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OXYGEN PHYSIOLOGY, NORMAL AND ABNORMAL

The Fifth Edsel B. Ford Lecture, 1956

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Oxygen physiology began in the 18th century with the discovery of oxygen and its necessity for the life of animals by Priestley in England and Lavoisier in France. The modern development of the field may be said to begin in the 1890's with the work on blood gases of Christian Bohr and August Krogh in Denmark and J. S. Haldane in England, where Douglas and Barcroft shortly after joined in an epoch of basic contributions. American work in the field was stimulated by Christen Lundsgaard who brought the lore of the Danish school when he came to the Rockefeller Institute for an active period of seven years beginning in 1917. Lundsgaard's demand for a rapid and accurate blood oxygen method was responsible for adapting the old Van Slyke "volumetric" CO_2 apparatus to oxygen determination, from which the present manometric method derived. Lundsgaard's studies of blood oxygen unsaturation in cyanosis and circulatory conditions led in the Rockefeller Hospital to Stadie's initiation of the arterial puncture and the practical application of oxygen therapy. Knowledge of blood oxygen in circulatory conditions has been brilliantly expanded in the past decade by the school of Cournand, Richards and Riley for the general circulation, and of Schmidt and Kety for the brain.

Anoxia. Haldane's early work showed that the brain is especially dependent on a continual supply of oxygen to maintain, not only normal function, but organic existence. As shown by Kety, the adult human brain normally uses about 45 ml. of oxygen per minute. If the brain's oxygen consumption is cut down by 10 per cent one begins to get the first mental signs, a little difficulty in concentrating thought. If the consumption is cut down by 20 per cent there is emotional instability and confusion. As Haldane observed, the effects are identical with those of alcoholic intoxication. If oxygen consumption is cut down by 40 per cent coma ensues. If the brain's blood supply is completely cut off, as by a cuff around the neck, unconsciousness follows in a few seconds, and irreversible damage after for or five minutes. Haldane's statement: "Lack of oxygen not only stops the engine, it wrecks the machinery," has become classic. Cerebral anoxia can be particularly dangerous because it can come on without subjective discomfort. A sudden rise to high altitude, or inspiration of air containing carbon monoxide, causes first disorientation, then loss of consciousness, without warning signs of distress.

Anoxia of degree less than that which causes serious immediate effects can have effects that are cumulative with duration of the anoxia, and may even increase after the anoxia has been relieved, affecting not only the brain, but the heart, the kidneys, and the capillaries. Fatal shock has been observed developing in aviators after their return to normal atmosphere.

Next to the brain, the kidneys appear to be the organs most likely to suffer cellular damage from anoxia. Renal ischemia such as is caused by a few hours of shock from

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decreased circulating blood volume can damage the tubular cells, casusing renal failure which may require weeks for recovery, or may progress to a fatal result.

Circulatory Adjustments and Oxygen Supply. From the work of the schools of Cournand, Kety, and Homer Smith, and others, one may take 5.3 liters per minute as the approximate average output of the adult human heart at rest, 0.7 liter going to the brain, 1.1 liter to the kidneys, and 3.5 liters to the other tissues. With activity the blood supply to the muscles, skin, and viscera can change greatly; e.g. work can multiply many times the blood flow through the muscles, and Barcroft reported a 50-fold increase in the blood flow of the arm caused by heat. Conversely the muscles and skin can tolerate reduced blood flow for some time. But the brain and kidneys appear to require, and under nearly all conditions of normal body activity, to receive a nearly constant supply of blood and oxygen. It is the task of the lungs and circulation to supply to the working muscles, the active gastrointestinal system, to the skin under conditions requiring accelerated heat removal, the increased supplies of blood and oxygen demanded by these organs, and at the same time maintain the regular supply to the brain and kidneys. Under stress the oxygen requirements of the other organs are met partly by increasing the output of the heart, partly by increasing the proportion of oxygen extracted from the blood that perfuses them. When the heart is weakened the increase in its output is limited, and the amount of activity that can be tolerated is diminished. If the demands of the muscles for work, or of the skin for heat removal, become imperious, the supply to the brain may be in part surrendered, with the results of cerebral anoxia. This can even occur in a normal man forced to great physical exertion on a hot, humid day, with resultant "heat exhaustion," the cerebral effects of which may go as far as coma. If the heart is weakened by disease or age, the tolerance to exertion or heat is decreased.

