# SOME OBSERVATIONS ON ANOXIA *

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"Anoxaemia not only stops the machine, it wrecks the machinery."

THIS statement of Haldane's (1) is undoubtedly true, but it is perhaps unfortunate that he did not stress that it is applicable also to any type of anoxia, either anoxic, anaemic, stagnant or histotoxic, or a combination of any of these.

The pathologic changes in the central nervous system that occur as a result of anoxia have been comprehensively reviewed by Hoff, Grenell and Fulton (2). They pointed out that the nerve cell damage is essentially the same whatever the cause or type of anoxia; what is more, they suggest that hypoglycaemia, by removing the substrate, and the anoxia of high altitudes are virtually the same as in both conditions the cell is unable to metabolise efficiently and so damages itself. They included oxygen lack, carbon monoxide poisoning, cyanide and anaesthetic agents—in short, all methods in which there is a depression of nerve cell metabolism. This conclusion is based on evidence observed in many species with a variety of histologic technics. There are many discrepancies, particularly regarding the extent of the neurologic damage and the duration and severity of the anoxic insult. For example, concerning anoxic anoxia, some workers conclude that no amount will produce nerve cell damage unless severe enough to cause death of the whole subject, while others believe that even small doses will produce demonstrable permanent neurologic change. Buzzard and Greenfield (3) suggested that central nervous tissue can suffer reversible damage from anoxia, whereas Thorner and Lewy (4) believed that the effect of it is cumulative and never reversible. It has recently been shown that recovery is possible under certain circumstances (5, 6) following anoxia. If anoxic insults are repeated at regular intervals, an irreversible state ultimately occurs, but if the time interval is irregular, there is no summation of effect and recovery is possible. The results of histologic study offer an explanation of this.

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The exact biochemical change that takes place inside the nerve cells of the brain under anoxia conditions is not known. All the evidence concerning pathologic dysfunction is based on histologic observation of the stained dead cell. This is, at best, a crude method and has many disadvantages. The main one, perhaps, is that it is necessary to fix the tissues in some way in order that they may be easily processed and produce some differentiation with staining technics. There are also individual variations in technic and interpretation. Many of the changes which have been described hitherto as the effect of anoxia can be produced experimentally by modifications in histologic technic and it is for this reason that much of the literature on anoxia must be examined critically, particularly that concerned with human material. Experimentally, the brain can be removed and fixed immediately after death, but clinically there may be a delay of some hours. During this time normal autolysis takes place and this may adversely affect the picture.

The earliest change that occurs in the anoxic brain cell is an intracellular oedema. This makes histologic study particularly difficult because the oedematous cell may easily disrupt in the process of fixation owing to too rapid withdrawal of water, so giving the classical acute anoxic change as described by Spielmeyer (7). This often gives a false impression of irreversible damage. This oedema accounts for the supposed accumulative effect of anoxia. If it is reabsorbed readily, then the cell recovers, but if it persists, then by purely mechanical means oxygen will be denied rapid access to the cell so that the anoxia becomes worse and a vicious circle is established which leads to death. This, then, may be the reason that regular intermittent anoxia has an accumulative effect because the time interval is not long enough for the oedema to be absorbed.

This postanoxic oedema has some practical importance in clinical medicine. For example, following the severe anoxia of cardiac arrest, the heart may be started and the cerebral circulation re-established with oxygenated blood, but unless some method of removing the intracellular oedema is begun at once, the brain cells may succumb. The withdrawal of fluid from the brain by hygroscopic or osmotic means is the basic principle underlying the treatment of cerebral oedema. The best method is the intravenous use of concentrated human serum in a dose not exceeding 50 milliliters per hour. Too rapid dehydration may produce convulsions. Theoretically, it would also seem reasonable to attempt to improve the blood supply to the brain. It has been suggested that in the postanoxic state there is a condition of vascular spasm which can be treated with intravenous procaine or bilateral stellate sympathetic block (8). Intravenous infusion of a week solution of histamine has also been used for this purpose (9).

