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The effects of anoxia upon animal cells and tissues

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Thesis
THE EFFECTS OF ANOXIA UPON ANIMAL CELLS AND TISSUES
by
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Introduction

Innumerable investigations have been carried out to ascertain the effects of high altitudes or simulated low oxygen tensions upon organisms, especially mammals. Comparatively little has been done on the effects of anoxia upon the individual organs and isolated cells and tissues. Most of the work done along the latter lines has been devoted mainly to two systems: the respiratory system, especially with regard to the chemo-receptors of the carotid and aortic bodies, and the circulatory system, in relation to the blood pressure, vasomotor affects and supply of extra red blood cells. Most of this material has been so well demonstrated and agreed upon, that it is incorporated as an integral part of most modern textbooks. This thesis will discuss some of the less known effects of anoxia upon the cells and tissues of various systems of the body.

Definition of Anoxia

Anoxia is a general term denoting oxygen lack regardless of how or in what part of the body it is produced.

Types of Anoxia

There are four types of anoxia (Bard, 1938).

Anoxic anoxia (anoxemia) results from reduced oxygen tension in arterial blood. Reduced oxygen tension may be brought about in the following ways: a) by interfering with the passage of oxygen from the air to the blood in the lungs, as in
drowning, weak respiratory movements, reduction in size of aerating surface by edema, consolidations, adhesions or exudate, b) by reduction in the partial pressure of oxygen in inspired air, as in inhalation of inert gases, c) by inhalation of air under reduced barometric pressure, as at high altitudes on mountains or in airplanes.

Anemic anoxia results from the reduction of available oxygen than can be furnished by the blood to the tissues. It is produced by: a) decreased number of hemoglobin, as in anemia and hemorrhage, and b) decreased ability of hemoglobin to yield oxygen to the tissues due to poisons such as carbon monoxide, nitrates, nitrophenols and chlorates, which change hemoglobin to methemoglobin.

Stagnant anoxia is caused by interference with the circulation of blood. In this case, a normal supply of oxygen may be available in the blood, but the capillary circulation may be defective, with the result that the amount of oxygen reaching the tissues in a given time is less than is required. It may be caused by such things as occlusion of arteries by embolism or by decrease in the size of the arteries due to disease or poisons.

Histological anoxia is produced by the inability of the cells to utilize oxygen, even though a normal supply is available. This type of anoxia occurs mostly in poisoning by cyanide, but also in poisoning by alcohol and by various narcotics, to a lesser extent.
The central nervous system and cardiac tissues are found to be most sensitive to oxygen lack. While other functions of the body, such as circulation, metabolism, digestion, and respiration are also disturbed because of anoxia, these alterations are brought about by affecting the regulating mechanisms of the central nervous system first.

Mechanism of oxygen supply to normal tissue

Normally, oxygenated blood travels through the arteries to the capillaries, where the following reaction occurs:

\[ \text{Hb} + \text{O}_2 \rightleftharpoons \text{HbO}_2 \]

In the capillaries there is an oxygen tension of about 90 mm, and a carbon dioxide tension of about 40 mm. The blood contains about 20 cc of oxygen per 100 cc of blood. A small amount of the oxygen is in physical solution in the plasma.

Back in the thick-walled arteries and arterioles, equilibrium exists, since there are no disturbances there. However, in the capillaries there is only a permeable endothelial wall between the blood plasma and the tissue fluid. The oxygen tension of the plasma is greater than that of the tissue fluid, since oxygen is continuously being diffused from the latter to the cells. The oxygen tension in the tissue fluid is about 35 mm, when the tissue is at rest. Therefore, the molecules of oxygen which are held in the blood plasma are forced through the capillary walls. The oxygen tension of the plasma falls rapidly, leading to dissociation of oxygen from the hemoglobin almost immedia-
The molecules of oxygen from the hemoglobin diffuse out of the red blood cells into the plasma, and from there, through the capillary wall into the tissue fluid. At the same time, carbon dioxide diffuses into the blood, since its tension in tissue fluid is 46 mm or more and its tension in blood is only 40 mm. The hemoglobin become more acid, with the result that their ability to hold oxygen decreases. Therefore, more molecules of oxygen are free to go into the plasma.

By the time the blood reaches the veins, it has about 15 cc of oxygen per 100 cc of blood. The oxygen tension is about 40 mm. Only about 35 per cent of the available oxygen has been used by the resting tissue. The amount of oxygen used by tissues is denoted by the coefficient of utilization. If the tissue is active, much more oxygen is utilized, since the oxygen tension in the tissue fluids is greatly reduced when cells use oxygen actively. The blood on the venous side may appear with less than 10 cc of oxygen in 100 cc of blood during moderate activity and as little as 5 cc of oxygen in 100 cc of blood during vigorous action or exercise. During great tissue activity, heat is produced, a fact which aids in the removal of oxygen from the hemoglobin to the tissue fluids.

Utilization of oxygen by the tissues

The gas taken by the tissue cells from the surrounding tissue fluid is called molecular oxygen (Barnes, 1938). This oxygen combines with the end products of digestion, such as
glucose, amino acids and fatty acids. Xanthine compounds, alcohols and many drugs and poisons are also oxidized. The bulk of the energy of the body comes from the oxidation of common foodstuffs. None of the above mentioned substances combine readily with molecular oxygen outside of the body, except at very high temperatures. However, in living cells they are readily oxidized. This condition is explained by the presence of enzymes in the living cells which do two things: a) increase the ability of oxygen to combine with oxidizable substances, called "activation of oxygen", and b) decrease the resistance of a substance to combination with oxygen, called "activation of the substrate".

Originally oxidation referred to the addition of oxygen to a substance. But it is now recognized that oxidation may be brought about by the removal of hydrogen (dehydrogenation), as well as by adding oxygen. This increases the proportion of oxygen in a molecule of substrate. Therefore, it is considered an oxidation.

The fate of oxygen in a cell is depicted on page 6 (Bard, 1938) in a simple manner. According to the diagram, the food material is called a metabolite. It is assumed that it occupies a compartment with two openings: a) one for the enzyme dehydrogenase which disturbs the electronic equilibrium of the metabolite so much, that it gives up hydrogen (2H). It is thus changed to dehydrogenated metabolite which is activated so that it can combine with active oxygen, and b) the other for the
Keilin's Scheme of Cellular Oxidation

CO₂

Metabolite

Dehydrogenated metabolite

2H

Dehydrogenase

Oxidized Cytochrome

3H

Reduction Cytochrome

H₂O₂

H₂O

O₂ (molecular)

H₂S

HCN

Narcotics CO
admission of active oxygen which is carried by oxidized cytochrome. Cytochrome is an oxidizing enzyme present in almost all aerobic cells except peripheral nerves. It is oxidized by the molecular oxygen. Later, it takes up the hydrogen from the metabolite as it gives up its oxygen to dehydrogenated metabolite. Thus, it becomes reduced cytochrome. Cytochrome is a hydrogen acceptor.

