THE BRAIN AND THE SYMPTOMATOLOGY OF THE ANOXIAS *

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Dr. DRINKER suggested as the title for my discussion "The effects of anoxia on the brain and higher centers." Since the symptoms and signs are important indicators of anoxia I paraphrased the words but kept the original meaning. Hence the title, "The brain and symptomatology of anoxia."

This subject is obviously of importance to the anesthesiologist for anoxia may become a threat at any moment during an operation, but this threat is one of acute anoxia rather than chronic anoxia. The signs and symptoms of anoxia seen during an operation are not necessarily those observed in a decompensated cardiac patient nor in an individual suffering from a pulmonary condition in whom the changes affecting the brain are usually outweighed by the peripheral effects on the cardiovascular system, the lungs and the gastrointestinal tract. Acute anoxia makes itself known by its neuromuscular changes, which in their most violent form appear as anoxic convulsions.

One type of acute anoxia cannot be avoided although fortunately it need not be excessive, namely histotoxic anoxia, the interference with the cellular oxidation in the brain which is part of the mechanism of anesthesia. There are also other types of acute anoxia which may occur during an operation. The surgeon may bring on the condition of stagnant anoxia and the tissues may no longer receive their quota of blood if shock occurs during an operation. With a severe hemorrhage and loss of red blood cells, anemic anoxia may supervene. Anoxic anoxia, too little oxygen in the arterial blood, may be produced

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by insufficient oxygen in the closed circuit anesthesia apparatus as well as by extreme depression of the respiratory centers, a result of deep anesthesia.

Anoxia, of whatever origin, exerts its baneful influence on the body by depriving the organism of energy. It is true that energy may be provided in the absence of oxygen, an anaerobic mechanism of great biological importance, for example, in sudden muscular activity. In the brain, however, although not by any means insignificant (1, 2, 3), the anaerobic release of energy is strictly limited. For that reason the brain is highly sensitive to oxygen lack. The great blood flow and oxygen intake of the brain are too well known to require review (4, 5).

In the absence of oxygen most of the energy usually available in the carbohydrate foodstuff of the brain (6, 7), glucose, cannot be realized. The brain thus bereft of energy (8, 9, 10) can no longer support its own functions, just as a steam engine cannot go on in the absence of a draft of air to maintain the coal fire. In applying this concept of energy deficit to the brain we recognize that a metabolic substratum is required for cerebral function.

Since this concept of energy deficit is fundamental to our discussion, it may be well to recall to mind the mechanism by which energy becomes available: glucose + dehydrogenase + coenzyme + cytochrome reductase + cytochrome B + cytochrome C + cytochrome A + cytochrome oxidase + O₂ yield H₂O + CO₂ + energy. Glucose, after a preliminary processing, yields hydrogen atoms, which by a sort of a bucket brigade procedure, finally are carried to oxygen and water is thus formed. Meanwhile carbon dioxide is split off. As a result of these reactions energy is available and this energy supplies the power for brain function.

The high rate of metabolism of the brain as a whole has been emphasized. In addition and also of great importance is the distribution of this high rate throughout the various parts of the brain, for it is not the same in all areas but in general exhibits a quantitative gradient along the neuraxis, most intense anteriorly and superiorly in the cerebral hemispheres and less so posteriorly and inferiorly until it reaches its lowest level in the medulla oblongata. This conception is borne out by the observations in excised cerebral tissue which shows a decreasing rate of oxygen intake as the neuraxis is descended (11, 12, 13).

Because this metabolic gradient exerts such a profound influence in the signs of anoxia it is well to consider briefly some of the evidence on it. Experiments made in dogs (14) in which brain metabolism was measured by drawing venous blood from the superior longitudinal sinus suggest a high rate of metabolism for the top parts of the brain since the superior longitudinal sinus blood, although not of unmixed origin, contains a large part of the return flow from the cerebral hemispheres. The value so obtained is significantly higher than that
for the brain as a whole which includes lower areas with a lesser metabolic rate. The actual values concerned are 4.5 cc. of oxygen per 100 Gm. per minute for the dog cortex in contrast with 3.3 cc. of oxygen per minute per 100 Gm. of tissue for the entire human brain. These observations in man were made by our group (4) and by Kety and Schmidt (5), but with different results. We observed a higher metabolic rate on one side when the oxygen intake was measured in both internal jugular veins simultaneously and regarded the higher one of the two as carrying the majority of the venous return from the cerebral hemispheres. Kety and Schmidt did not disclose a significant difference between the two internal jugular veins. Their results are surprising because the literature reveals that in only 8 of the 125 (15, 16) skulls examined was there a confluence of blood from the superior longitudinal sinus carrying chiefly blood from the cerebral hemispheres, and the straight sinus, with the subcortical venous return. On such a basis, a similarity of blood from both jugular veins should be expected only in approximately 6 per cent of individuals. Pending the solution of this discrepancy we may point to another bit of evidence in favor of a hierarchy in metabolic rate. As is generally accepted today the brain burns chiefly carbohydrate (6, 7) which is obtained from the blood in the form of glucose. For that reason hypoglycemia renders an individual unconscious. In order to combat hypoglycemic coma, carbohydrate must be administered, and it was observed that a larger amount of glucose was required to restore the functions of the cerebral hemispheres than for the subcortical areas (17). Presumably, a greater amount of foodstuff is necessary to support a higher rate of metabolism.

