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THE PHYSIOLOGICAL AND PHYSICAL FACTORS GOVERNING THE UPTAKE OF ANESTHETIC GASES BY THE BODY *

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THE various theories of narcosis, despite their differences as to the exact mechanism whereby the narcotic substance produces its effects upon the neuron, are in general agreement that depth of anesthesia depends primarily upon the concentration or the partial pressure of a particular anesthetic in the brain, and further that the rate of recovery or induction of anesthesia is governed by the rate of change of this brain tension. Anesthetic gases in general are physiologically inert. They undergo no significant oxidation or utilization by the body, are released from the body eventually in exactly the same amount as was originally taken up, and they obey the simple physical laws of diffusion and solubility. Considerable thought and some experimental investigation have been brought to bear on the problem of inert gas exchange in the body. The names of Haggard, Behnke, Morales and Smith stand out among those who have made significant contributions to this problem. Much of what I shall say is based upon lines of thinking initiated by them.

The tension of an inert gas in the brain depends upon two primary factors; one, the tension of the gas in arterial blood, and two, the supply of that arterial blood to the brain, that is, the cerebral blood flow. Let us consider these two items separately, and turn first to the factors which regulate the tension of an anesthetic gas in arterial blood. This in turn depends upon two other factors: the tension of the gas in the alveoli, and the nature of the pulmonary diffusion surface. This latter factor depends upon the size of functioning lung, on the thickness

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of the diffusion membrane, the presence or absence of edema, and the adequacy of pulmonary blood flow. With normal lungs diffusion is rarely a limiting factor in uptake of inert gas, and therefore arterial tension may be said, in general, to equal alveolar tension.

We may turn then to a discussion of the factors which regulate alveolar tension. The first of these is the effective respiratory minute volume, that is, the liters per minute of inspired gas which reach functioning diffusion surface. This is obviously a very important factor since all the gas taken up by the body has to be breathed into the lungs. This function is equal to the tidal volume minus the dead space, multiplied by the rate of respiration. It is apparent that six breaths of one liter each are more effective than twenty breaths of 300 cc. each, even though both give one a total minute volume of 6 liters.

The second factor governing alveolar tension is the lung volume, that is, the volume which dilutes each inspired breath of gas. It is obvious that a small room is more quickly filled with cigarette smoke than a large. Similarly, a small lung is more readily and rapidly filled with gas at a certain tension than is a large lung. A third factor is pulmonary blood flow. Except in congenital heart disease and in those rare cases of pulmonary hemangioma, pulmonary blood flow is equivalent to cardiac output.

Why is pulmonary blood flow so important in regulating the alveolar partial pressure of a foreign gas? It is the pulmonary blood flow which carries anesthetic gas away from the alveoli, especially in the early stages, and therefore tends to lower its partial pressure in the alveoli. Along with pulmonary blood flow belongs another equally important factor which is the solubility of the gas in blood. This may be expressed as the partition coefficient (λ) which equals the ratio of the concentration of gas in blood to the concentration of that gas in air at equilibrium. Thus, ether which has a λ of 15 and represents the most soluble of the usual anesthetic gases will exist in the blood at a concentration of 15 mg. per 100 cc. when the blood is in equilibrium with air containing only 1 mg. per 100 cc. Thus the blood concentration is fifteen times as great as the concentration in the air. The solubility in blood and the pulmonary blood flow are the factors responsible for the loss of gas from the alveoli. A more soluble gas is more easily carried away by the blood and therefore the alveolar tension of such a gas will build up more slowly.

Thus we come to the last of the factors regulating alveolar tension, the partial pressure of the gas in the mixed venous blood coming back to the lungs. Since this brings gas back to the alveoli it helps to raise the alveolar tension. If the tension in venous blood is rising rapidly, this will permit alveolar tension to rise rapidly, but if venous tension stays low it will keep alveolar tension low for a longer period of time. Mixed venous tension of an inert gas depends upon three other factors:

(a) the cardiac output in general, but in particular on the blood flow to muscles and fat, which constitute the bulk of the gas-absorbing regions of the body simply by virtue of the fact that they represent the greatest tissue bulk in the body; (b) the mass of muscles and fat and (c) the partition coefficient of the gas between fat and blood. The solubility of gases in general is the same for muscles as for blood, but all inert gases are much more soluble in fat. A large amount of fat or a high fat solubility will cause the removal of large quantities of that gas from the blood, and will therefore tend to keep venous blood tension low, keeping alveolar tension down and slowing the rate of induction.