The enzyme, oxidase, is involved in the transfer of oxygen to reduced cytochrome. It takes molecular oxygen from the tissue fluid and activates it so that it will oxidize cytochrome. Without oxidase molecular oxygen could not be utilized by the cell, since this enzyme furnishes a means of entering into the cell. Thus, it oxidizes hydrogen acceptors so that they can be returned to active duty after being saturated with hydrogen from the foodstuff oxidized.

The final hydrogen acceptor is molecular oxygen in tissue oxidations. Probably there are a few additional enzymes that aid in the transfer of oxygen to reduced cytochrome, and the transfer of hydrogen from it. It is possible that complex organic peroxides are formed in exchanging hydrogen from the cytochrome and oxygen from the oxidase. It may be that an enzyme, peroxidase, is involved. It is believed that in the peroxide \( \text{H}_2\text{O}_2 \), half a molecule of active oxygen (0) is taken up and water \( \text{H}_2\text{O} \) is left.

\[
\text{H}_2\text{O}_2 \rightarrow \text{H}_2\text{O} + \text{O}
\]
It is assumed that the water diffuses out of the cell from the site of its formation.

Furthermore, when the active oxygen (O) combines with the metabolite which has been previously activated by the dehydrogenation, the metabolite is oxidized and CO₂ is formed. The CO₂ is assumed to diffuse out of the cell like the water.

There are other enzymes present, but those mentioned above are the main ones concerned with the effects of anoxia upon the cells.

Summary of the action of enzymes

Oxidizing System:
Molecular oxygen $\rightarrow$ oxidase $\rightarrow$ peroxidase $\rightarrow$ reduced cytochrome $\rightarrow$ oxidized cytochrome $\rightarrow$ activated metabolite.

Dehydrogenating System:
Metabolite (hydrogen donator) $\rightarrow$ dehydrogenase $\rightarrow$ oxidized cytochrome (hydrogen acceptor) $\rightarrow$ reduced cytochrome $\rightarrow$ peroxidase $\rightarrow$ oxidase $\rightarrow$ oxygen.

Enzymes and anoxia

Injury to any one of the enzymes upsets the whole system of oxidation in the cells.

Oxidase is so affected by cyanide, sulfide and carbon monoxide (in the dark) that it cannot carry oxygen to reduced cytochrome. Thus the reduced cytochrome cannot be oxidized.
The activity of dehydrogenase is reduced by the action of narcotics, such as urethane and barbiturates. This prevents the reduction of oxidized cytochrome.

Thus, a normal supply of oxygen may be available, but the above mentioned agents may so interfere with the enzyme system of the cells that anoxia is produced because the cells cannot utilize the oxygen.
The effects of anoxia on the metabolism and activity of tissue of mammals and frogs

Nervous Tissue

The central nervous system is more sensitive to the effects of oxygen lack than any other system except the cardiac system. This is due to the fact that the nervous system has a very high rate of oxygen consumption. Constant respiratory activity of the brain depends upon two things; a minimum of glucose available and a constant supply of oxygen to the brain rather than a rich one (Quastel, 1939). The effects of oxygen deprivation are reversible if the period of anoxia is not too long. After thirty minutes of anoxemia in dogs whose circulation have been stopped and re-initiated at intervals, neurons in the brain can still regain their function (Heymans and Bouckaert, 1935). There is also, a recovery of respiration, vasomotor and pupillary reflexes.

Early effects of oxygen lack on nervous tissue can be detected by changes in the movements of the eyes in mammals (McFarland, Knehr and Berens, 1937). These investigators, subjected human beings to anoxemia in special respiratory chambers. They found that anoxemia causes a decreased efficiency of ocular movements, which they attribute to a diminished amount of oxygen being delivered to the nervous tissue, subcortical as well as cortical.

If the brain tissue of dogs is examined in a minced or
chopped condition, suspended in a medium of cyanide or carbon monoxide, its respiration, or oxygen uptake, is greatly inhibited (Quastel, 1939). However, the action of these two chemicals is not identical. The cyanide attacks the oxidase, while the carbon monoxide inactivates the dehydrogenase. This points to the fact that brain respiration proceeds mostly through the cytochrome-oxidase system. In the administration of narcotics, an available supply of oxygen is present, but the enzymes of the brain cells are inactivated and anoxia ensues (Quastel, 1939). The narcotics attack the same point as the carbon monoxide, namely, the dehydrogenases.

The synthesis of acetylcholine in the brain depends upon an intact respiratory metabolism (Mann, 1938), which, in turn, depends upon a constant supply of oxygen to the central nervous system.

Anoxia depresses somatic excitability at cortical, subcortical and spinal levels (Gellhorn, 1941). These conclusions are supported by the work of previous investigations. Anoxia depresses the somatic excitability as measured by the lingual-maxillary reflex (Greenberg and Gellhorn, 1940) in cats. The endings of the lingual nerve in the tongue were stimulated with condenser discharges and a record of the contractions of the digastric muscle which is innervated by the motor branch of the trigeminal nerve was made. Respiration and blood pressure were recorded in the same experiment. It was found that anoxia decreases somatic excitability as measured by the reflex. At
the same time blood pressure rises and respiration increases. The effects of anoxia are not altered by denervation of the carotid sinus and bilateral vagotomy, although it is well known that the chemoreceptors of the buffer nerves do not exert an excitatory influence on somatic, only on autonomic and respiratory centers.

By stimulating the hypothalamus of cats and recording the contractions of the nictitating membrane, Carlson, Darrow and Gellhorn (1940) also found that anoxia decreases somatic excitability. At the hypothalamic level there is also an increase in autonomic excitability. This suggests that the somatic centers are more sensitive to anoxia than the autonomic. This fact may cause the autonomic centers to react with signs of marked increased activity while the somatic centers are depressed (Gellhorn, 1941).

The nerve endings in the bowel are, in general, resistant to the effects of low oxygen (Alvarez, 1937). This investigator showed histologically that there are fine nerve fibrils in the small bowel of rabbits that probably enable thousands of muscle fibers to contract as a unit. These are resistant to anoxemia. Long nerve pathways running the length of the bowel and the mesentery are also immune to anoxemia. This indicates that they are unbroken by synapses. However, other nerve endings and pathways which are greatly concerned with peristaltic rushes are found to be sensitive to anoxemia. These latter nerve pathways appear to be broken by synapses.
The inhibiting influence which normally holds the intestinal muscle in check fades after thirty minutes of exposure to anoxemia and is lost completely during the next two hours. No similar work has been done since the investigations of Alvarez.