If we accept the concept of a metabolic gradient then it must follow that not all parts of the brain will be equally affected by anoxia but that those regions with highest rates would succumb first and those with lowest, namely the medulla, last. Then with Hughlings Jackson’s idea (18) that the brain is so constructed that the higher anatomical and new phylectic portions contain areas which regulate and control the lower anatomic and older phylectic areas we might expect a series of release phenomena as each area in turn succumbs to a more severe degree of anoxia. The term release phenomenon is not a new one. We are all aware of the release phenomenon of decortication as the hypothalamus and lower parts of the brain are freed from cortical constraints and sham rage with all its somatic and visceral components becomes apparent. Mechanisms formerly under the control of cortical areas are now permitted unhindered expression.

It is necessary to remember both the metabolic gradient and the release mechanism if we are to understand the series of signs with acute anoxia. These signs were demonstrated in a series of patients who respired undiluted nitrogen administered by means of a mask (19). The duration of this anoxia was about five minutes. Early there was
a brief period during which consciousness became impaired as the cerebral hemispheres were the first to suffer from the decrease in available energy (Area 1, fig. 1). The first phase ended as environmental contact was lost. With the loss of consciousness a series of dramatic neuromuscular reactions occurred beginning with a period of aimless motor restlessness which ensued after the subcorticodiencephalon acquired freedom from cortical restraint (Area 2). Next came torsion spasms along the long axis of the body and tonic spasms with flexion of the arms and extension of the legs as the midbrain was released (Area 3). Finally, opisthotonos or emprosthotonos was seen. These signs are release phenomena and indicate decerebration of a functional origin (Area 4). At this point the inhalation of nitrogen was stopped to prevent involvement of the medullary centers (Area 5). With the subsequent administration of air or oxygen the normal cerebral integration was rapidly restored.

![Fig. 1. Representation (transverse section) of the brain disclosing the five phyletic areas: 1, cerebral hemispheres; 2, subcorticodiencephalon; 3, midbrain; 4, pons and upper medulla; 5 medullary centers.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931713/)

It is well to make comparisons with the results of metabolic depression other than those produced by anoxia. If the signs are due to a metabolic deficit then the same or at least a similar series of signs should be produced irrespective of the manner by which the metabolic deficit is created. As an example let us consider hypoglycemia, a condition in which glucose is no longer available to the brain. Since glucose is the chief foodstuff of the brain (6, 7, 20), the metabolic fires falter because of the decrease in the coal to be burned. Hypoglycemic coma brought about by an injection of large doses of insulin affords an excellent opportunity to study the results of metabolic deprivation because of the greater time element. Instead of a period of five minutes as in the inhalation of nitrogen, insulin hypoglycemia may afford a period of five hours (21), thus permitting us to view the signs as if through a magnifying glass (fig. 1). During the first stage, which
may last two hours, the patient gradually loses the functions allocated to the cerebral hemispheres, sensations become dulled and abnormal, understanding is impaired and motor activity poor in execution. Perspiration covers the body and salivation is excessive. Environmental contact is lost as the cerebral hemispheres are no longer functional and the patient becomes unconscious, the beginning of the second stage. Three types of phenomena are observed in this stage. First are changes in motility reminiscent of those seen in a newborn baby with motor restlessness and primitive movements of many types. Second, there is an increased sensitivity to stimulation and finally the alterations in the autonomic system with sympathetic predominance indicated by waves of dilatation of the pupils, exophthalmos, accelerated heart rate, rise of blood pressure and perspiration.

The subsequent stages of hypoglycemia all exhibit decreased sensitivity to stimulation. In the third stage, as in acute anoxia, the midbrain is released and both torsion and tonic spasms develop. The further progress of the metabolic depression yields extensor spasms, the opisthotonos of a functional decerebration. Finally in the fifth stage, the cold gray clammy skin, the slow and feeble heart, the greatly depressed respiration, the muscular flaccidity all give evidence that the metabolic depression is now affecting the medullary centers.