Types of Anoxia. Barcroft in 1932 divided anoxias into four different types according to their causes. With slight modification this classification holds today: (1) *Arterial anoxia,* in which the oxygen saturation of the arterial blood falls below the normal 98 per cent, because the oxygen concentration in the air breathed is low, or mechanical conditions in the lungs prevent free access of air to the blood, or a right-to-left shunt of blood in the heart-lung area mixes venous with arterial blood. (2) *Anemic anoxia,* caused by a lack of hemoglobin to carry oxygen, or a loss of ability to carry it, as in carbon monoxide poisoning or methemoglobinemia. (3) *Stagnant anoxia,* in which the rate of blood flow through the tissues is slowed, as in decompensated heart failure, peripheral arterial disease, or vascular constriction. (4) *Histotoxic anoxia,* in which tissues are poisoned, as by cyanide, so that they cannot use to a normal extent the oxygen that is brought to them. There is evidence that alcohol and some of the other narcotics act thus on the brain tissue. One could add *high requirement anoxia,* in which the metabolic requirement for oxygen is so increased that it cannot be met even by the acceleration provided by normal lungs, heart, and vessels. Such is the condition in the muscles of a sprinter who develops lactic acid acidosis.

In Figure 1, which is developed from a design of Lundsgaard's, are represented some of the relations of arterial and mixed venous blood oxygen and hemoglobin that are encountered in some normal and pathological conditions. In considering them it should be noted that the oxygen tension of the tissues is most nearly indicated by

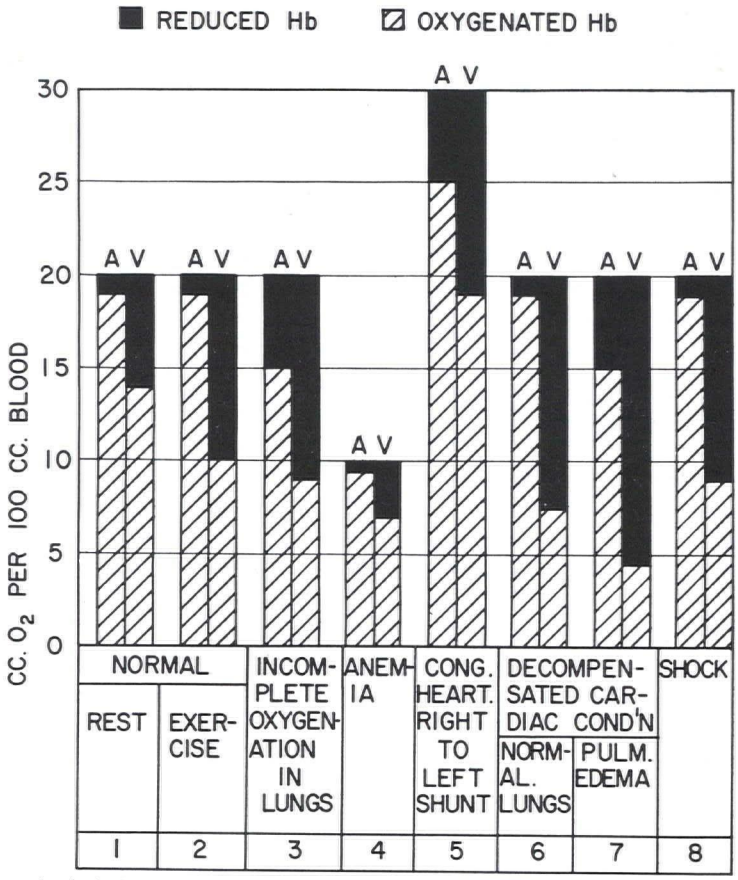

Figure 1. A design of Lundsgaard's representing some relations of arterial and mixed venous blood oxygen, and hemoglobin.