As has been previously mentioned, the eye is extremely sensitive to anoxia. The central visual acuity of the eye is unaffected by oxygen deprivation; however, in man there is an increase in the size of the angioscotoma, until it obliterates the visual field except for a region of eight to ten degrees around the macula, during progressive oxygen lack (Evans and McFarland, 1938). Measurements were made using the technique of angioscotometry. The increased angioscotoma refers to a defect related to the retinal perivascular spaces. The investigators postulate that this angioscotoma reaction may be explained on the basis of the disfunctioning of synapses in the retina due to low oxygen. These postulations coincide with the investigations of Alvarez on the innervation of the bowel which have been mentioned previously. The latter found that the only nerve pathways that were sensitive to lack of oxygen were those where there appeared to be synapses in the region of the bowel. Both investigators feel that anoxia effects the synapses. Evans and McFarland (1938) suggest that just as there are certain parts of the brain more sensitive to oxygen lack than others, so there are certain parts of the retina more sensitive. As anoxia progresses, the sensitivity of the eye in man to dark adaptation is decreased (McFarland and
Evans, 1939). It is probable that during the first four or five minutes of exposure to low oxygen the cones are involved, and during the next five to twenty minutes the rods become effected. The results of these experiments suggest that the changes occurring are concerned with neural elements of both the retina and the central nervous system. The investigators believe that the effects are probably due to the conductive nervous system of the visual mechanism and the connecting pathways from the retina to the cerebral cortex. Anoxia is also followed by a dimness of the visual field (McFarland and Halperin, 1940).

All the experiments on the effects of low oxygen upon the eyes emphasize the delicacy and sensitivity of the ocular system, and the close relationship between eyes and the central nervous system. All the investigations on eyes were performed on men and women who were exposed to low oxygen in respiratory chambers.

The same factor that depress the somatic excitability at cortical, subcortical and spinal levels (anoxia), stimulates the respiratory and vasomotor centers by its action on the chemoreceptors of the carotid and aortic bodies. The fact that respiration can be profoundly influenced by reflexes set up in the region of the carotid sinus under low oxygen tensions, has been shown by diffusion experiments performed on cats and dogs many times (Heymans and Bouckaert, 1933; Heymans et al., 1931; Heymans et al., 1933; Owen and Gessel, 1931; Selladurai and
Wright, 1932; Schmidt, 1932; Gemmill and Reeves, 1933; Gayet, Bennati and Quivy, 1935; Green and deGroat, 1935; Winder, 1937; Smyth, 1937).

The major, if not sole, function of the carotid bodies and very probably the aortic bodies is now known to be due to the presence within them of chemoreceptors, i.e., nerve endings specialized to respond to certain changes in the chemical composition of their environment (arterial blood), such changes giving rise to reflexes which can produce physiologically important effects upon respiration and circulation (Schmidt and Comroe, 1940).

Respiratory and vasomotor stimulation induced by anoxia is not of direct central origin, but due mainly to reflex excitation of the centers through cardio-aortic and carotid sinus chemoreceptors (J.F. and C. Heymans, 1927; Heymans et al., 1935; Owen and Gessell, 1931; Selladurai and Wright, 1932; Comroe and Schmidt, 1938; Lambert and Gellhorn, 1938). The carotid sinus and vago-sympathetic-aortic nerves are essential to respiratory stimulation by oxygen lack (Bouckaert, Grimson and Heymans, 1931 and Selladurai and Wright, 1933). In their absence, low oxygen depresses respiration. In cats the pulmonary ventilation of breathing tends to be less after carotid denervation than before. According to Bouckaert (1938), hypoxemia stimulates respiratory and vasomotor centers primarily by means of the carotid sinus and vagus nerves; however, the vagal chemoreceptors are less important.
In decapitated dogs (Bouckaert, 1938) and decapitated cats (Mathison, 1910) hypoxemia depresses the respiratory and vasomotor centers. In such animals, not only the receptors have no central connection, but also the medullary centers were removed. It is, therefore, probable that spinal centers as well as medullary centers are stimulated by oxygen lack.

The most effective stimuli to the chemoreceptors are asphyxia, anoxia (produced either by low oxygen pressure in arterial blood or by poisons such as cyanide which inhibit cell oxidation), acidosis, and drugs with nicotinic properties. There has been a great deal of controversy as to the effectiveness of hypercapnia as a stimulus. One group claims that physiological responses to carbon dioxide involve the carotid reflexes. The other group maintains that in dogs and cats, at least, the carotid reflexes play no essential part in the response to hypercapnia, although they are the major factor in the hyperpnea of anoxemia (Heymans, 1933, 1931, 1933; Schmidt, 1932; Gemmill and Reeves, 1934; Smyth, 1937; Comroe and Schmidt, 1938; Bard, 1941).

Comroe and Schmidt (1938) consider the carotid body specialized for response to interference with oxidations within itself, i.e., in the capacity of an accessory mechanism brought into action by emergencies such as foreign chemicals and anoxemia, rather than being an essential part of the normal respiratory center. During anoxia acidosis results from incomplete oxidation in tissues (Bard, 1941). There is a possibility that
the effects of oxygen lack on the chemoreceptors are due to the acid changes brought about by anoxia, since both the carotid and the aortic bodies are effected by changes in pH.

It is probable that nerve cells of the respiratory center may be stimulated by anoxia, too, since after section of the sinus and depressor nerves in dogs, distinct anoxemic hyperpnia remains in many cases (Schmidt and Comroe, 1940). Bard (1941) states that more and more respiratory neurons are activated by increasing anoxemia, and the neurons with the greatest sensitivity to chemical stimulation are most resistant to inactivation by adverse circumstances such as cyanide and oxygen lack. Comroe and Schmidt (1938) maintain that the carotid body receptors are more resistant than the cells of the center to depression by anoxia; therefore, this keeps respiration going when the cells of the center have lost all ability to respond to changes in environment.

It may be concluded, therefore, that anoxia causes an increase in respiration and a rise in blood pressure, due to stimulation of the chemoreceptors of the carotid and aortic bodies. The action is reflex, and not direct upon the center.

Heymans, Bouckaert and Regniers (1933), experimenting on dogs, were the first to show that vasomotor and cardioinhibitory centers are affected in the same direction as the respiratory center, by changes in the chemoreceptor activity. This has been confirmed many times since then. The increase in respiratory volume and rise in blood pressure tend to improve
the oxygenation of tissue by increasing the oxygen tension of alveolar air and by improving the circulation of the heart and brain. The respiratory response is a finer indication of anoxia than the blood pressure, since in mild anoxia in cats, dogs and man, respiratory responses may occur without change in blood pressure (Gellhorn, 1941). If the respiratory response is poor or artificially curtailed by pneumothorax, the blood pressure rises markedly in proportion to the reduction in respiration. In either case, the chemoreceptors are the activating forces.

