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CEREBRAL ANOXIA AND ITS RESIDUALS*

II. RESPIRATION, NORMAL AND PATHOLOGICAL

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From our present viewpoint it is not surprising that the story of the clinical development of asphyxia had its inception at the same time as that of the physiology of respiration. No sooner does the inquisitive physician discover a new disease entity than he begins to investigate the phenomena upon which it is based. It was Aristotle who first wrote of difficulty of respiration in high altitudes; he also postulated that the prime purpose of respiration was to cool the blood. Although his idea of respiratory physiology was a little naïve, it was but a token of the long interval of ignorance which was to intervene before the physics and chemistry of respiration were to be understood.

This long wait was due to man's slowness in comprehension of the chemical aspects of living matter. And this in turn was a result of his inability to cope with the manifold problems presented by even his most superficial investigations in the realm of biology. Inventive genius was then too deeply buried beneath the snows of dogma and authority. But when Boyle invented the air pump (1666), it was only a step to prove that air was an unequivocally fundamental necessity of life. This was easily demonstrated by exhausting a chamber containing a living animal. The fact was also proved in another way by Hooke (1867), who found that an animal could be kept alive by passing air through its perforated and collapsed lung.

Lower (1669) and Mayow (1673) concluded that the action of air in respiration and combustion was similar to that of niter in the combustion of gunpowder. They believed that the "nitro-aerial spirit" in the air was absorbed into the blood from the lungs, whence (according to the theory of Descartes) it was carried to the brain, distilled into the ventricles, to reach ultimately the muscles *via* the nerve tubules.

It was almost a century later before the next development in the physiology of respiration occurred. In 1754 Joseph Black discovered that "fixed air" (carbon dioxide) was given off from the lungs in respiration. Shortly thereafter this concept was enlarged by Priestley (1774), who found that "dephlogisticated air" (oxygen) disappears in both animal respiration and combustion, but it is produced by green plants. Lavoisier (1777) unified these two isolated ideas by demonstrating the chemi-

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cal formation of carbon dioxide from oxygen and carbon, a product which is formed by an animal in approximately equivalent amounts to the oxygen consumed (Lavoisier and Laplace [1783]). But all that Lavoisier got for his efforts was the doubtful privilege of being guillotined in the Place de la Revolution on a sunny morning of May, 1794. The new republic, so they said, had no use for bourgeoisie investigators.

The next step in the physiology of respiration was the discovery by Legallois (1812) that respiratory failure and death followed the destruction of a small area in the floor of the fourth ventricle. Thus was identified the "respiratory center." But this discovery was somewhat of an ectopic departure, for there was still much to be learned about the chemical aspects of respiration. Magnus (1837, 1845) found a way to liberate the gases from the blood (by exposing it to a vacuum), proving thereby that less oxygen and more carbon dioxide were given off from venous than from arterial blood. With the development of the mercurial gas pump by L. Meyer, Ludwig, and Pflüger, it was found that oxygen is taken up from the lungs by the blood; that it forms an easily dissociable compound with hemoglobin; and that this gas is taken up from the tissues as the blood circulates through the capillary system. It was learned that the oxygen-depleted venous blood also accumulated a supply of carbon dioxide carried in a loose chemical combination to be discharged in the lungs.

But this last bit of historical lore sounds strangely like our present-day physiology of respiration, which indeed it is. Let us see, then, what our modern concepts of the mechanics, the physics, and chemistry of respiration really involve.

NORMAL RESPIRATION

A study of normal respiration reveals that a number of factors are involved: (1) the mechanics of chest movement, which results in the inhalation and exhalation of air, (2) the physical principles governing exchange of gases, (3) the chemical reactions that have to do with transportation of oxygen and carbon dioxide in the blood and tissue respiration,

