the arterial blood. Furthermore, the circulation through the central nervous system, and especially the brain, is so large that the concentration of ether in the nerve centres becomes almost immediately the same as that in the arterial blood. This uniformity of the pressure of ether in the lungs, blood, and brain is similar to that which we know from the work of Haldane and his collaborators holds true of carbon dioxide. The pressures of carbon dioxide in the lungs and in the brain are equal; and so, too, of ether.

These are facts not only of great theoretical interest, but of direct practical importance. Haggard has demonstrated that the condition of surgical anaesthesia depends on nothing else but the concentration of the anaesthetic in the central nervous system. The degree of saturation of the rest of the body has no direct influence on anaesthesia. Formerly we had supposed—and certainly superficial appearances during the induction of anaesthesia suggest—that a certain time is required to saturate the body up to the point at which the state of anaesthesia occurs. This appearance is fallacious. We can, in fact, calculate the length of time that it would take for the body to become even half saturated. It would be about two and a half hours.

Now that we know that the sole condition for full surgical anaesthesia is the concentration of ether in the brain, and that this is immediately determined by the concentration in the lungs and blood, we see that theoretically it is possible to carry a man from full normal consciousness clear into full surgical anaesthesia in a period of not more than two or three minutes. This is not only theoretically possible, it is actually practised, and it is of great advantage to the patient.

The coefficient of distribution of ether between the vapour phase at body temperature and its solution in blood is 15; this means that there is equilibrium when a certain volume of the blood contains 15 times as much ether by weight as an equal volume of pulmonary air. The anaesthetic tension of ether is 3.7 to 4 per cent. of an atmosphere, which comes to about 1.2 grams of ether per litre of blood. The anaesthetic concentration is probably the same for everyone, even for the most recalcitrant old alcoholic case. The reactions prior to attainment of anaesthesia, and the amount of difficulty in administration which they produce, are the real variables as between different patients, and not the concentration at the point of full anaesthesia.

Technique for Rapid Induction of Anaesthesia.

The practical problem facing us, then, is that of how ether can be volatilized and the vapour passed into the lungs rapidly enough to raise the concentration in the arterial blood immediately to the full anaesthetic amount. Obviously some device far more efficient than a mask or cone and dropping bottle is needed to vaporize the amount of ether needed. But that is only the mechanical side of the problem. Owing to the high solubility of ether in blood, fifteen out of every sixteen parts of ether drawn into the lungs at first pass into the blood. Haggard and I⁶ have recently shown that the circulation in a normal man is much larger than has generally been believed heretofore. About the same volume of blood flows through the lungs in a minute, even during rest, as the volume of air normally breathed in that state. Owing to the dead space (the mouth, trachea, and bronchi) only two-thirds of the air breathed reach the lungs. So it follows that, in order to induce full anaesthesia within two or three minutes with no more than normal breathing, the concentration of the ether vapour inhaled would have to be extremely high.

Extremely high concentrations of ether vapour have, in fact, frequently been used, especially in Germany, during the initiation of anaesthesia. But such concentrations have an irritating effect upon the lungs, especially when the vapour is very cold, and are objectionable on other grounds also. So the problem of rapid, safe, harmless induction resolves itself into this: How can a large amount of ether, 6 or 8 grams a minute, be introduced into the pulmonary blood? Or, to restate the question: How can 9 to 12 grams of ether a minute be introduced as vapour into the inspired air without increasing the concentration of ether in this air to appreciably more than 7 or 8, or at most 10, per cent. vapour?