Circulatory System

In its attempt to counteract the ill effects of anoxia, the body makes many adjustments in the circulatory system, some of which have been referred to in the discussion of the carotid and aortic bodies, i.e., rise in blood pressure and stimulation of the cardio-inhibitory centers.

Oxygen lack never accelerates the perfused heart; it decreases its rate (Barcroft, 1934). In order to effect a perfused heart, there would be needed a degree of anoxemia which could not be tolerated by the brain. In man, there is a rise of blood pressure in the left ventricle and an increased rate of ventricular ejection (Sands and DeGraff, 1935 and Bard, 1941). The ventricular rhythm of man as measured by the electrocardiogram is persistently and unexpectedly regular (Greene and Gilbert, 1921). Oxygen lack causes reduced oxygen usage by the
heart of cats that have breathed from a gasometer in which the nitrogen flow can be controlled (Verzar, 1913).

Anoxemia causes dilatation of blood vessels as shown by the following experiment. The hindlimb of a dog perfused with blood from a heart-lung preparation shows vasodilatation, if the lungs of the preparation are ventilated by air containing a deficiency of oxygen (Bard, 1941).

When large arterial and capillary areas are dilated, reservoirs of red blood cells come into action. It is a well-established fact that the hemoglobin and erythrocytes of the blood increase during anoxia. The hemoglobin and blood cells increase in rabbits (Campbell, 1937a, 1937b), rats (Campbell, 1937b; Escobart and Baldwin, 1934; Myer, Severs and Beatty, 1935), cats and cavies (Campbell, 1937b), and in dogs (Escobar and Baldwin, 1934; Bard, 1941), when exposed to low oxygen in respiratory chambers. The increase in hemoglobin allows blood to carry more oxygen per cubic centimeter and thus, relieves the vital organs such as the heart.

This increase of hemoglobin and erythrocytes comes mainly from the spleen and bone marrow. Barcroft (1935) suggests the following scheme:

Possible methods of increasing the blood count

- Abstraction of water
- Opening of capillary areas
- Contraction of the spleen
- Unrecognized methods
- Activity of bone marrow
It was suggested in 1894 by Heger that the spleen is a reservoir of erythrocytes. He poisoned dogs with carbon monoxide and then examined their blood, which was taken from various organs as soon as the animals fell into convulsions. The blood of the spleen and bone marrow retained their normal spectrosopic appearance, while that of the general circulation contained considerable carboxyhemoglobin. Barcroft (1923) made similar observations. When the hemoglobin of spleen pulp in rats breathing 1.0 per cent carbon monoxide is compared with that in the general circulation, there is a lag between the percent of carboxyhemoglobin in the general circulation and that in the spleen pulp. Computations were made on a spectroscope. A chart of the results will be found on page 31. This work is verified by Hanak and Harkey (1924) on rats, and by Barcroft (1925) on guinea pigs. The spleen is used when there is an immediate need for blood richer in corpuscle or an increase in blood volume.

Oxygen want causes contraction of the spleen so that corpuscles are pushed into the circulation. During anoxia, the spleen may be reduced to one half its size in guinea pigs (Barcroft, 1923) and in cats (deBoer and Carrol, 1924) due to splenic contraction.

When other emergency methods are exhausted, the final means of obtaining an increase in hemoglobin is to increase the production of red cells by bone marrow. In 1906 Zuntz and his colleagues (quoted from Barcroft, 1925) observed the venous
The Effect of Carbon Monoxide on Hemoglobin of Rats

(Barcroft, 1923)

![Graph showing the effect of carbon monoxide on hemoglobin concentration over time.]

- Time Minutes of Exposure to 0.1% CO in Air
- % COHb (Carbon Monoxide Hemoglobin)
- x = general circulation
- ● = spleen
- ○ = liver
blood coming from the bone marrow of animals and also sections of the bone marrow itself. They found increased activity of the bone marrow and an increase in the number of erythrocytes and reticulated cells. This has been shown in guinea pigs and rats (Dallwig, Kolls and Loevenhart, 1915 and Myer, Seavers and Beatty, 1935 and Richardson and Dock, 1938), which were exposed to excess amounts of nitrogen in respiratory chambers.

The reticulated cells of humans are young red blood cells. They normally spend their lives in bone marrow, but during anoxia there is an increase in the blood. The cavity of the bone contains mostly bone marrow, although there is some fat there, too, together with a storage of maturing reticulated cells. To make room for the new bone marrow, the reticulated cells are thrust out into the blood; the corpuscles of the blood increase in the same ratio as the bone marrow (Barcroft, 1935). The increase in the reticulated red cells of the blood shows evidence of new blood cell formation.

Anoxia also effects white blood cells. In rabbits, rats, cavies and cats (Campbell, 1937a, 1937b) white blood cells increase. Stammers (1933) reports a 14 per cent rise of lymphocytes after examining 171 healthy young Europeans who live 5759 feet above sea level. However, he attributes this to the high degree of ultra violet radiation rather than oxygen lack. Rabbits exposed to oxygen deficient air show a decrease in the number of lymphocytes (Elias and Kaunitz, 1933).

Rabbits develop leucocytosis (Elias and Kaunitz, 1933),
Stimulating Effect of Reduced Blood Oxygen Concentration Upon Red Bone Marrow

Changes on the left tend to initiate an automatic adjustment in the opposite direction.

(Carlson and Johnson, 1941)

- Decreased $O_2$ in Air Breathed
- Decreased $O_2$ in Blood
- Increased $O_2$ in Blood
- Decreased Red Count (Anemia)
- Increased Red Cell Count
- Increased Red Cell Destruction
- Increased Red Cell Protection

Chemical stimulation of red bone marrow
as do rats, a condition followed by a persistent leukopenia in the latter case (Meyer, Seevers and Beatty, 1935). Meyer et al. suggest that the temporary leucocytosis following the reduced oxygen tension is due mostly to the emptying of reservoirs of cells such as the spleen and bone marrow, whereas the subsequent leukopenia results from a functional depression of bone marrow and lymph nodes which prevents the delivery of leukocytes to the circulating blood.

Breathing air with 10 per cent oxygen in it for one hour causes an increase in total plasma proteins, globulin and non-protein nitrogen, and a decrease in albumin and in the colloidal osmotic pressure of the blood in dogs (Kasugai, 1936). In dogs and humans, there is a rise in the non-protein carbon after short periods of anoxia (Spitz, 1934). In man, the serum calcium is reduced 0.4 per cent approximately under acute anoxemia (Goralewski, 1937). The glutathione of the blood falls 10-12 per cent during anoxia (Binet and Bochet, 1937).