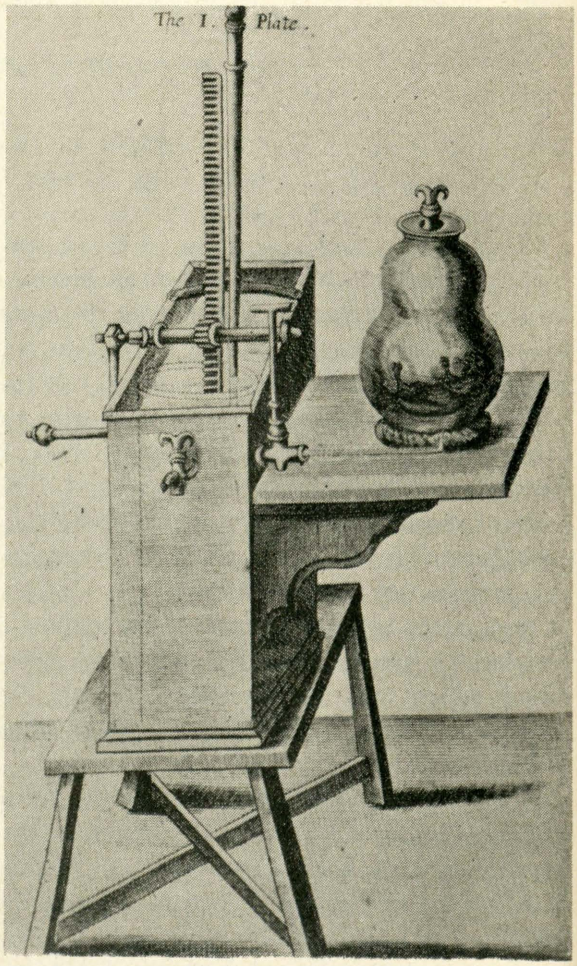

Fig. 1.—An early type of air pump used by Boyle in his experiments.

and (4) the nervous factors that control respiratory activity. In this brief review only the most essential features of these factors can be considered.

Mechanics of Breathing.—An investigation into the mechanics of respiration indicates that the lungs play a passive rôle, expanding

and contracting with the chest walls; that inspiration is largely an active process, and expiration is almost wholly passive; that the chest is enlarged in all its diameters during inspiration, whereas during expiration the thoracic cage of its own weight resumes its resting position; and that the distended lungs recoil, and the now relaxed muscular diaphragm is pulled upward into the chest.

This alternating recurrence of active and passive movements results in the in-and-out passage of air chemically altered in the lung by the gaseous exchange through the alveolar and capillary walls. The gases of this *alveolar air* come into a balanced state with that of the capillaries in the alveolar wall. These small pockets of air must be constantly renewed by the addition of fresh air from the outside. This is accomplished as follows:

> By the end of each expiratory movement most of the air in the distended sacs is expelled into the bronchioles and thence into the bronchi. With the next inspiration this air is again forced back into the alveoli, while the fresh air now fills the air passages. The oxygen from the new air is diffused throughout the alveolar air, and the carbon dioxide in turn is diffused into the air in the air passages. Mixing of the alveolar air with the inspired air seems to be fundamentally mechanical and incident to respiratory movement and the changes in temperature between the residual and inspired air.

It is assumed that at complete rest there is about 150 cc. of air in the respiratory passages where the thickness of the walls precludes any gaseous exchange. In expiration most of this air is exhaled. On an ordinary inspiration 500 cc. of air is inhaled, 150 cc. of which fills this "dead space" of the bronchial tree. The remaining 350 cc. is mixed with the air which has remained in the lungs after expiration. With the next expiration the now well-mixed air is forced out of the alveoli into the bronchial system. Part of it is exhaled; the remainder occupies the bronchial passages. We thus learn that all the air from the previous inhalation is not exhaled in turn but that several respiratory acts are necessary to completely exchange all the air which is in the lungs at a given time.

The Physical Laws of Gases and Their Influence on Respiration.—In the exchange of oxygen and carbon dioxide through the alveolar-capillary wall, four laws governing the activity of gases are known to play a part. It is recognized that if under constant temperatures the volume of a gas is altered, the pressure of that gas varies inversely (Boyle's law). On the other hand, if the temperature of a gas is raised 1° Centigrade its volume at 0° Centigrade expands by 1/273 if the pressure is kept constant (Gay-Lussac's law). The pressure exerted by any given gas in a mixture of gases is that of the gas in its unmixed state (Dalton's law). The amount of a gas which goes into solution is proportional to the partial pressure of that gas and its relative solubility (Henry's law).

In applying these laws to the exchange of oxygen and carbon dioxide between the alveolar air and the blood plasma, we find that the oxygen is forced into the plasma because of its higher partial pressure in the alveolar air. In turn, the higher concentration of carbon dioxide in the blood plasma results in escape of this gas into the alveolar air (Henry's law).

In this interaction each gas behaves as though it were the only one present, exerting its own partial pressure (Dalton's law). In accord with the principle of Boyle's law, oxygen passes into solution in the blood plasma of the pulmonary capillaries because of the lower temperature, but in response to the higher temperatures in the tissues it is more readily given off. Also because of this higher temperature in the tissues, increased molecular action produced thereby favors the solution of carbon dioxide in the blood plasma (law of Gay-Lussac).

Chemical Factors in Respiration.—The transportation of oxygen from the lungs to the

tissues is accomplished through the complex substance, hemoglobin, resident in the red blood cells. Relatively little of this gas is carried in solution. Nevertheless, this dissolved gas plays its part in the release of oxygen in the tissues, for when it has been used up the lowered O_2 tension in the solution initiates the dissociation of oxygen and hemoglobin.