the *oxygen tension of the venous* blood, and that the latter depends on the *proportion* of venous hemoglobin that is oxygenated. When 50 per cent of the hemoglobin is oxygenated, the oxygen tension is approximately 30 millimeters of mercury, and this, in the mixed venous blood, appears to be about the minimum that may be considered within the optimal physiological range. Column 1 shows normal resting conditions, with 98 per cent of the arterial and 70 per cent of the venous blood oxygenated. Column 2 shows the normal effects of exercise. Respiration is so increased that the arterial blood is still 98 per cent oxygenated. The heart output is increased enough so that oxygenation of the venous hemoglobin does not fall below 50 per cent. Column 3 shows a condition of arterial anoxia. When the tissues extract their allowance of oxygen, even at rest the venous hemoglobin becomes half deoxygenated, and there is no margin available for exertion. Column 4 illustrates conditions in anemia. Circulation may be accelerated so that the venous blood remains 70 per cent oxygenated at rest, as in the case illustrated, but if exercise caused extraction of as much oxygen as in column 2, the venous blood would be completely deoxygenated. Only limited exertion is possible. Column 5 indicates conditions that may be met in a congenital heart case, with a shunt from right heart to left. In response to the chronic anoxia a compensatory

polycythemia has developed. In consequence, although a normal 6 volumes per cent of oxygen is extracted from the blood, the venous hemoglobin is still about 70 per cent oxygenated, and the tissues enjoy normal oxygen tension, despite the fact that the amount of reduced hemoglobin present causes cyanosis. (In more severe cases tissue anoxia *is* present.) Colum 6 shows the effects of stagnant anoxia from retarded cardiac output. Column 7 shows the added anoxia that is suffered when pulmonary edema adds arterial anoxia to the stagnant anoxia. The last column shows the effect of shock and retarded circulation on the mixed venous blood. In all the conditions, the degree of the anoxia can vary in the different tissues, and be influenced by changes in the blood flow distribution to different sites. But whenever there is a low oxygen tension in the mixed venous blood, the organism can maintain local oxygen tension, in the brain for example, only at the cost of restriction elsewhere.

Cyanosis. Lundsgaard studied the causes of cyanosis and came to the conclusion that when the mean capillary concentration of reduced hemoglobin, estimated as midway between arterial and venous, exceeds about 5 grams per 100 ml. of blood (an oxygen unsaturation of 6.6 volumes per cent), cyanosis is likely to become apparent. Referring to Figure 1, we can see the significance of this estimate in the conditions exemplified if we take the venous unsaturations as representing blood from the skin. The mean capillary unsaturation value as estimated by Lundsgaard is indicated by the midpoint between the two black columns in each of the eight examples, the distance measured from the top indicating the volumes per cent oxygen unsaturation. In the normal exercising subject it is 5.5 volumes per cent, somewhat short of the cyanotic threshold. In column 3, representing arterial anoxia, the mean unsaturation is 8 volumes per cent, and cyanosis may be expected. In column 4, representing anemia, even complete utilization of the oxygen, with none left in the venous blood, would not produce enough reduced hemoglobin to show as cyanosis. In anemia it is evident that even severest anoxia is not likely to reveal itself by cyanosis. By contrast, in column 5, showing arterial anoxia and polycythemia, there is 8 volumes per cent mean unsaturation, well over the cyanotic level. Nevertheless, because of the great concentration of hemoglobin, the venous blood is 64 per cent oxygenated, and the tissue oxygen tension indicated is such that no embarrassment from low oxygen activity in the cells is to be expected. Such a subject, despite marked cyanosis, may have no symptoms of anoxia, unless the arterial anoxia is greater than in this example. In both of the decompensated cardiac cases mean capillary unsaturation is well into the cyanotic range, the greater being in the case in which pulmonary edema adds arterial anoxia to stagnant anoxia.

Controlled Oxygen Therapy. A year after Lundsgaard came and started his work the 1918 influenza epidemic swept the world. Many cases developed bronchopneumonia. Cyanosis was frequent, and a grave prognostic sign. It was uncertain whether the cyanosis was due to a stagnant anoxia, from decreased heart output, or was due to arterial anoxia, from incomplete oxygenation of the blood in the lungs. Dr. W. C. Stadie had charge of part of the pneumonia patients in the Rockefeller Hospital and decided to apply Lundsgaard's criteria to find the cause of the cyanosis. The only way to know certainly whether the anoxia was arterial was to analyze arterial blood, and the arterial puncture was not at that time a recognized clinical procedure. A technique for it had been demonstrated in 1912 in Germany by Hürter, but had not been applied

by others. Stadie experimented with the technique, proved it safe, and proceeded to use it in the study of his patients. Stadie was an engineer before he went into medicine, and was able to design a chamber that was arranged for regulation of temperature and humidity as well as oxygen. So far as I know, it was the first such oxygen chamber that was used clinically.