Most interesting is the work of Kempner (1937a) on the effect of low oxygen tension upon the rate of respiration of individual cells. It had been a generally accepted fact that cellular respiration is independent of oxygen tension ever since the early work done by Warburg (1937), on nucleated red blood cells of geese, bacteria and non-nucleated red blood cells of rabbits. Kempner, too, finds that on working with old bacterial cultures, injured nucleated blood cells and non-nucleated human erythrocytes, that there is no difference in
their rates of respiration at normal or reduced oxygen pressure. However, when he performed the same experiments upon young, undamaged cells in their physiological environment (contrary to Warburg's method), he finds a great decrease in respiration at oxygen tension as high as 5 volumes per cent as compared with air (20 volumes per cent of oxygen). His results are the same for erythroblasts, leucemic leucocytes, and red blood cells of fowls and alligators. In the complete absence of oxygen, a great deal of lactic acid is formed. At an oxygen concentration of 3.4 volumes per cent there is no lactic acid formation, in spite of a 60 per cent decrease in respiration. The respiration of goose erythrocytes (Kempner, 1937b) at 3.8 volumes per cent is inhibited by 65 per cent as compared with air. Anoxia, as produced by adding nitrogen to the medium, causes a decrease in the respiration of cells both sensitive and insensitive to the effects of carbon monoxide and cyanide, including lymphatic and myeloid leucocytes.

No work has been done on the determination of the effect of low oxygen upon the level of blood sugar. There have been some investigations upon the relation between oxygen deprivation and low blood sugar produced by insulin injections, however.

Anoxia, which has no effect upon normal rats exposed to it for a long time, causes animals with insulin injections to undergo severe convulsions (Glickman and Gellhorn, 1938 and Kraines and Gellhorn, 1939). The convulsions are not accompa-
nied by further decrease in blood sugar. It was reported that, clinically, it appeared as though the insulin injected animals were suffering from a relative anoxia which was greatly aggrava-
ted when exposed to reduced oxygen tensions. A mild degree of oxygen lack under conditions of low blood sugar gives symp-
toms similar to those obtained at a normal blood sugar level and under extreme anoxia. The investigators (Glickman and Gellhorn, 1938) suggest that low blood sugar interferes with the oxygenation of the central nervous system, that is, that hypoglycemia leads to a deficient oxygen usage by the sensitive nerve cells.

On inhaling a mixture of oxygen and nitrogen containing 6 per cent oxygen, there is only a very slight rise in blood pressure in anesthetized dogs. Insulin injections alone do not cause an appreciable change in blood pressure. However, inhalation of a 6 per cent oxygen mixture together with low blood sugar causes a definite rise in blood pressure (Gellhorn et al., 1938). Kraines and Gellhorn (1939) confirm these investigations; they report that insulin alone does not alter the blood pressure response to 8 per cent oxygen as long as the blood sugar level is high. When the blood sugar is reduced with progressive anoxia, the blood pressure goes up.

Cardiac Tissue

Almost equal to nervous tissue in its sensitivity to anoxia is cardiac tissue. Actually, heart failure from lack of
oxygen does not occur until the oxygen tension of the arterial blood falls to about 30 mm Hg (Bogue, Chang and Gregory, 1938). Then it happens quite suddenly. At first there is a steady impairment of the heart, but oxygen utilization is maintained until the point of severe damage is reached. This was found in the isolated perfused rabbit heart.

The activity of the heart depends upon two variables: a) the alkalinity of the medium, and b) the available sugar supply, normally. During anoxia the isolated hearts of dogs use a great deal of extra carbohydrate (Clark, Gaddie and Stewart, 1933 and Evans, 1939). The breakdown of carbohydrate into lactic acid furnishes the energy for the heart to beat when there is an insufficient supply of oxygen. If the medium is not alkaline at least to the extent of pH 8.0, the lactic acid accumulates and the heart is readily stopped (Evans, 1939). A rise of 0.15 per cent lactic acid in the heart is sufficient to stop it (Clark, Gaddie and Stewart, 1932). Excretions of lactic acid occur freely at a pH 8.5, but are slow at pH 7.0. Gaddie et al. found that the hearts of frogs could maintain their activity and glycolysis under anoxia even though the phosphagen content of the heart falls.

Normally the beating mammalian heart does not liberate lactic acid, but instead uses it in considerable amounts. Cardiac tissue is quite permeable to lactates and has such a rapid recovery process that it can deal with the lactate produced by itself and take in and utilize lactate from the blood
during diastole. Ample oxygen is necessary for this process. If the oxygen supply is restricted, the lactate usage diminishes and is ultimately replaced by lactate production. Falling oxygen tensions five effects on the dog's heart in the following order:

1. Transient increase in usage of lactate and glucose probably due to an increase in the coronary flow.
2. Reduction of oxidation of glucose and sugar.
3. Reduction of oxidation of lactates.
4. Increased glycolysis.

(Bogue, Chang and Gregory, 1938 and Evans, 1939)

It seems evident from the foregoing investigations that during oxygen lack there is an increased usage of carbohydrate and a reduced usage or ultimate formation, of lactic acid.

There is disagreement as to the source of energy for the heart to beat during anoxia. As has been pointed out previously, there are some investigators that believe the energy is derived from the breakdown of carbohydrate into lactic acid. This is the result of work on frogs and dogs under anoxia. Chang (1937) suggests that phosphagen breakdown rather than glycolysis furnishes the energy for the contraction of the heart, since, at asphyxial arrest, the glycogen content is two thirds its normal value, while the phosphagen is only one third its normal value, in the cardiac tissue of rabbits. The phosphagen and the mechanical activity of the heart of the rabbit apparently decrease together, according to these investigations,
under extreme oxygen lack. Later work on the effect of acute anoxia upon the adenosinetriphosphate of the rabbit heart (Chang, 1938) again shows that mechanical activity and phosphagen decrease proportionately. Analysis of the chemical content of the heart after extreme oxygen lack shows that there is: 3/4 of the normal phosphagen, 9/10 of the normal glycogen, and 3/4 of the normal adenosinetriphosphate. Revival of the auricles restores the phosphagen to normal rapidly; the restoration of the adenosinetriphosphate is much slower and less complete.

Thus Chang again finds evidence of the decrease in mechanical activity with a fall in phosphagen content of the heart. Although there is disagreement as to the source of energy for the activity of the heart during anoxia, it is generally agreed that there is a lowering of the phosphagen index during oxygen deprivation (Bogue et al., 1938; Chang, 1937, 1938; Evans, 1939).