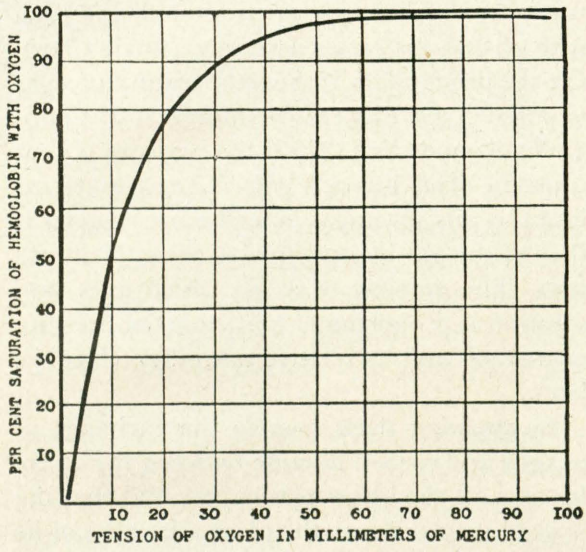

Fig. 2.—Dissociation curve of oxygen and hemoglobin. (Barcroft.)

Oxygen enters into a loose chemical combination with the hemoglobin (2 atoms of oxygen uniting with each atom of iron in the hemoglobin) to form oxyhemoglobin. It has been demonstrated graphically (the oxygen dissociation curve of hemoglobin) that there is a well-defined relationship between the partial pressure of oxygen and the percentage saturation of hemoglobin with this gas. (Figure 2). Although there is a slight variation in this curve as it occurs in experimental solutions compared with human blood (owing to changes in the pH of the blood and its temperature), the fundamentals are applicable.

When the blood leaves the lungs, about 95 per cent of the hemoglobin has become oxyhemoglobin. When the tissue capillaries are reached, the low oxygen tension of the tissue fluids and cells favors the dissociation of hemoglobin and oxygen, and the released gas diffuses through the capillary membrane into the tissues. This process of dissociation increases as the blood flows through the part because of the increase in temperature and increased amounts of carbon dioxide and lactic acids poured into the capillary blood stream.

In spite of this facile dissociation of oxygen and hemoglobin, the blood loses only from 1/5 to 1/4 of its oxygen supply. This fraction of oxygen lost to the tissues is designated as the "coefficient of oxygen utilization." If, for example, the brain needs a greater supply of oxygen through increased activity, this increase is supplied through an increase in blood flow or an increase in the coefficient of oxygen utilization, or both.*

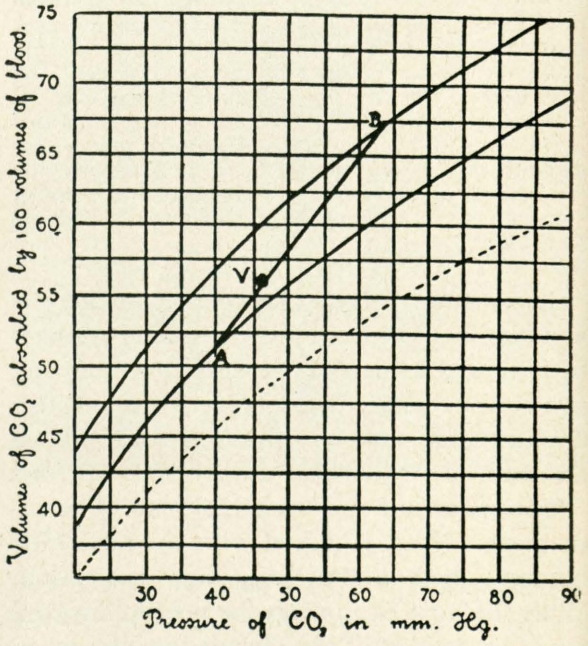

Fig. 3.—Carbon dioxide dissociation curve of fully reduced human blood. (Modified from Christiansen, Douglas, and Haldane, by Best and Taylor, [1945].)

* It is a point of interest to note that in the course of an epileptic seizure there is a tremendous acceleration of the cerebral circulation, so much so that the blood passes into the venous system still red

Much experimental work has been done on the problem of tissue respiration, but as yet there is no precise information available as to the exact methods of oxygen utilization by the cell. It is obvious, of course, that the chief source of cellular energy is the oxidation of metabolites. When this process ceases, cell death follows, as is seen in cases of serious degrees of anoxemia in which profound damage to the cerebral tissues results. It is believed that this process involves the removal of electrons from the involved metabolites and that glutathione and ascorbic acid may assist somehow in the process. Just how this is actually accomplished is as yet unknown.

Be all this as it may, it is clear that the venous blood which returns to the lungs is deficient in oxyhemoglobin and is surcharged with carbon dioxide. When carbon dioxide enters the blood from the tissues, it combines with water of the plasma to form H_2CO_3. This action is facilitated by an enzyme, carbonic anhydrase, found in the erythrocytes. Most of this weak acid combines with a base to form bicarbonates.