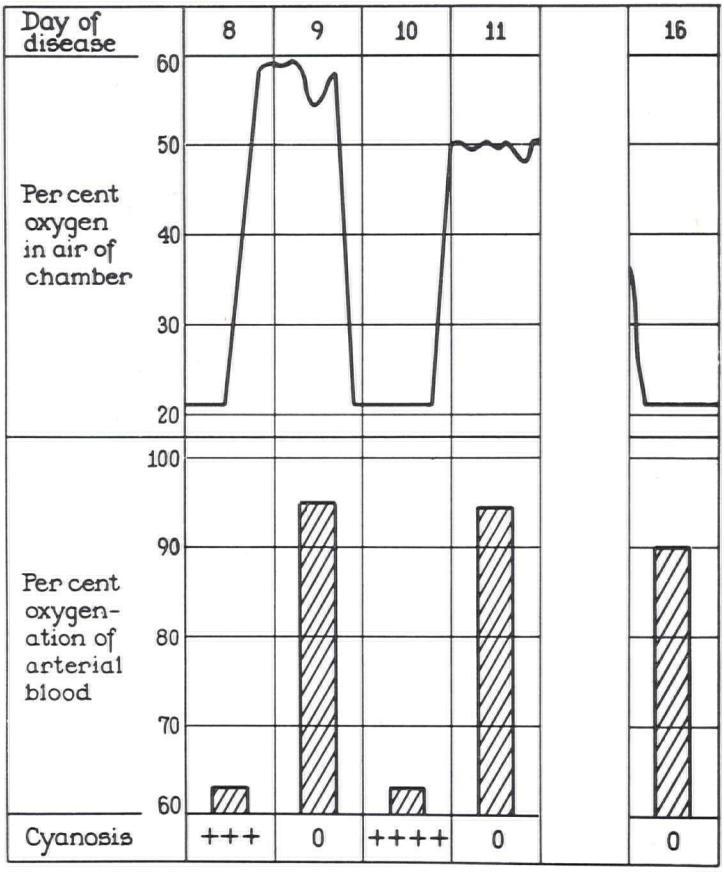

Figure 2. Results with a typical case from Stadie's series.

Figure 2 shows results with a typical case from Stadie's series. It was a patient with intense cyanosis, with a little over 60 per cent arterial oxygenation. When the patient was placed in an atmosphere with 60 per cent of oxygen the arterial saturation went up to 95 per cent. When the patient was returned to ordinary air the arterial unsaturation and the cyanosis returned. On return to the chamber oxygenation was restored and cyanosis disappeared. Eventually the patient recovered. The clinical effects of the oxygen treatment were that delirium disappeared, heart rate went down, respiration became eased. There was no indication that the course of the infection was altered, and Stadie made this clear in his publication, but the stress conditions under which the patient labored were eased. The degree of arterial anoxia that the patient showed in atmospheric air was such as would be caused by an altitude of about 20,000 feet, enough to incapacitate many normal men.

Stadie's work may be fairly said to mark the start of effective systematic oxygen therapy. He laid down the principles of both technique and control. His results were quickly applied in other clinics, and were expanded so rapidly that few of those who now use oxygen therapy as a routine procedure realize the debt that they and their patients owe to Stadie, and, farther back, to Lundsgaard, Haldane, Barcroft, and Bohr.

With the decrease in pneumonia achieved by antibiotics, and with the increased knowledge of blood oxygen in circulatory conditions contributed by Lundsgaard, by Cournand and Richards, Robert Levy, Alvin Barach and others, the application of oxygen therapy has shifted largely to cardiac failure, shock, and other circulatory and pulmonary conditions, the indications and precautions required for oxygen administration have been ascertained, and oxygen administration, more or less adequately controlled by blood oxygen analyses, has become standard procedure.