Anoxia produced by the admission of cyanide to the perfusion fluid of the dog's heart, was found to have little effect on the glycogen breakdown (Bogue, Yule and Evans, 1939).

Cardiac tissue poisoned with iodoacetic acid forms a favorable system on which to measure low oxygen effect because its mechanical response is abolished by complete oxygen lack in one or two minutes. Under these conditions the mechanical activity of the hearts of frogs is depressed in the following order (Clark and Kingisepp, 1935):

1. Decrease in the amplitude of the ventricular contraction and decrease in the duration of
QRST complex.

2. Decrease in the speed of A-V conduction.

3. Decrease in the sinus frequency.

The glutathione content of the guinea pig heart rises from 25 per cent to 40 per cent during fourteen days of exposure to low oxygen (Santavy, 1939). This evidence has not been challenged, but it has not been confirmed.

To summarize, during anoxia large amounts of carbohydrate are used and lactic acid is being formed instead of being utilized. There is a decrease in the phosphagen content of the heart, too. However, it is not agreed upon whether the energy for the beating of the heart is obtained from the breakdown of carbohydrate or is related to the fall of phosphagen. Mechanical activity is depressed. Glutathione is increased.

Liver and Kidneys

There is no agreement as to the effect of anoxia on the glutathione content of the liver. Binet et al. (1937) find that the glutathione of guinea pig liver rises from 25-40 per cent during fourteen days exposure to low oxygen. Santavy (1937) finds, on the other hand, that dogs kept for two to three hours under reduced oxygen show nearly a constant glutathione content. These conflicting results are probably due to the difference in length of exposure to low oxygen.

When mice were exposed to low oxygen in respiratory chambers and their livers removed, it was found that the liver
metabolism goes down and the accumulation of fat is slower than in animals at normal oxygen tensions (Chevillard, Hamon and Mayer, 1937). The water content of the liver is increased, too. The respiratory quotient of the isolated mouse liver falls with the lowered rate of metabolism (Laser, 1937). Aerobic glycolysis of this tissue is also increased. Laser ascribes the change in metabolism to a change in the enzymatic activity of the liver under low oxygen pressures.

At oxygen tensions between 15 and 60 mm Hg, i.e., at those oxygen tensions that actually occur under physiological and pathological conditions in the body, the deaminization of amino acids by minced or sliced kidneys is inhibited (Kempner, 1938). This refers particularly to dl-alanine, dl-valine and dl-leucine. Normally, oxidative deamination is practically the only reaction by which animal organisms carry out the deaminization of amino acids. The site of the deaminization is not only in the liver, but also in the kidney, where the rate of deamination is even markedly greater (e.g., deamination of dl-alanine is five times as great in the kidney as in the liver). No other work has been done along the lines of Kempner's investigations.
The effects of anoxia on the activity and metabolism of protozoa and arbacia eggs.

One celled animals are just as susceptible to the ill effects of anoxia as are higher animals.

In peritrich ciliates all activity of the contractile vacuole and of cilia is rapidly stopped in the presence of pure hydrogen (Kitching, 1939a). On readmission of oxygen there is a very rapid recovery. In the case of Amoeba proteus, pure hydrogen causes the rapid stopping of the contractile vacuole; however, the amoeboid motion continues for a long time, although with a decreasing rate. These effects are also reversible upon the admission of oxygen. The movement of the contractile vacuole and the amoeboid motion of the small rhizopod, Flabellula mira, is stopped in the presence of hydrogen. These effects, too, are reversible in the presence of oxygen (Kitching, 1939a). The limitation of the activity of the cells in these cases may have been caused by inadequate diffusion of oxygen into the cells, or the inability of the cellular respiration system to utilize oxygen at such a low oxygen tension.

The presence of cyanide in the medium, as a means of producing anoxia, gives results similar to those obtained in the hydrogen medium. In the case of cyanide, however, the effect was probably due to the fact that the cyanide combined with an iron containing enzyme, thereby incapacitating the cell respiratory mechanism. This would, of course, keep the cells from taking up any available oxygen.
The majority of investigators agree that paramecia can live for several hours without oxygen at a temperature range of 20 C to 25 C. However, in order to survive and grow, an ample supply of oxygen is necessary. Kitching (1939b) produced anoxia in paramecia with both hydrogen-oxygen mixtures and nitrogen. In both cases there were no effects at first. After a while the speed of swimming decreased and the rate of output by the contractile vacuole lessened. Finally the organism stopped entirely. Kitching observed that after the organisms had ceased their movement, trychocysts were discharged, the anterior end of the body was constricted in some cases; and blisters were formed at the surface of the body followed by cytolysis. On the readmission of oxygen there was a rapid recovery even by those paramecia that had blistered.

Upon inducing oxygen lack in Vorticella nebulifera it has been observed that the pulsations of the vacuoles are slowed and the ciliary motion in the spiral (adoral) is stopped (Moldavskaya, 1937). Anoxia also causes the development of the ciliary ring and its separation from the stalk and finally its development into the free state. Readmission of oxygen restores the activity of the vacuoles and cilia to normal, but the formation of the ciliary ring goes to completion.

It has long been recognized that cell division of fertilized arbacia eggs cannot take place in the complete absence of oxygen or in the presence of moderately high concentrations of respiratory inhibitors such as cyanide or phenylurethane.
Further investigations along this line (Clowes and Krahl, 1940) with oxygen-nitrogen mixtures in various concentrations show that cell division is greatly inhibited when there is 3 per cent oxygen in the medium. The greatest slowing of the development occurs at the prophase stage of mitosis, suggesting that this stage of development is probably the most sensitive to anoxia. At 0.3–0.4 per cent oxygen there is complete inhibition. Harvey (1927), employed the hanging drop method in a modified Engelmann's Chamber to which pure hydrogen was admitted. Observing the eggs under a microscope, she found that complete lack of oxygen gives immediate and reversible cessation of development at all mitotic stages in fertilized Arbacia eggs. This is verified by studies of fixed and stained slides of sea urchin eggs (Clowes and Krahl, 1940).

The use of CO as a respiratory inhibitor to induce anoxia causes an inhibition of cell division and oxygen consumption. KCN inhibits similarly (Clowes and Krahl, 1940). These experiments indicate that sea urchin eggs depend, almost exclusively upon an adequate supply of oxygen as a source of energy for cell division. The only effect on the division of cells appears to be that arising from the decrease in the oxygen consumption of cells.
The effects of anoxia upon the permeability and absorption in animal tissues.