The second factor regulating the tension of anesthetic gas in the brain is the rate of cerebral blood flow. It is apparent that the more rapid the cerebral blood flow, the more anesthetic will be brought to the brain per minute which, therefore, will permit a more rapid accumulation of tension in the brain and hasten the induction of anesthesia. Cerebral blood flow in turn depends upon two other factors: the first, mean arterial blood pressure, which is the force responsible for pushing blood through the brain, and second, cerebrovascular resistance which represents the total of all the factors that tend to impede the flow of blood through the brain. There persists an old concept that cerebral blood flow passively follows the blood pressure. This idea is based upon studies in animals in which, as a result of anesthesia and fairly drastic surgical procedures, whatever intrinsic reflexes exist were destroyed or obtunded with the result that the brain lost much of its intrinsic control. Then, indeed, the cerebral blood flow did passively follow the blood pressure. We know today that in normal human beings there is a great deal of intrinsic control of the cerebral circulation, in fact that mean blood pressure has very little to do with regulating the blood flow through the brain except in so far as the pressure must be sufficiently high to permit a normal blood flow. Only when the blood pressure falls sharply is cerebral blood flow influenced by the pressure; at normal levels most of the influence is obtained by intrinsic mechanisms within the brain.

This takes us to the intrinsic regulation which we have called the cerebrovascular resistance. It depends, among other factors, upon viscosity. Patients with polycythemia show a much greater resistance to the flow of blood than do normal or anemic patients. Intracranial pressure also affects resistance since patients with high cerebrospinal fluid pressure show a restriction of cerebral blood flow. It depends upon the patency of the small vessels in the brain so that in cerebral arteriosclerosis one finds an increase in resistance and a decrease in cerebral blood flow. Finally it is governed by the physiologic or functional tone of cerebral vessels. This regulation may be chemical or neurogenic.

Under the chemical influences carbon dioxide has a powerful effect. The inhalation of 5 to 7 per cent carbon dioxide will increase the cerebral blood flow markedly to about 75 per cent above its former value, conversely a low carbon dioxide tension in the blood will significantly depress the blood flow by constriction of cerebral vessels. With moderate hyperventilation cerebral blood flow will fall an average of 35 per cent. Acidosis itself is apparently capable of dilating cerebral vessels, for in diabetic acidosis which is not associated with a high carbon dioxide tension (in fact, the carbon dioxide tension is quite low), there is seen a decrease in cerebrovascular resistance and a tendency for the cerebral blood flow to increase. Oxygen tension also exerts an effect. When tensions of oxygen are breathed which are close to 100 per cent there is moderate constriction of cerebral blood vessels and a decrease of 12 per cent in cerebral blood flow. On the other hand, anoxemia obtained by the inhalation of 10 per cent

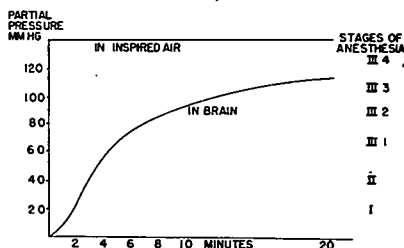


FIG. 1. The rate of rise of brain tension and simultaneous depth of anesthesia following inhalation of a constant partial pressure of an anesthetic gas. The actual values are rough approximations to those expected with cyclopropane.

oxygen has resulted in vasodilation in the brain comparable to that seen with 5 or 7 per cent carbon dioxide. Thus it can be seen that anoxemia is just as potent a vasodilator as are these concentrations of carbon dioxide.

The neurogenic regulation of cerebrovascular tone is not clearly defined. Apparently there is little tonic constrictor innervation entering the brain by way of the cervical sympathetic chain, at least Harmel in our laboratory was not able to show significant increase in cerebral blood flow or decrease in the vascular resistance of the brain following bilateral stellate ganglion block. It is possible that in acute conditions there may be a reflex spasm of cerebral vessels mediated through the sympathetic cervical chain, but there was no evidence in his work for a normal constrictor tone.