These questions almost answer themselves. Obviously, to introduce a large amount at a comparatively low concentration is possible in one way only—that is, by means of a large volume of breathing. The principles to which I have already referred, controlling the absorption of a gas or vapour, teach us that any relatively slightly soluble volatile substance is absorbed, and eliminated again, nearly in proportion to the circulation—that is, to the volume of blood flowing through the lungs per minute. On the other hand, these principles demonstrate that a quite soluble vapour, such as that of ether, is absorbed almost in proportion to the volume of air breathed, or, more exactly, to the pulmonary ventilation. Thus if fifteen-sixteenths of all the ether vapour drawn into the lungs at first are taken up by the blood, it is only necessary to increase the volume of breathing so that the necessary absolute amount of ether will be drawn into the lungs in a sufficiently large volume of air. Thus a huge absorption is effected without allowing the concentration in unit volume of the air to rise high enough to irritate the passages and chambers of the lungs. Thus we are again led to see the advantage of stimulating respiration, by means of carbon dioxide, up to several times the ordinary resting volume, and then running in a sufficient concentration of fully vaporized ether to produce in the shortest possible time the concentration of ether in the blood, and thus in the brain, necessary for full anaesthesia.

Relation of Respiration to Blood Alkali.

One of the topics which has excited the greatest interest during recent years in the borderland between physiology and clinical medicine has been the balance of acids and bases in the blood and other fluids of the body. The resultant of this balance is the so-called hydrogen-ion concentration. Modern chemistry teaches that this is the essential element in what we formerly called acidity, and that it is a factor in most of the reactions of substances in solution. It has become clear that the concentration of hydrogen ions in the blood has a normal value, and that the automatic processes of the body tend to adjust it to this value. It is thus another of the vital constants, such as body temperature, arterial pressure, the amount of salt and of sugar in the blood, and the other conditions whose uniformity constitutes health. From the standpoint of physiology, disease may be defined as a disturbance, or a perversion to an abnormal value, of one or more of these normal vital constants.

The two chief factors in the acid-base equilibrium of the blood are: (1) the amount of alkali in use in the blood, which is chiefly the sodium bicarbonate of the plasma; and (2) the pressure of carbon dioxide maintained in the blood by respiration, and thus the amount of carbonic acid in simple solution. As is well known, this equilibrium tends to be disturbed in anaesthesia. The blood alkali after a prolonged and difficult anaesthesia may be reduced to an extent which is recognized as a serious departure from the normal for health. It is the condition now, rather loosely, called acidosis.

The term "acidosis" has long been applied to such conditions as occur in acute diabetes; and the post-anaesthetic state has obvious points of similarity to diabetic coma. The word "acidosis" suggests that the clinical condition is due to poisoning by acids resulting from disturbed metabolism. We are coming to realize that this conception is far too simple and too crassly mechanistic.

But it still exerts a great influence; and the hold which it has upon medical thought was greatly strengthened by the introduction of the term and conception "alkaline reserve" to signify the blood alkali, and particularly the sodium bicarbonate of the plasma. Thus, when it was found that in conditions of so-called "acidosis" the blood alkali was below normal, this fact seemed to be a direct demonstration of the idea that the alkali had merely been partially neutralized by acids.

I have recently shown⁷ that there are very serious discrepancies in this general conception. For instance, the real alkaline reserve of the blood is now known to be composed to only a quite small extent of the plasma bicarbonate; it is to a much greater extent the haemoglobin alkali of the corpuscles. Thus the mere addition of a moderate amount of acid to blood does not reduce the plasma alkali correspondingly. Even when an amount of lactic or other strong acid is found in the blood corresponding to the lowering of the bicarbonate, this fact does not justify the conclusion that the lowering is due to neutralization by the acid. Most of the acid is neutralized by alkali from the corpuscles; and some additional factor must be looked for to explain the greater part of the lowering of the plasma alkali. Such a factor was found by Haggard and myself in respiration.⁸ When the lungs of an animal were ventilated excessively by means of artificial respiration an excessive amount of carbon dioxide was removed from the blood. This removal would leave the blood alkali in relative excess; and we found that a compensatory decrease occurred. Presumably this was due to the passage of alkali from the blood into the tissues. Similarly, when we depressed respiration by means of morphine, and then administered an inhalation of air to which 8 or 10 per cent. of carbon dioxide was added, we found that the carbonic acid of the blood was at first raised out of balance to the alkali. But under these conditions physiological readjustments developed, so that a considerably increased amount of alkali was, as we expressed it, "called into the blood" in the course of half an hour. These and similar experiments reveal to a very considerable extent the normal mode of control of the amount of alkali in use in the blood. The living body is not merely a beaker containing a slightly alkaline solution, in which the amount of alkali is determined by the amount of acid that is spilled into it, or by the excess of base in the food. On the contrary, this factor in the vital economy is regulated physiologically, and in this regulation respiration is one of the prime elements. When respiration is excessive, the pressure of carbon dioxide in the blood is lowered and alkali tends to pass out of the blood; when respiration is depressed, the pressure of carbon dioxide in the blood is increased and tends to call more alkali into the blood.