It is difficult to explain the nature of the effects of low oxygen tension upon cell permeability, since authorities do not agree among themselves as to the exact composition and structure of cell membranes. At most, the rates of absorption of various tissues may be measured under the influence of anoxia and their values compared to absorption or permeability under conditions of normal oxygen supply.

Cellular permeability is increased in the cerebral hemispheres as well as in the subcortex of cats under reduced oxygen tension (Spiegel and Spiegel, 1939). They explain this by referring to the boundaries of the cells as surface films rather than cell membranes. Thus, they attribute the increased permeability of the cells to the fact that anoxemia lowers the density of the surface film of the cells.

The experiments of Landis (1928) on the capillaries in the mesentery of frogs show that anoxia greatly increases the permeability of capillary walls. If the capillary walls are exposed for only three minutes, they become damaged and are then permeable to proteins. If the period of anoxia is not too long, normal permeability may be regained on the admission of oxygen. Landis' results are challenged by McMichael and Morris (1936). Their investigations on the capillaries of man show that there is little change in permeability under low oxygen.
This difference may be accounted for by the fact that Landis' experiments involved chronic oxygen lack, while the others maintained only an acute anoxia.

Dealing with a variety of specimens, investigators have not been able to agree upon the effects of low oxygen upon water absorption. Water penetrates arbacia eggs less rapidly under conditions of anoxia than under normal atmospheric pressure, as observed by using a galvanometer to detect changes in the volume of the eggs (Keckwick and Harvey, 1934). In contrast to these results is the work of Hunter (1937) who found that oxygen lack has no effect upon the permeability of fertilized and unfertilized eggs to water. In sea water, however, the eggs undergo a slight, but insignificant, decrease in volume. Hunter found, too, that low oxygen has no effect upon the penetration of water into the red blood cells of chicks.

There is no appreciable effect upon the absorption of distilled water from the intestine of dogs at 15.37 per cent oxygen, but at 13.28 per cent oxygen there is a decrease in absorption (Van Liere, David and Lough, 1936). However, at higher degrees of anoxemia, absorption takes place much more rapidly from the small intestine of the anoxemic animals than the controls. It might be pointed out here that water is not normally found in the intestine at the ileal level, at which level Van Liere et al. made their investigations. It has been shown that distilled water is actually toxic to the lower
ileal epithelium (Dennis, 1940). In fact, it is injurious to any part of the small intestine since it is hypotonic. However, the results of Van Liere were obtained with comparison to controls under normal atmospheric pressure. Therefore, the results may be accepted as reliable.

It is difficult to explain why anoxia has so many contradictory effects upon the water absorption of cells and tissues. These differences may be the result of the variety of tissues used.

The only two investigations on the effect of lack of oxygen on cell permeability to non-electrolytes are in disagreement with each other. Hunter and Harvey (1935), working with Arbacia eggs, claim that ethylene glycol penetrates more rapidly under reduced oxygen tensions than under normal conditions. Hunter (1937) finds that oxygen lack has no effect on the permeability of Arbacia eggs to ethylene glycol. He also claims that the permeability of beef erythrocytes to ethylene glycol, diethylene glycol, thiourea, monacetin, diacetin and malonamide, and that of rat erythrocytes to glycerol is unaffected by anoxia. The penetration of glycerol into beef erythrocytes is slightly decreased under anaerobic conditions, although it is not known why. The decrease, however, is insignificant.

Work on the absorption of inorganic salts under oxygen deficiency has been done mainly by Van Liere and his coworkers on the small intestines of dogs. Their method of investigation
has been to expose a measured loop of intestine in two animals at a time, both of them anesthetized. Into each loop they placed a definitely known quantity of some substance. The intestines were replaced, the wounds closed and one of the two animals subjected to anoxemia in a steel respiratory chamber. After a given time the loops of both dogs were removed and the contents carefully measured. This method was used in the experiment previously mentioned on the effect of oxygen lack on water absorption.

As has been pointed out previously, anoxia increases the absorption of water in the small intestine. However, the absorption of the electrolyte, NaCl, in the small intestine under low oxygen is different. Van Liere and Sleeth (1936) ran tests on 126 animals to determine the effect of oxygen lack on NaCl (0.9 per cent solution) absorption. They found that anoxemia is most effective in decreasing the amount of absorption of NaCl at oxygen percentages of 10.56 and 8.35. Lower percentages of oxygen, 7.03 and 5.78, do not decrease the amount of absorption as much as the above mentioned percentages. There is a significant decrease even at 15.32 per cent oxygen, which is a very mild degree of anoxemia and corresponds to an altitude of about 8000 feet. It is difficult to explain why severe degrees of anoxemia are less effective in reducing the amount of absorption than the more moderate grades of anoxemia. It may be that very low oxygen tensions injure the cells of the intestine and thus render them more
permeable to the passage of the NaCl molecule.

The absorption of the sulfate ion is not affected very much by ranges of anoxia compatible with life in barbitalized dogs. There is only one level at which the absorption of sulfate ions is affected, but that is not very significant (Northrup and Van Liere, 1939). In the presence of sulfate ions, under conditions of low oxygen, NaCl absorption is further depressed than in the above mentioned experiment. (Van Liere and Vaughan, 1940). Moreover, the presence of the sulfate radical distinctly depresses the fluid absorption of the small intestine. This may be due to the non diffusibility of the sulfate ion which enables it to exert an osmotic pressure against tissue fluids, thus tending to hold water in the intestine.

The chloride content and the acidity of the stomachs of dogs go down after the animals are subjected to a partial pressure of oxygen of 63 mm Hg, corresponding to an altitude of 28,000 feet (Sleeth and Van Liere, 1937; and Pickett and Van Liere, 1939). At oxygen percentages of 12.88 and 10.56, corresponding to 444 and 383 mm Hg pressure respectively, the amount of free and combined acids secreted is distinctly depressed. The period of gastric secretion is definitely prolonged. This is to be expected, since anoxemia prolongs the gastric emptying time. Later investigations (Pickett and Van Liere, 1939) show that anoxia produces a steady decline in the total acidity which is significant at 80 mm Hg. The pH of the
gastric juice is not affected until 63 mm Hg; then the pH rises with progressive anoxia. There is a steady fall in the volume of gastric juice secreted as the anoxia becomes more severe, although it is not significant until 80 mm Hg is reached; at that time the secretory cells of the stomach are depressed. The total chlorides are not affected by anoxia as low as 63 mm Hg. This suggests that the chloride is probably being secreted in some other form than HCl, probably as NaCl.

All the experiments in which the acidity was determined show a definite decrease under anoxia. One investigator finds that at certain critical levels of anemic anoxia caused by hemorrhage, gastric acidity decreases (Apperly, 1936). This is confirmed by Alvarez and Vanzant (1939) who finds that a fall in hemoglobin because of anemic anoxia is also followed by a decrease in gastric acidity.