A third factor modifying cerebral vascular functional tone I have had to call an ill-defined factor. Prominent in this group is the disease

of essential hypertension. In this condition, despite a mean blood pressure which may be twice normal, the cerebral blood flow is kept within normal range by virtue of a high degree of cerebral vascular tone, the exact nature of which is still obscure.

Now that the individual factors have been discussed, let us turn to a consideration of the relationship among these factors and how they affect the arterial and brain uptake curves. For simplicity now and for the remainder of the discussion, let us assume that a constant tension of each gas is inspired by means of an open system, and that such tension is just great enough to produce deep surgical anesthesia if continued indefinitely. For example, in figure 1 a constant partial pressure of cyclopropane of 140 mm. of mercury is administered. I make no claim that this is exactly the tension which will eventually

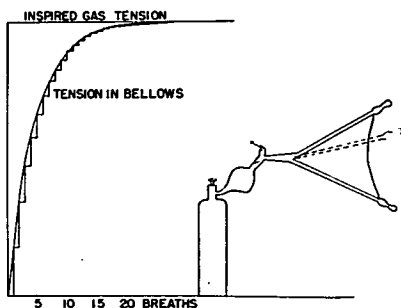


FIG. 2. The curve of tension of an anesthetic gas developing within a bellows (the lungs) where each stroke represents one-fifth of the total gas volume in the bellows. The anesthetic gas is administered at a constant tension by means of an open system.

produce deep surgical anesthesia. Quantitatively this figure may be in error, but qualitatively the principle remains the same. It is apparent from figure 1 that deep surgical anesthesia does not immediately ensue, but rather that anesthesia develops gradually along a curve which approximates the curve of increasing brain tension. Why does this increase in brain tension occur so leisurely? Why does not the brain tension immediately become equal to the inspired tension? The answer to that is the number of processes which are involved in going from the tension in the tank or in the mask to the tension in the brain.

The first of these processes is the accumulation of alveolar tension, and since arterial tension is practically equivalent to alveolar tension this factor would also mean the rise of arterial tension. The first phenomenon in this consideration is the phase of lung washout which I can best illustrate by a bellows (fig. 2). This bellows, let us assume,

has a 2500 cc. capacity and each stroke of the bellows instead of emptying it expels or inhales only 500 cc. Therefore, the gas which is inhaled is diluted fivefold with the gas in the bellows. If this bellows is connected by means of an open system to a tank supplying a constant tension of anesthetic gas and follow the concentration in the bellows what will be observed? The concentration of that gas in the bellows starts at zero. In the first breath it goes one-fifth of the way toward the inspired concentration since the tank gas is diluted by 5 volumes of air still in the bellows. On the second breath it moves another fifth of the distance toward the concentration in the inspired air, and so on in stepwise progression toward the inspired concentration, each breath bringing the concentration in the bellows one-fifth of the way toward completeness, finally reaching complete equilibrium only after numerous breaths. These steps may be smoothed out so that an exponential

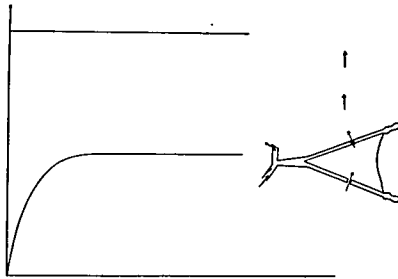


FIG. 3. The effect of a constant leak in the bellows (pulmonary blood flow) on the bellows (alveolar) tension of anesthetic gas.

curve is obtained, that is, one which constantly approaches a limiting plateau. It is obvious that if ventilation were increased or if the volume of the bellows were decreased this rate of washout would be faster. In fact, it may be said that the rate of washout depends upon the ratio of effective minute volume of respiration to lung volume.

The picture so far is quite over-simplified and different from the conditions which obtain in the body. We know that in the body the lungs are not merely a bellows, but that they have passing through them a considerable flow of blood. Let us then complicate this picture somewhat by including pulmonary blood flow. This may be done as in figure 3 by creating a leak in the bellows through which fresh air enters and bellows air leaves in addition to the process of respiration which is occurring through the neck of the bellows. It is now obvious that the concentration in the bellows will never reach the concentration in the tank, because after several hours or even days each breath from the

tank will be diluted by fresh air through the leak. Therefore, the bellows concentration approaches a new level which is determined by the ratio of the respiratory minute volume to the size of the leak. If the leak is small, the final level will be close to the inspired concentration; if the leak is large, the final value will be very low. This leak is analogous to pulmonary blood flow which carries gas away from the alveoli and prevents it from reaching inspired tension. The size of the leak depends upon pulmonary blood flow and the solubility of gas in blood.