In the treatment of cardiac arrest under anaesthesia, it is essential to obtain an adequately oxygenated cerebral circulation. Time is

vital. To do this, artificial respiration must be started at once. Simultaneously, the heart must be made to function as a pump by means of cardiac massage. Intracardiac injections with epinephrine or any other drug are useless because it is unlikely that the heart will resume beating effectively, but will merely fibrillate and consume further valuable oxygen and time (6, 10). Moreover, from the point of view of ultimate recovery, the heart which is in ventricular fibrillation is more difficult to start than one which has completely stopped. Experimentally, it can be shown that cardiac massage in the presence of ventricular fibrillation produces a very poor output and under these conditions it is impossible to restore normal rhythm. If, on cardiac massage, the heart is found to be in this state, every effort must be made to overcome it. Electrical defibrillators have been described for this purpose but they are not always readily available (11, 12). In dogs, the application of ice to the fibrillating heart will inhibit it and enable normal rhythm to be started. This is, of course, applicable in man only when the thorax is open. An alternative method of stopping ventricular fibrillation is to supply the myocardium with oxygen. This can be done by intra-arterial transfusion with oxygenated blood at sufficient pressure to force it back into the coronary circulation.

A second example of the relationship of postanoxic oedema and reversibility is anaesthesia. In 1875 Claud Bernard (13) discussed the association between anaesthetic agents and asphyxia and concluded that their analgesic effect was due to interference with the oxidation of the nerve cells of the brain. This has been demonstrated exprimentally by Quastel and Wheatley (14). If this hypothesis is true, that is, that anaesthesia is a state of histotoxic anoxia, then, under certain circumstances, there may be a summation of effect. It would seem obvious that central nervous tissue can recover from small anaesthetic insults without any permanent damage, but this is not proven. Since the normal architecture of the brain has not yet been worked out satisfactorily, it may be that anaesthesia does permanent harm to a small number of cells, but such is the enormous compensatory power of the brain that this damage is not noticed. This is unlikely, but prolonged anaesthesia, or intermittent doses with too short a recovery period in between, may be harmful. Similarly, if at the end of a period of normal anaesthesia there is superimposed anoxic anoxia, this may result in an irreversible change.

Is there any way of making the brain more resistant to the effect of anoxia? Normally, it is only the foetus and newborn who are so, a fact observed by Robert Boyle (15) in 1670 when he noted that kittens survived longer than their mothers under asphyxial conditions. This can be explained on the basis that the newborn brain has a greater store of carbohydrate than that of the adult and that this can be broken down anaerobically to provide energy for the cell under anoxic

conditions (16). If some method could be discovered of stimulating anaerobic respiration in the adult under anoxic conditions, it would be of great value for anoxic emergencies. A number of drugs has been investigated. Both ascorbic acid and methylene blue increase the tolerance of adult rats to high altitude (17) and ascorbic acid itself has been used in the treatment of experimental shock in cats, with good effect (18). Adrenal cortical extract is effective in the anoxia of high altitudes and animals acclimatized to altitudes of 20,000 feet show adrenal hypertrophy (19). It is relevant that the newborn has a greater amount of adrenal cortex than the adult and this slowly diminishes in the first six months (20). What is more, children with cyanotic congenital heart disease do not show this involution (20) and in this condition resistance to anoxia is maintained (21). Another substance which has been shown to have some value in increasing anoxic tolerance is the tissue oxygen enzyme cytochrome-c (22).

This problem is in no way solved. It may be that one will have to turn to comparative respiration for the answer. Some of the diving mammals, for example the seal, can remain under water for long periods and come up to the surface with a blood oxygen saturation of virtually nil, yet these animals are conscious and do not appear anoxic (23). It would be interesting to find out exactly how they do this. The answer might be of great use in everyday clinical medicine.

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