In dealing with urine formation in the perfused kidney of the dog, most investigators agree that anoxia causes oliguria (Van Liere, Parker, Crisler and Hall, 1935; Toth, 1935; Beck, Kempton, and Richards, 1938; Toth, 1937; Toth, 1940). However, Toth (1937) finds polyuria in a few cases. Toth (1935, 1937 and 1940) and Van Liere et al. (1935) show that there are increases in epinephrine of the urine under anoxia along with oliguria. This suggests that low oxygen affects the secretion of the medulla of the adrenal gland, which secretes excess epinephrine that may, in turn, cause a decrease in urine formation. Toth (1937) produced polyuria, instead of oliguria,
in his animals when he cut off the blood supply from the adrenals. His later experiments (1940) suggest that the renal nerve supply rather than the adrenals are necessary for oliguria during anoxia. This is in agreement with the belief of Van Liere et al. (1935). However, Beck, Kempton and Richards (1938) feel that oliguria is caused by a decrease in glomerular filtration during low oxygen.

In perfusion experiments on the kidneys of frogs with both nitrogen and cyanide, Beck and coworkers (1938) found that the permeability of the glomerular membrane increases. Definite traces of albumin were seen in the urine, indicating an increased permeability to proteins of the blood. This agrees entirely with the observations of Starling and Verney (1925) who performed similar experiments on the perfused kidneys of dogs. Observations by workers in the Keil laboratories (Detering, 1926; Hober and Mackuth, 1927; Bruhl, 1928; Ferrari and Hober, 1933) show that urine formation is decreased by the additions of cyanide to the perfusion fluid or by the absence of oxygen from it. The rate of arterial perfusion flow is not correspondingly diminished. This effect is ascribed to the suppression of a secretory process in the glomerular membrane rather than a decrease in glomerular filtration (Beck, 1938). Bruhl (1928) observed the glomerular capillary flow by direct microscopic examination. Beef erythrocytes were added to the perfusion fluid to render the glomerular flow visible. He could see no marked change in the number of glomeruli perfused
and reported his results as confirmatory of the glomerular secretion hypothesis.

It may be concluded that anoxia causes a definite oliguria of the kidneys, although the exact mechanism involved is not agreed upon.

One lone experiment was performed on the proximal tubules of the chick kidneys (Chambers, Beck and Belkin, 1935). Normally, if fragments of the proximal tubules of the chick mesenephros are explanted in a healthy culture, they become converted into blind tubular segments in whose lumina phenol red and other dyes are accumulated. Inert gases, cyanide, hydrogen sulfide and phenylurethane inhibit the accumulation of the phenol red in the tubules.

So little of the work on the relationship between anoxia and cell permeability has been confirmed that it is not wise to draw conclusions as to definite effects. One may say with certainty that low oxygen does exert an influence upon the activity of cells, i.e., decreasing or increasing the permeability and secretions. This may be seen from the results obtained when two independent investigations were carried out to determine the effect of anoxia upon the absorption of non-electrolytes; both differed. Again, the three investigations on the effect of oxygen deprivation upon water absorption showed conflicting results. It is evident that the work already done is a mere scratch on the surface.
Conclusion

The central nervous system is the system most sensitive to the ill affects of anoxia. Its inhibition has far reaching influence, since both the viscera and the periphery are ultimately affected. However, secretory and absorptive functions of various cells and tissues may be affected independently of the nervous system. Furthermore, cells may become inactivated due to harm done to the enzyme systems of the organism or because of drastic upsets in the chemical reactions occurring in cells under normal conditions. It is difficult to define the nature of the various effects of anoxia on specific cells and tissues, because there is so little material available. Most of the investigations thus far have been unsubstantiated by other workers. In many cases, the same problem has been worked on by several people, all of whose results are contradictory. While a great deal of investigation has been carried out upon the effects of oxygen lack on the whole organism, especially with stress upon the respiratory and circulatory systems, comparatively little has been done with other tissue.
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Abstract

Anoxia is a general term denoting oxygen lack regardless of how or where in the body it is produced. There are four general types of anoxia: anoxic anoxia (anoxemia), anemic anoxia, stagnant anoxia and histological anoxia.

In normal oxygenation of tissues, oxygen is given up to the tissues because of a difference in oxygen tension in the capillaries and the tissue fluid, the greater tension being in the capillary. Oxygen can be carried into the cells only by the enzyme, oxidase. With the aid of various enzymes, oxygen is brought to the metabolite in the cell which is oxidized. Injury to any of the respiratory enzymes of the cell causes anoxia due to the inability of the cell to take up available oxygen.

Nervous tissue is extremely sensitive to the effects of oxygen lack. However, a constant supply of oxygen rather than a rich one is necessary for its functioning. Anoxia decreases somatic excitability and increases autonomic excitability, suggesting that somatic centers are more sensitive to oxygen lack than the autonomic centers. The nerve endings in the bowel are, in general, resistant to anoxia. The eye, on the other hand is extremely sensitive and is believed to be a good indicator of the early effects of lack of oxygen upon the central nervous system of mammals. Anoxia causes an increase in respiration, rise in blood pressure and cardioinhibition due to stimulation of the chemoreceptors of the carotid and aortic bodies. The
action is reflex.

In the circulatory system, oxygen lack causes vasodilatation of blood vessels, contraction of the spleen and increased stimulation of bone marrow, and increase of hemoglobin, erythrocytes and reticulocytes. There is an increase in total plasma proteins, globulin, non-protein nitrogen and non-protein carbon in the blood. There is also a decrease in albumin and calcium and glutathione. Oxygen lack decreases the respiration of blood cells only if they are in their physiological surroundings.

During anoxia, large amounts of carbohydrate are used by cardiac tissue and lactic acid is being formed instead of being utilized. The phosphagen content of the heart is decreased. There is no agreement as to the sources of energy for the heart to beat during anoxia. Mechanical activity is depressed.

A mild degree of oxygen lack under conditions of low blood sugar gives symptoms similar to those obtained at a normal blood sugar value and under extreme anoxia.

Liver metabolism decreases and deaminization of amino acids by the kidney is inhibited.

Ciliary movement, amoeboid motion and pulsation of the contractile vacuole are inhibited by anoxia in protozoa. The cell division of arbacia eggs is halted.

Cellular permeability is increased in the cerebral hemispheres of cats and in the capillaries of frogs. There is no agreement as to the effect of anoxia upon the absorption of
water or non-electrolytes. Oxygen lack decreases the absorption of NaCl in the small intestine of dogs. The presence of sulfate ions further depresses the absorption of NaCl. Anoxia causes oliguria in the kidneys.