The role played by hemoglobin in the transportation of carbon dioxide has not been fully appreciated until quite recently. It was long presumed that this gas was carried alone in chemical combination in solution. It is now recognized that hemoglobin actually has a double action in this respect: (1) it carries a considerable amount of base, which it yields up on losing its oxygen, and (2) it actually unites with carbon dioxide to form carbhemoglobin (2 to 10 per cent of carbon dioxide is carried in this way). About 5 per cent of this gas is carried in simple solution, and the remaining 85 to 93 per cent is carried as a bicarbonate.

In the lungs the carbon dioxide is rapidly unloaded, a necessity, for the blood remains only one second on an average in the capillaries of the lungs as in other body tissues. This rapid release of carbon dioxide is made possible by (1) the action of carbonic anhydrase (which serves in both phases of the reversible reaction) and (2) by the rapid release of this gas from combination with hemoglobin.

Nervous Regulation.—As the result of animal experimentation, Markwald (1887) came to the conclusion that respiration was under specific nervous control. Lumsden (1923) suggested that the respiratory center was located in the medulla at the level of the *striae medullares acusticae,* and that this center was normally dominated by an inhibitory or pneumotoxic center in the upper end of the pons. Pitts, Magoun, and Ranson (1939) recently found that the respiratory center (in the cat) was located in the reticular formation of the medulla, and that it was divided into two portions, an inspiratory (apneustic center of Lumsden) and an expiratory division (Figure 4). It was learned that regular respiration can be produced by stimulation of either divison.

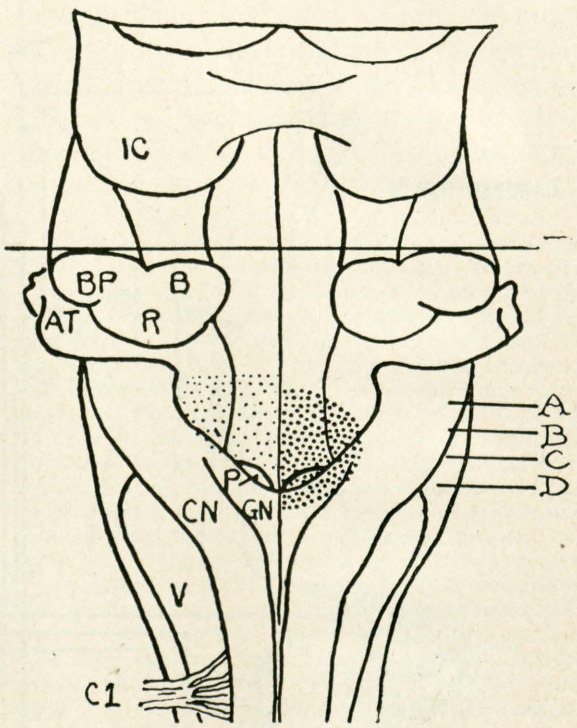

Fig. 4.—Location and extent of the respiratory center in the cat. (According to Pitts, Magoun, and Ranson.)

Although it was for a time denied by some,

with its high percentage of oxyhemoglobin. This too rapid circulation does not permit an adequate release of oxygen to the tissues, and a state of partial tissue anoxia results. It has been assumed that the advanced degrees of cerebral atrophy found in chronic epileptics is the end result of repeated episodes of partial anoxia.

it is now known that the respiratory center may act spontaneously, and this activity is inherent on the inspiratory portion of the center. It is recognized, of course, that this center is also influenced by emotional factors and, further, that it may be controlled temporarily by volition.

mans (1927) discovered the carotid reflex. In the carotid and aortic bodies two types of receptors were isolated. The pressoreceptors were capable of being stimulated by mechanical means, while the chemoreceptors could be stimulated by chemical means. Comroe and Schmidt (1938) demonstrated that