Even this picture is not the complete story, however, for the blood which flows through the lungs eventually comes back to the lungs again carrying somewhat smaller amounts of the gas, but does not carry the gas away forever. Therefore, let us introduce a final complication

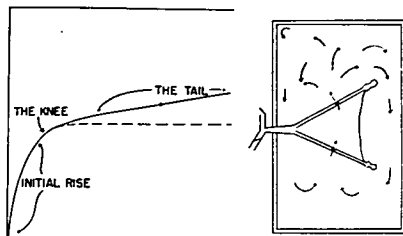


FIG. 4. The effect of enclosing the leaking bellows within a sealed room; representing respiration, pulmonary blood flow, tissue saturation and recirculation. The curve is characteristic of the alveolar or arterial tension curve of any inert gas breathed by the body at a constant inspired tension. The rate of the initial rise is largely a function of ventilation, the height of the knee is determined by the size of the leak (pulmonary blood flow and blood solubility of the gas). The rate of rise of the tail is a function of the size of the leak and the size of the room (mass of muscles and fat and fat solubility of the gas).

into the picture of the bellows as shown in figure 4. The bellows have been placed into a hermetically sealed room, so that gas from the bellows leaking out is diluted by air in the room which represents the body tissue. As time goes on, however, the concentration in the room builds up, and therefore, instead of fresh air coming back through the leak, more and more gas in question comes back to the bellows, so that if enough time elapses the gas in the room and in the bellows will eventually equal the inspired concentration. This washout of the room is a much slower process since the room is much larger than the bellows; therefore, the tail of the curve rises comparatively slowly. The rate at which the tail rises depends upon: (1) the size of the leak, that is, a rapid cardiac output, although it depresses the knee of the curve, speeds the latter part of the curve; (2) the size of the room, that is, a large mass of muscles and fat plus a large fat solubility will make it more

difficult to increase the gas tension in the body and will therefore slow the rate at which the tail approaches the inspired tension.

In figure 3 is shown an example of the general nature of the alveolar or arterial tension curve of every inert gas. The shapes of these curves may vary one from the other depending upon physical factors, but they all have the following similarities: a characteristic initial rise dependent upon lung washout; a point of inflection (the knee) which corresponds to the point at which the slower process takes over, and the slowly rising tail which depends upon the rate at which the body becomes saturated with the gas at the inspired tension. In a given individual with a single value for all the physiologic constants, that is cardiac output, minute volume of respiration, lung volume, body fat, and so forth, any differences among the rates of induction with different anesthetics must depend upon differences in the solubility of the anesthetic gases in blood and fat.

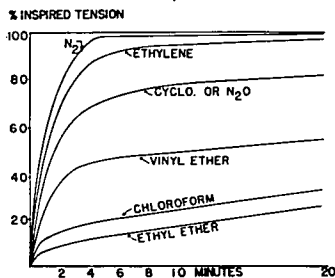


FIG. 5. The effect of solubility in blood of the inert gas on its alveolar or arterial uptake curve, all physiologic factors remaining constant. This demonstrates roughly why rate of induction or recovery is largely a function of blood solubility.

In figure 5 are shown diagrammatically the arterial curves of seven different gases with different blood solubilities. These curves could have been obtained in the same individual, each gas being administered in concentration just enough to produce deep anesthesia if continued long enough. In the case of nitrogen and nitrous oxide more than one atmosphere of pressure might have to be used; the argument however remains the same. Notice that nitrogen, being the least soluble and, therefore, corresponding to a bellows with a small leak, fills the alveoli and reaches arterial equilibrium with inspired tension quite rapidly. Ether, being extremely soluble and corresponding to a bellows with a large leak, builds up little on the initial rise and depends upon recirculation for its equilibration. I have not attempted to show differences in fat solubility which only affect the tail, but actually ether would outstrip the chloroform curve since chloroform is much more soluble