With this conception to justify us, Haggard and I turned to the study of the blood alkali in patients following prolonged anaesthesia. We found, in agreement with others, that the amount was often much below normal, and that it tended to rise only slowly, and in the course of many hours. We then tried the effects of inhalations of air and 8 or 10 per cent. of carbon dioxide, or whatever concentration was necessary to produce a distinct effect upon the visible physical condition of the patient. In all such cases we obtained, not only a rapid elimination of the anaesthetic and a return of a full normal circulation, together with relief of cyanosis and recovery of a pink skin colour, but also a rapid return of alkali to the blood, so that in the course of half an hour this element in the balance was back at very nearly its normal value.

For a considerable time we met with criticism and opposition, especially from biochemists, who alleged that a low blood alkali is a definite indication of "acidosis"—that is, of an excess of acids in the blood; and that the administration of carbon dioxide was therefore absolutely contra-indicated. Their view of the matter was that the post-anaesthetic state is similar to that following an asphyxia, and that the condition of the blood may be regarded as essentially an "asphyxial acidosis." I accept these premises, but not the conclusion. Facts, both experimental and clinical, demonstrate that carbon dioxide, both after

anaesthesia and after asphyxia, instead of exacerbating the condition called "acidosis," tends to relieve it.

I am inclined to the view that the lowering of the blood alkali by anaesthesia is to be explained as a secondary result of acapnia, the excessive blowing off of carbon dioxide, rather than as due to an excessive production of acids. In fact, I doubt whether such a condition, as the term "asphyxial acidosis" implies, occurs even in persons overcome by carbon monoxide. The orthodox fundamental conception implied by that term is probably erroneous. But I prefer to recognize that in this whole field of tissue respiration we have still a great deal to learn. I have tried to avoid the error of overthrowing a false conception by substituting for it another which might ultimately prove equally misleading. It would be a mistake to overemphasize theoretically the direct benefit of an increased pressure of carbon dioxide in the blood and tissues. Acapnia is not the whole story. Oxygen is also a factor in the vital economy, and the inhalation of carbon dioxide, by improving respiration, causes both a greatly improved oxygenation of the blood and a greater readiness in the blood to give off oxygen to the tissues.

All theorizing aside, I take my stand on the absolutely demonstrable fact that inhalation of air or oxygen to which a considerable percentage of carbon dioxide has been added is of very great benefit; in fact, is usually brilliant in its effects, alike after a prolonged anaesthesia and after asphyxiation.

Haemorrhage and Respiration.

Closely related to the disturbances and hazards involved in anaesthesia are the effects of haemorrhage. The parts played by anaesthesia and by haemorrhage in the depression of vitality, or more extremely in the degree of shock, are so much alike that it is often difficult to estimate their relative contributions. A few words on haemorrhage may therefore be in order, even at the end of a paper into which I fear too many topics have already been introduced.

What is haemorrhage physiologically? In other words, what is the intermediate factor through which a decrease of blood volume leads to shock and death? Physiologists would, until recently, have answered unquestioningly and unanimously that this factor is lowered arterial pressure. Thus the chain of causation would run: loss of blood, decreased blood volume, lowered arterial pressure, shock. During the war this conception was developed practically and therapeutically by one of the most eminent of British physiologists, the late Professor Sir W. M. Bayliss.⁹ He introduced the so-called gum saline solution for purposes of infusion, because he found that this solution does not pass out of the blood vessels as normal saline alone does. It replaces the lost blood with a medium by which arterial pressure is quite well restored and maintained.