The metabolic march and even some of the presenting signs of hypoglycemia remind one strongly of those produced by acute anoxia and suggest that the signs of anoxia might resemble those of hypoglycemia even more closely if the oxygen withdrawal could be intensified so gradually as to extend over a period of five hours. It is therefore not too much to expect that the signs of cyanide poisoning should also bear a resemblance to the anoxic picture and especially so because the action of cyanide is a histotoxic one, rendering even a plentiful supply of oxygen unavailable due to the combination of cyanide with cytochrome oxidase. This enzyme is thus inactivated and the metabolic chain is stopped at that step. When cyanide, in doses of 0.6 mg. per kilogram is injected intravenously in human subjects (22) the entire anoxic episode takes place rapidly with the signs of a functional decerebration as the most prominent reaction. Yet some analysis may be made. An early effect is that of hyperpnea as the carotid bodies are stimulated. Soon unconsciousness supervenes as the cerebral hemispheres become obtunded. Next comes a series of motor phenomena indicating midbrain involvement with flexion of arms and extension of legs; and an upper medullary site with opisthotonos. Apnea may occur with the opisthotonos. A clear definition of the order in which the various parts of the brain become involved may be seen in animals subjected to cyanide given intravenously. The progression of the metabolic depression was evidenced by the electrical changes as one part of the brain after another became silent for want of metabolic support (23). The first area of the brain to be depressed was the cerebral cortex as
the brain waves disappeared from the cerebral hemispheres; next came the hypothalamus; after that the structures of the midbrain, and finally, the medulla became involved and apnea resulted. The brain waves afford additional evidence for the descending metabolic depression.

Turning to the problem of pentothal anesthesia, we find that pentothal, like the other barbiturates, exerts a metabolic inhibition which is most marked in the brain and relatively unimportant in other organs (24, 25, 11). Measurements of brain metabolism made on human beings in the second and third stages of pentothal anesthesia reveal a decrease of approximately one-third (26). This fall is less than that observed in the second stage of insulin hypoglycemia when the cerebral metabolic rate is decreased by three fifths and more (9). The exact place where the metabolic release of energy is stopped is not definitely known but it may be either at the cytochrome reductase stage, or at the cytochrome B component or an unknown intermediate between these two respiratory enzymes (27, 28). The metabolic inhibition is the cause for certain similarities between barbiturate narcosis and anoxia and especially so for the march of the signs down the neuraxis with deepening anesthesia. The barbiturate question is discussed after procedures employing only metabolic deprivation for the problem is more complicated and involves additional factors. Some characteristic pharmacologic actions of pentothal, not necessarily based on metabolic deprivation, have been elucidated and are available in the literature. They include specific effects exerted upon certain nuclear masses which are especially sensitive to barbiturates: those involved in the coordination of the corneal reflex, those situated in the hypothalamus (29) as well as the respiratory centers. Although general anesthetics raise the threshold of the synapse (30) and thus interfere with the transmission of the nerve impulse, pentothal in common with some other barbiturates possesses a relatively poor development of this synaptic depression on the sensory side (31, 31, 32). This lack permits continued access to sensory stimulation at a time when other cerebral functions are noticeably depressed, for example, when the spontaneous brain waves have disappeared (31). Nevertheless, with sufficient depth of narcosis, motor expression cannot be evoked, and particularly so because the elevation of the threshold makes it difficult for supporting (long-circuiting) impulses to attain the motor neurone (33, 34) due perhaps to impeded recovery after impulse propagation (32).

A review of the signs of pentothal anesthesia (24) discloses an early stage owing in part to a metabolic inhibition of the cortex and characterized by euphoria, loss of fine discrimination and impaired environmental contact. Because of the maintenance of sensory pathways analgesia is not a conspicuous element.

Next in stage 2, that of hypersensitivity, there is loss of consciousness and release of the second phyletic layer including the hypothalamus. Nevertheless some depressive influence is apparent. Be-
cause of the specific susceptibility of the hypothalamus to barbiturates we do not find the hypermotility seen in anoxia or hypoglycemia unless the patient is disturbed by a painful stimulus. The application of pain will, however, elicit hyperactive responses characterized by exaggerated and inappropriate movements of the arms and legs, responses which are rapidly damped after the cessation of the stimulus, probably because of the specific hypothalamic depression.

During the third stage, the various planes disclose a descending metabolic depression, with differentiating signs made possible by the maintenance of sensory nerve function. In the plane of light surgical anesthesia the second layer is only moderately depressed. The pupillary constriction to light remains and a painful stimulus evokes a muscular response even though it is diminished. With the moderate surgical plane the midbrain suffers a more profound but not complete obtundation. The reaction to light is lost although the pupils still dilate and respiratory changes occur in response to pain. Yet muscular reactions are completely suppressed. During this period the anoxemia becomes an important deterrent to any further deepening of the anesthesia in the operating room, a result of the peculiar sensitivity of the respiratory centers to barbiturates. Nevertheless, a plane of deep surgical anesthesia with deeper depression of the midbrain in which the patient is bereft even of the visceral responses to pain may be obtained.