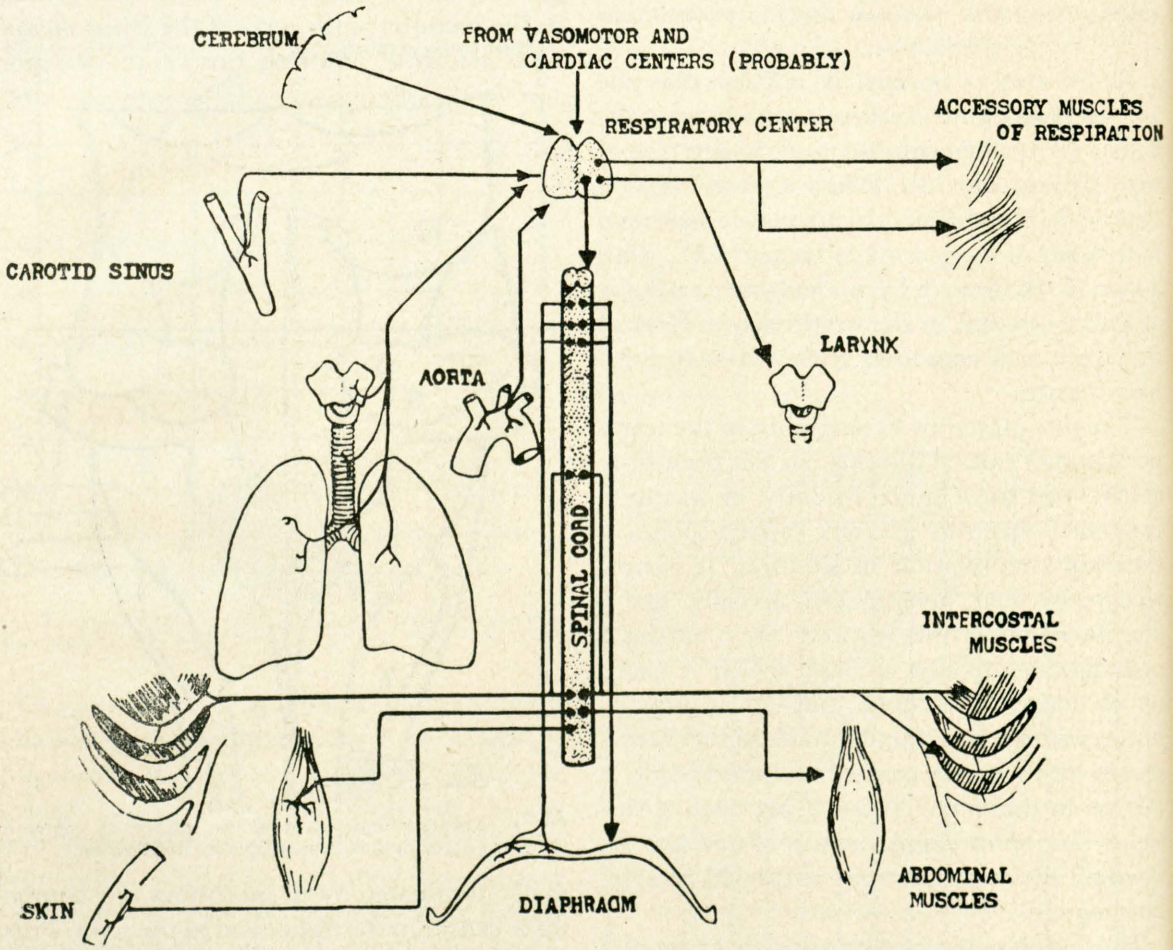

Fig. 5.—The nervous control of respiration. (Best and Taylor.)

The major controls, however, seem to be on a reflex basis, as was shown as long ago as 1868 (Hering and Breuer), being influenced by respiratory activity. These investigators showed that inflation of the lungs inhibited inspiration, and, conversely, that deflation inhibited expiration. More recently Heymans and Hey-

the chemoreflex mechanism of the carotid and aortic bodies was resistant to the influence of anoxia; this mechanism is therefore the last line of defense against respiratory failure.

It has long been known that carbon dioxide has had a specific action on the respiratory center. With an increase in this gas in the

blood, the center was stimulated to increased activity. It would seem as though the cells in the center are highly specialized, capable of sampling the blood for its oxygen content (Best and Taylor).

At this point one might investigate the pathologic physiology of a variety of respiratory episodes (Cheyne-Stokes or Biot's respiration), which are so often a part of certain disease syndromes. But even though anoxia, at least to a relative degree, may play its part in the production of some of them, these conditions *per se* are not of major concern to us in this connection. We are interested, to the contrary, in those more serious, even lethal, conditions which leave their unmistakable stamp on the tissues of the brain to produce the characteristic anoxic symptom-complexes. But before we study these cerebral lesions themselves, a word about the various types of anoxia is in order.

ANOXIA—ITS TYPES AND CAUSES

We are now in a position to investigate the pathologic physiology of anoxia, the subject here being considered. We shall find that there are many causes for an ultimate decrease in the amount of oxygen delivered to the tissues of the body in general and the brain in particular. Barcroft (1920) described three types of anoxia based on the functional disturbances in the physiology of respiration: (1) the anoxic type (due to defective oxygenation of the blood in the lungs); (2) the anemic type (incident to a lowered capacity of the blood to carry oxygen); and (3) the stagnant type (the result of a slowing of movement of blood through the capillary system). To these three types Peters and Van Slyke (1932) have added another: (4) the histiotoxic type (in which there occurs an interference with interval respiration, the oxygenation of the tissues themselves) (Figure 6). The specific etiology and mechanism of these types will be given brief attention.

Anoxic Anoxia.—In the production of this type of anoxia we have a considerable number of causes which may be responsible. In it are to be found a variety of conditions not uncommonly experienced in medical practice. Three subgroups of causes may be distinguished: (a) mechanical interference with passage of air into the alveolar sacs, (b) a decrease in oxygen tension in the inspired air, and (c) certain congenital cardiac lesions which limit the amount of blood reaching the lungs. In any of these situations both the oxygen and carbon dioxide tensions in the blood become lowered, so that even that oxygen which is present in the blood is not readily available to the tissues.