in fat. Nitrous oxide would exceed the cyclopropane curve likewise since cyclopropane is more soluble in fat. It may be noted that the clinically recognized differences in the rates of induction or recovery correspond to the rates at which the anesthetic tension is built up in arterial blood which, in turn, depend upon the solubilities of the individual gases. If the top of the graph were to correspond to the deepest part of the third stage of anesthesia, ethylene would have reached better than 80 per cent of that level in the arterial blood in three minutes, cyclopropane better than 60 per cent while ether would be less than 10 per cent toward that level in the same period of time. It would take hours of breathing such a tension of ether to obtain deep anesthesia. The clinical anesthesiologist already knows how to get around that; he does not start with the tension which he eventually hopes to achieve, but with a much higher tension which, if continued indefinitely, would kill the patient. As the patient approaches that extremely high

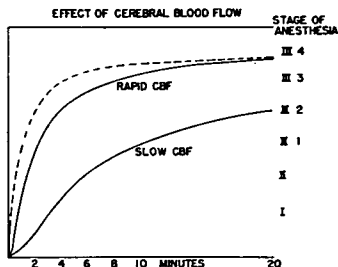


FIG. 6. The effect of a rapid or a slow cerebral blood flow on brain tension of an anesthetic gas and depth of anesthesia with the arterial curve (dotted line) the same for both.

tension, the anesthesiologist delicately lowers the inspired tension until both he and the patient arrive at the same desired level of anesthetic tension.

I have been speaking only of the arterial curve of tension, but this arterial tension of gas still has to get into the brain. That depends largely upon cerebral blood flow. In figure 6 is indicated the effect of different rates of cerebral blood flow on the brain concentration curve of anesthetic gas where the concentration curve in arterial blood (indicated by the dotted line) is the same. Thus, both hyperventilation and the inhalation of 5 per cent carbon dioxide will produce about the same arterial curve with cyclopropane, with a rapid rise and a high knee, but hyperventilation produces a decrease in carbon dioxide tension and therefore a severely depressed cerebral blood flow which results in a deficient supply of cyclopropane to the brain and a slow uptake by the brain. On the other hand, the inhalation of 5 per cent carbon dioxide

accelerates the cerebral blood flow, delivers more cyclopropane per minute to the brain which results in a rapid rise in the brain concentration. Thus, with the rapid cerebral blood flow the patient would arrive at the second plane of stage three in two minutes while it would take twenty minutes to achieve the same anesthetic level with a slow cerebral blood flow. The well known effect of carbon dioxide on induction and recovery from anesthesia thus depends not only upon its effects on the arterial curve of the anesthetic but also, and of equal importance upon its effects on cerebral blood flow.

Much of what has been said about the uptake of anesthetic by the body and the factors governing it apply equally well to the release of anesthetic from the tissues and from the arterial blood; in fact the recovery curve which is achieved by simply stopping the inhalation of the anesthetic would look exactly like the uptake curve turned upside down. That is easy to understand since with the anesthetic removed the patient is nevertheless breathing a constant inspired tension of anesthetic gas. It merely happens that the inspired tension is zero. It is in recovery from the gas that all these factors which have been mentioned are most easily demonstrated since clinically the induction of anesthesia is rarely achieved by the inhalation of a constant tension. In recovery that is practically always the case, however, and therefore what has been said about the differences of the anesthetics from the point of view of their physical properties, and therefore their rates of induction, will apply equally well and even more clearly to the rates of recovery from them.

The ramifications and corollaries of these few principles are extensive. These few fundamental principles, however, may help one in predicting or explaining what various combinations of these physiologic and physical factors actually do in their various clinical associations.

THE NEW YORK SOCIETY OF ANESTHESIOLOGISTS, POSTGRADUATE ASSEMBLY

The New York State Society of Anesthesiologists will hold its Fourth Annual Postgraduate Assembly December 7-9, 1950, at the Hotel New Yorker, New York City. There will be nine scientific sessions devoted to fundamental and recent subjects of concern to surgeons and anesthesiologists. Each session, in panel format, will be conducted by an accepted authority in the subject to be discussed. One panel will be presented by residents and fellows in anesthesiology discussing original investigations in which they have participated.

This meeting, presented in this educational form each year, has attracted the largest audience of any anesthesia meeting in the country. Physicians desiring to attend may secure a registration form from the office of the above society at 137 West 11 Street, New York City.