In the lowest stage of impending failure probably equivalent to the fourth stage of hypoglycemia or anoxia the metabolic depression involves the pons and upper medulla but the specific barbiturate effects threaten to engulf the medullary centers and the patient with extreme depression of respiration, profound anoxia and low pulse pressure is truly in a precarious position.

These signs, as a group were obtained in nonoperative and non-premedicated human subjects and under special conditions, which must be observed if they are to be reduplicated. The pentothal was given in dilute solution, 1 per cent, and very slowly. A fast induction, as practiced in the operating room, will telescope the stages and make more difficult any differentiation between them. It must also be remembered that after the drug is given the anesthesia may become lighter and show signs of previous stages. Because of the effects of pentothal on the respiratory centers it is not advisable to bring the patient beyond moderate surgical anesthesia with that drug but rather to use an adjuvant. If, in addition to pentothal, nitrous oxide and curare are employed, the eye signs may still remain as indicators of the planes of surgical anesthesia. Even a mild dose of atropine does not seriously interfere with them, but with cyclopropane and ether to complicate pentothal, the eye signs are no longer diagnostic.*

To conclude this section, we admit freely that it may not be practical

* Personal communication from Dr. B. Etaten.
to apply our landmarks of pentothal anesthesia in the operating room; yet from the point of view of understanding the reactions of the central nervous system they yield an insight which is of aid in elucidating the mechanisms involved in barbiturate narcoses.

I shall not say much about ether anesthesia because I have not had direct experience with it, but my general interest was aroused by the statement in Goodman and Gilman’s textbook (29), probably representing the consensus, that the pattern of ether anesthesia is an irregularly descending one which skips the medulla and goes on to the spinal cord. Ether, however, presumably stops the oxidative chain and does so at the same place as the barbiturates and therefore should include all suprabulbar areas in a metabolic inhibition before encompassing the medulla oblongata. An explanation for the differences between pentothal and ether must therefore be sought in their different specific effects. One of these is the action of ether to raise the synaptic threshold and especially so on the sensory side (31). In this regard ether and the barbiturates, are opposites. The specific effect of ether to prevent sensory stimulation is a source of its analgesia. The interference with the sensory impulse blocks reflex action and is part of the mechanism of the relaxation produced by ether. Perhaps this generalized elevation of the reflex threshold has been misinterpreted as an action localized in the spinal cord. Certainly, the similarity between the first stage of pentothal and that of ether is striking except for the analgesia with ether (34). Stage 2 of pentothal and of ether anesthesia likewise show strong similarities. Ether, however, does not exert a specific effect on the hypothalamus and the hypermotility may therefore be more marked than with pentothal.

Because of the different special effects of ether and pentothal the signs of their third stages are quite different. The pupils enlarge with ether instead of contracting; the time of the loss of corneal reflex is more consistent with ether; respiration is less depressed, and greater relaxation is obtained with ether, the so-called curariform-action already briefly described. Nevertheless by careful observation one can find in plane 2 of surgical anesthesia a relative constriction of the pupil which may be an effect of ether in releasing the Edinger-Westphal nucleus (29), thus indicating a midbrain rather than a spinal allocation for that plane of surgical anesthesia. The downward metabolic march form the cortex in the first stage, subcorticodiencephalon in the second, through the midbrain in the third is carried on to the medulla if medullary paralysis supervenes.

This review supports the viewpoint that metabolic inhibition is only a part of the phenomena of anesthesia and therefore takes into consideration the fact that anesthesia is more than metabolic inhibition. With metabolic deprivation as seen in anoxia, cyanide poisoning and hypoglycemia, the brain ceases to function because it is deprived of the energy to carry on.
In anesthesia not only is there some inhibition in the energy transfer but specific effects are exerted upon the functioning of various nerve areas and an important one is the elevation of the synaptic threshold. To this and to other specific effects are attributed the differences between pentothal and ether, for these specific properties render each anesthetic unique in its action. That should not blind us to the possibility that one element of this complicated picture is a metabolic one, common to all anesthetics which work through their effects on the brain. Such a metabolic element yields an explanation for the stepwise passage in the allocations of the signs down the neuraxis and also affords a basis upon which the specific effects of each anesthetic agent may be superimposed.

REFERENCES


PROGRAM
1949 ANNUAL MEETING
AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC.
Wednesday, December 7th
MORNING
East Room
9:00 A.M.
Meeting of the Board of Directors of the A. S. A.

AFTERNOON
Parlors E and H
12:30 P.M.
Luncheon for the Board of Directors of the A. S. A.

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