Mechanical defects in the respiratory apparatus include obstructive occlusion of the upper air passages by foreign bodies, by acute inflammatory lesions of the throat (tonsillar abscess with rupture), cervical tistues (cellulitis of the neck) or of the larynx and trachea (diphtheria), or by throttling in assault or hanging. Interference with respiration in the lungs themselves may occur in suffusion of these spaces by fluids (drowning, pulmonary edema, pus from rupture of an abscess of the lung or adjacent tissues, blood from ruptured aneurysm), or by thickening of the alveolar wall or occlusion of the entire sac by disease processes (pneumonia, tuberculosis, emphysema, asthma, collapse of the lung). Failure of the nervous centers would, of course, play an important part in the production of anoxia. The present writer has considered these possibilities in case of depression of the respiratory center by certain anesthetic agents, notably nitrous oxide (Courville [1937, 1939]), but also by ether (Courville [1941]). Congenital defects in the lung are rarely responsible for asphyxia in the newborn.

As for a lessened oxygen tension in inspired air, anoxia may result from the presence of a number of gas substances such as nitrogen, or the presence of fumes of sulfur, fermenting liquors, or decaying substances. Even the presence of foul air in mines (as has already been referred to in the section on history) may cause serious if not fatal asphyxia. Suffocation by smoke in fires is another example of this mechanism.

Another mechanism which causes this type of anoxia is that occurring in high altitudes. The long-recognized form of mountain sickness has been briefly referred to; the more modern type incident to air travel in rarefied atmosphere has received attention in the recent war.

Insufficient aeration of the blood may occur in congenital lesions of the heart and great vessels (septal defects, patent ductus) because much of the blood is shunted by the lung field.

Anemic Anoxia.—This occurs characteristically in any form of anemia, resulting either acutely from hemorrhage or chronically by destruction of red cells or by failure to produce them. Under these circumstances the oxygen tension is normal, but not enough of this gas can be carried by the deficient amounts of hemoglobin. In this type of anoxia the situation is often relative, the evidence of impaired oxygenation making its appearance only on exertion.

Under this designation may also be included anoxia after carbon monoxide, which interferes with the oxygen-carrying power of the blood by production of methemoglobin. Poisoning by nitrates, chlorides, and certain other chemicals also produces anemic anoxia.