It was later shown by a number of investigators, especially in America, that gum saline solution has distinct toxic properties, and that it is not a satisfactory substitute for a transfusion of blood from a donor. But that matter is apart from the point to which I wish to call your attention, and which is as follows: Investigations in my laboratory,¹⁰ also during the war, led to quite a different conception of haemorrhage. According to this view, haemorrhage is essentially asphyxia. It is the loss of red blood corpuscles, which is the critical initial factor. In consequence of the loss of corpuscles the capacity of the blood is invalidated in at least three respects: (1) its capacity to transport oxygen from the lungs to the tissues, (2) its capacity to transport carbon dioxide from the tissues to the lungs, and (3) its capacity to maintain the normal acid-base balance in the blood. These are the three functions which we now recognize that the haemoglobin of the corpuscles normally enables the blood to perform. Accordingly, a series of symptoms and conditions develop after haemorrhage closely analogous to those occurring under carbon monoxide asphyxia. Excessive breathing, induced by oxygen deficiency in the brain and tissues and culminating in air hunger, is a significant phenomenon. We found, in fact, that quite soon after a large haemorrhage in an animal we

could foretell the final outcome by means of two measurements of the volume of breathing spaced about an hour apart. If the volume of breathing held steady recovery almost invariably followed; if, on the contrary, it increased progressively, there was almost invariably a fatal termination.

For the anaesthetist who is asked to pilot a patient through an operation after a haemorrhage of unknown amount, a measurement of the volume of breathing would, I believe, afford an indication of the risk more significant than the arterial pressure. It would tell him whether he should first insist on a transfusion of blood. It would warn him of the special need to keep up the oxygen supply and to avoid both acapnia and anoxaemia with the utmost care. In fact, if the conception is correct that haemorrhage is essentially a form of asphyxia, the observation and control of respiration which, as I have here tried to show, are essential to skilful anaesthesia should be extended so as to afford an understanding and a means of counteracting to a large extent the effects of haemorrhage as well.

SUMMARY AND CONCLUSIONS.

The essentials of good anaesthesia are rapid induction, uniform concentration of vapour, and rapid termination. In the drop method of administration the vaporization of a liquid anaesthetic is often irregular. A more reliable and more uniform method of producing the vapour in proper concentration in air is desirable and is afforded by many of the forms of apparatus introduced recently.

The use of a controllable amount of rebreathing is also advantageous in the maintenance of a nearly uniform concentration of the anaesthetic vapour and of oxygen and carbon dioxide.

An almost complete control of respiration is afforded the anaesthetist by the use of carbon dioxide mixed with oxygen. By its use rapid induction and termination of anaesthesia and any desired volume of breathing and depth of anaesthesia are at his command.

It is not the amount of anaesthetic in the body which determines anaesthesia, but that in the nervous system. The amount in the nervous system at all times follows closely the concentration in the arterial blood; and the concentration in the arterial blood is in turn determined by the volume of the breathing and the concentration of the anaesthetic vapour in the air inhaled. Thus control of respiration is the essential element in the control of anaesthesia.

The use of carbon dioxide as the means of controlling respiration applies also to asphyxia of the newborn, alcoholic intoxication, carbon monoxide asphyxia, and related conditions.

The restoration of an approximately normal content of carbon dioxide in the lung air and in the blood and tissues of the body at the termination of anaesthesia probably tends strongly to prevent the development of a post-anaesthetic pneumonia. It is also a means of restoring a nearly normal acid-base balance in the blood.

Finally, the close similarity of haemorrhage to asphyxia renders it another of the elements whose effects are to be understood and controlled through the application of the principles of the physiology of respiration.

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