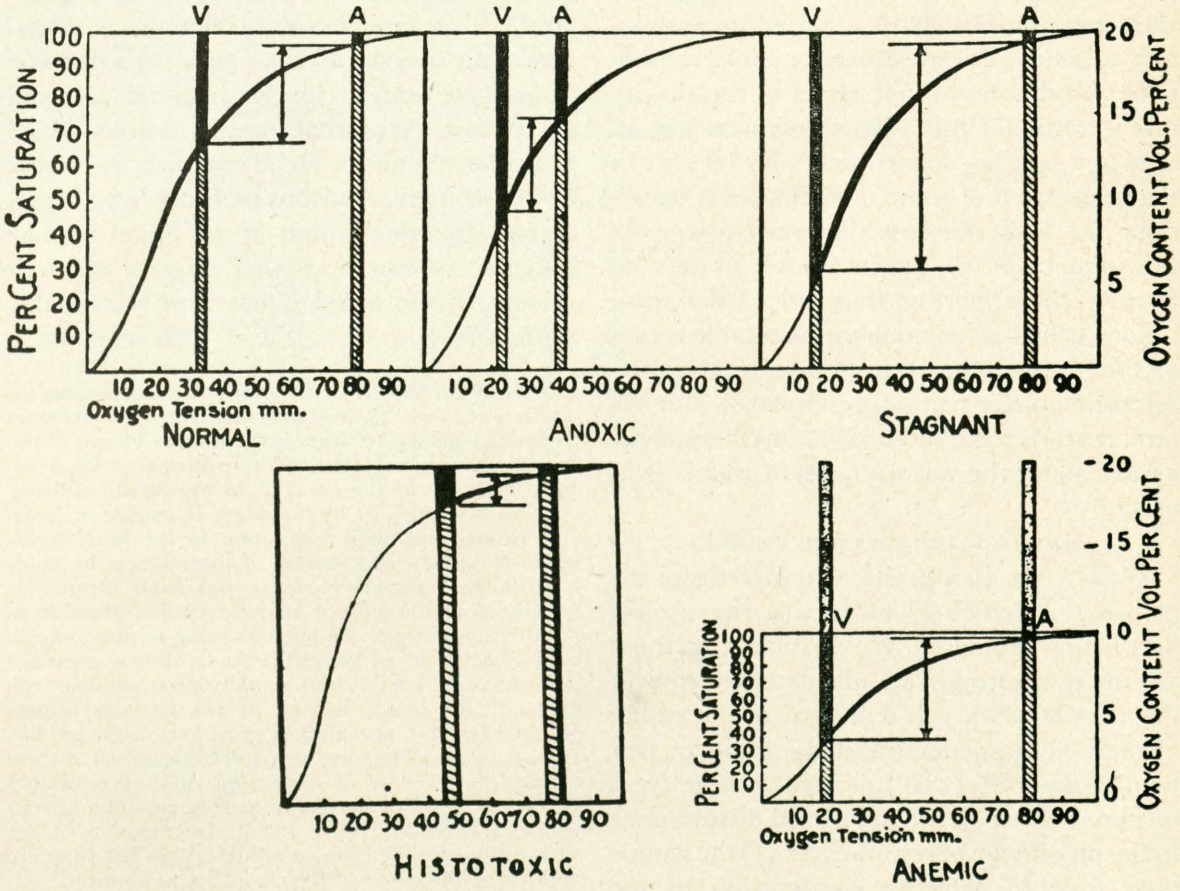

Fig. 6.—Diagram illustrating types of anoxia. Columns representing arterial blood (A) and venous blood (V) are superimposed upon the oxygen dissociation curve. The black portion of the columns represents reduced hemoglobin, and the shaded portion, oxygenated hemoglobin. In the case of anemic anoxia the dotted portion of the columns represents hemoglobin that is either lost, as in true anemia, or unfit for oxygen transport, as in carbon monoxide poisoning. The perpendicular arrows denote the volume of oxygen given up to the tissues from a unit of blood. (From Best and Taylor. Modified from Means.)

Stagnant Anoxia.—This type is characteristically seen in cardiac failure with slowed circulation. The oxygen content and the oxygen tension in the blood are normal, but the oxygen actually supplied to the tissues is reduced incident to the slowed blood current. The failure of the circulation consequent to

surgical shock, if long continued, will produce tissue changes incident to the anoxia produced (Rand and Courville [1936]).

Histiotoxic Anoxia.—This has been described by Peters and Van Slyke and is attributed to an interference with tissue respiration by toxic substances such as cyanide. The cells are apparently unable to utilize the oxygen brought to them even though it is sufficient in amount and is under adequate tension.*

THE PATHOLOGIC PHYSIOLOGY OF CEREBRAL NECROSIS

It has been recognized that the evil effects of anoxia are most evident in the tissues of the brain. It is true, however, that minor changes are found in the viscera. For example, thick-

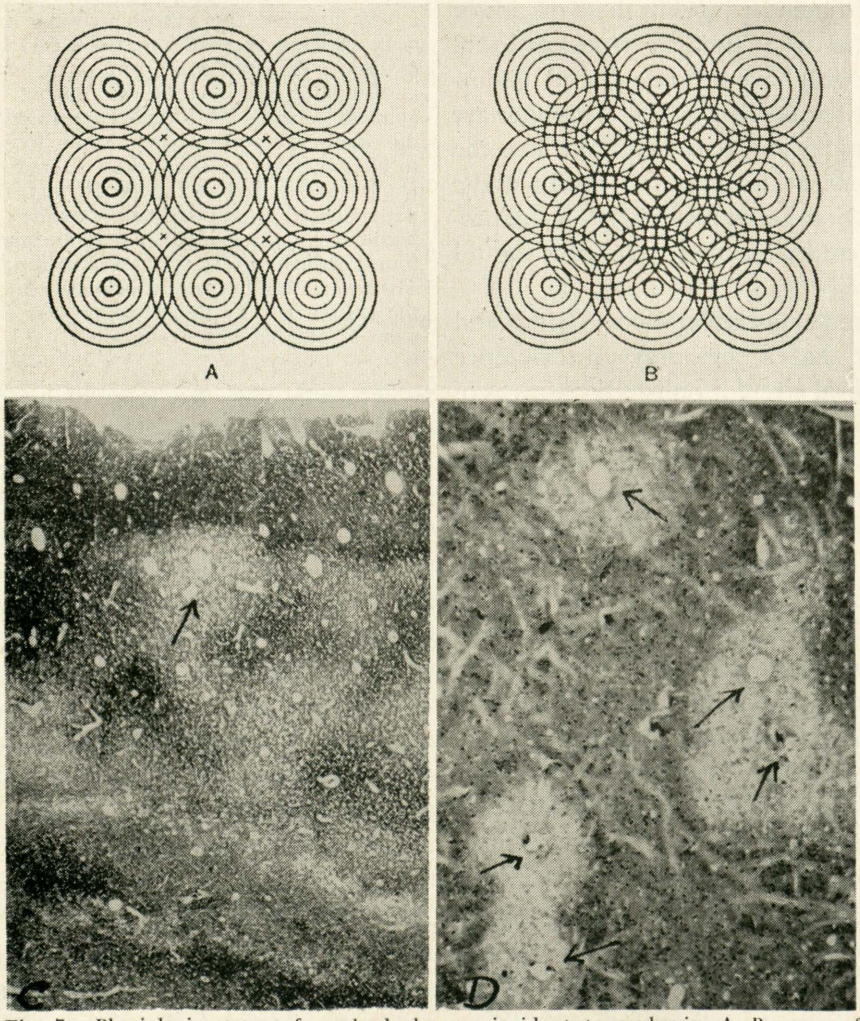

Fig. 7.—Physiologic status of cerebral changes incident to asphyxia. A. Pressure of oxygen in tissues. B. Increased circulatory activity under conditions of minor oxygen want. C. Focal cortical necrosis after asphyxia showing changes about a dilated capillary with preservation of intercapillary tissues. D. Showing relationship of necrosis to capillary blood vessel.

* This concept has also been utilized to explain the action of alcohol (as well as of certain anesthetic agents) on the brain. The presence of alcohol in the tissue fluids is presumed to result in an interference with the use of oxygen. The resultant mild and recurrent form of anoxia is attributed to be the cause of cerebral atrophy in chronic alcoholics.

ening and cellular infiltration of the walls of the pulmonary alveoli, brown atrophy and focal necrosis of the cardiac muscle fibers, necrosis of the liver lobules, chiefly in the region of the efferent vein, acute degeneration of the renal epithelium, cellular infiltration of the spleen, and hemorrhages in these organs or the membranous structures (pericardium, pleura, meninges) have been described (Courville [1939], literature). But these changes are not, as a rule, sufficient to cause death. It is the cerebral lesions at least which produce the most crippling and fatal residuals. To the production of these lesions brief attention should be given.

It was learned experimentally by Gildea and Cobb (1930) that a temporary interference with the cerebral circulation produces areas of focal necrosis in the cerebral cortex. These *Herde* or areas of necrosis are now recognized to be the characteristic cerebral lesion of asphyxia (Courville [1937]). A careful analysis of these lesions makes clear that (1) the earliest evidence of the lesion is found in an enlargement of the perineuronal space associated with moderate shrinkage of the nerve cell and degenerative changes in the surrounding interstitial tissues; (2) the areas of focal necrosis are usually found surrounding a dilated blood vessel; and (3) the larger cortical lesions are but a progressive fusion of these areas of focal necrosis.

The co-ordination of impressions as to the physiology or oxygen consumption by the tissues and physical damage to the brain incident to anoxia may be assisted by comparing the accompanying diagram by Barcroft (Figure 7, A) with the photomicrograph (Figure 7, C) showing the evidence of focal damage to the cerebral cortex in case of asphyxia. Barcroft's diagram was designed to show the effect of oxygen pressure in the tissues. The dot in the center of each series of concentric circles in A represents a capillary containing oxygen with an oxygen pressure of 30 mm. Hg. Between the succeeding concentric circles the oxygen pressure falls 5 mm. Hg. It is evident that at the points marked x the oxygen pressure is zero and under ordinary circumstances, evidence of tissue damage would occur at these points. It is assumed that additional capillaries (Figure 7, B) would open up to supply the deficiency.

A study of photomicrographs taken of the cerebral cortex after asphyxia (as with nitrous oxide) indicates that this postulate does not hold under pathologic conditions. The localization of destruction in the immediate environs of the capillary implies to the contrary that the vessel, once the source of life-giving oxygen, has now become the source of a noxious product which is histiotoxic and histiolytic in its behavior. Since, however, this vascular change is not uniform, only scattered areas of necrosis occur. Because nitrous oxide *per se* is not toxic, one must assume that some additional factor must be responsible in the ultimate analysis. It may be that the accumulation of carbon dioxide in the pericapillary tissues because of a failure to absorb it by the chemically altered plasma flowing with markedly reduced speed through the vessel (stagnant anoxia) is primarily responsible. At any rate, it becomes visually evident that in anoxia there is a profound disturbance in tissue respiration, in which there is a reverse of the usual diffusion of oxygen through the tissues. In this disturbed process the tissue fluids seem to play an important role.

Therefore, in the case of anoxia following nitrous oxide anesthesia the present writer has presumed that these cerebral lesions occur primarily as the result of a triple mechanism: (1) the general reduction of oxygen tension in the blood, (2) a temporary cessation (or at least a marked slowing) of the blood current incident to the often attendant cardiac failure, and (3) a dilatation of the small cortical blood vessels. It is the last of these factors that apparently determines the focalization of the early areas of cortical necrosis, as suggested by the presence of an enlarged central vessel. As the situation grows more serious, more or less of the vascular bed becomes dilated and extensive lesions result from a confluence of areas of focal necrosis to form laminar degeneration, with ultimate fusion of these lamina to form subtotal destruction of the cortex.

In short, the cortical lesions are the apparent combined results of *two types* of anoxia: the anoxic form and the stagnant form. But the details of the nature of the resultant lesion will be reserved for the following section.

NOTE.—The bibliography will appear at the end of the completed article.

(To be continued)