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THE THERAPEUTIC USE OF OXYGEN.[1]

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Oxygen has been used as an inhalant occasionally for many years, but its efficacy has always been doubted by many, chiefly on the theoretical grounds that as the oxyhemoglobin of the blood is already nearly saturated, no increase in this can be obtained by the mere raising of the percentage of oxygen in the inhaled air. A further objection has been urged that the oxygen may act as an irritant to the respiratory passages. It may be as well to dispose of this objection at once. It is quite true that if animals be placed for a short time in an atmosphere which contains three atmosphere pressures of oxygen they soon contract pneumonia, and, further, Lorrain Smith has shown that this also occurs if animals are kept for several days in an atmosphere of pure oxygen; but it has also been shown that an atmosphere of pure oxygen can be breathed for

[1] Read before the Academy of Medicine, Toronto, February, 1920.

many hours without any evil effects, and also that, an atmosphere containing under 70 per cent. of oxygen can be breathed with impunity for any length of time.[2] Thus we need have no fear that in giving inhalations of oxygen for ten to fifteen minutes at a time we are running any danger of causing irritation of the air passages.

In recent years much work has been done on oxygen by such men as Haldane and Leonard Hill on the physiological side, and clinically its value has been greatly enhanced by the experience of the War. In the acute respiratory inflammations produced by enemy gas, nothing proved so useful in giving relief as did oxygen. Lately, Dr. Meltzer, of the Rockefeller Institute, has written strongly urging its value in pneumonia. Using a special apparatus, which I will presently demonstrate, he has shown that such cases may not only be symptomatically relieved, but that life may be saved in some apparently hopeless instances.

Looking first of all at the physiological side of the question, it is undoubtedly true that when a healthy individual is breathing quietly the percentage of oxygen in ordinary air (about 20 per cent.) is not only enough to sufficiently saturate his hemoglobin and to supply the needed partial oxygen pressure in his blood plasma (which is about one-fortieth of that of the hemoglobin), but the percentage of oxygen in the inhaled air may be reduced to perhaps 14 per cent. without causing any distress to the patient. In other words, the atmosphere contains a higher percentage of oxygen than is required for the needs of the healthy resting individual. But let that individual exert himself, and soon he will become breathless, and then it is found that an increasing of the oxygen content of the air will help him. This has been abundantly proved by Leonard Hill and others, who have shown that a man can do more physical work without distress if he is breathing an atmosphere artificially enriched with oxygen than if he is depending upon the ordinary air. Evidently the difference between the 14 per cent., which is all the oxygen that a man at rest requires, and the 20 per cent. of the ordinary air is, as Meltzer puts it, a "factor of safety," and while this factor of safety is sufficient for meeting the increased demands of ordinary exertion, it is not enough for emergencies. A man suffering from some interference with his respiration may be likened to the healthy one undergoing extra exertion.

Further, at high altitudes the partial pressure of oxygen may be less than that of an atmosphere containing only perhaps 14 per cent. of oxygen, and here there is no margin of safety, and the least exertion may bring on symptoms of want of oxygen (often very suddenly), and, of course, if a still higher altitude is attained, as is often done by airmen, then these symptoms will come on without any exertion.

[2] Flack and Hill: Text-book of Physiology, p. 304.

Again, it has been found that at altitudes of 6000 feet and over cases of pneumonia do very badly,[3] this factor of safety being now missing. Haldane says here: "Even in ordinary cases of croupous pneumonia the alveolar oxygen pressure may be a matter of decisive importance. This is clearly shown by the fact that these pneumonias do very badly at high altitudes. At Cripple Creek (altitude, 10,000 feet), in the Rocky Mountains I found that this was so well recognized that all cases of pneumonia were put on the train and sent down to the prairie level."[4]

Oxygen is very essential to the living tissues. As a leading writer in the *British Medical Journal* says, "A man may go for weeks without food, for days without water, but for seconds without oxygen.[5]

Anoxemia is the term applied by Haldane to "the condition when the rate of supply of oxygen is insufficient for the normal carrying on of life."[6] The causes of it are four: (1) Defective saturation of the arterial blood with oxygen; (2) slowing of the circulation; (3) defective proportion of available hemoglobin in the blood; (4) an alteration of the dissociation curve of the oxyhemoglobin, so that this gives off its oxygen less easily than usual.

Most of these causes are evident. For example, any decrease in the oxygen pressure in the inspired air, or any interference with the passage of air to the blood from outside, will produce a defective saturation of the arterial blood with oxygen, as will also any increased using up of the arterial oxygen if a new supply be not immediately available.

Slowing of the circulation will tend to anoxemia both by allowing the blood to dwell too long in contact with the tissues and also by delaying its return to the lungs for recharging.

Anemia means a want of hemoglobin in the blood, and poisoning with carbonic oxide gas with nitrites and with arseniuretted hydrogen will prevent the carrying of oxygen by the hemoglobin.

The alteration of the dissociation curve of the oxyhemoglobin is a less evident cause of anoxemia. Bohr, of Copenhagen, showed that if the carbonic acid in the blood be lowered the hemoglobin tends to cling to its contained oxygen, and thus the peculiar condition may exist of an anoxemia with the hemoglobin laden with oxygen which it will not part with.

As regards the relation of anoxemia to cyanosis it may be said that cyanosis always means anoxemia (the hemoglobin being more or less in the form of reduced rather than oxyhemoglobin); but while anoxemia is generally accompanied by cyanosis, this is not necessarily the case: for example, in carbonic-oxide poisoning the blood is cherry red, and yet the patient may die of want of oxygen. Again, when the carbonic acid is deficient, the tissues may be suffering from

[3] Sewall, Henry: Forchheimer's Therapeutics, vol. i, p. 281.
[4] British Med. Jour., February 10, 1917, p. 182.
[5] Ibid., July 19, 1919, p. 81. [6] Ibid., p. 65.

anoxemia, and yet the blood may be red with hemoglobin, which will not part with its oxygen (according to Bohr's law) because of the lowness of the CO_2.

Respiration depends upon two main factors: (1) the presence of sufficient CO_2 in the blood and (2) a want of oxygen. Normally the CO_2 in the alveolar air of the lungs is about 5.6 per cent. of this air, and the least rise in this percentage causes such a stimulation of respiration that the percentage is quickly reduced. On the other hand a slight fall causes the condition of apnea, and then in consequence the percentage quickly rises again. The CO_2 acts through the blood by stimulating the respiratory center.

The effects of fluctuations in the percentage of oxygen in the alveolar air are not nearly so great. Want of oxygen does cause increased breathing, but only to a slight extent. It is possible for a person to be blue from want of oxygen and yet have no increase in respiration if the CO_2 be lower than it should be. But the respiratory center consists of cells which require oxygen for their proper function, just as do all the cells of the body, and when the oxygen in the inspired air is sufficiently reduced the respiration becomes weak and then fails. As Haldane says, "One of the most important effects of prolonged or extreme anoxemia is a temporary partial failure of the respiratory center, so that oxygen or even artificial respiration may be required for many hours."[1]

I have seen this fact beautifully demonstrated by Professor Macleod in the physiological department of our University, where the tracing of the respiratory movements of an animal deprived of oxygen shows gradual failure which quickly disappears when oxygen is again administered.

It is well to remember that after all it is the amount of oxygen in the blood plasma that really counts. Usually this is only about one-fortieth as much as is contained in the hemoglobin, but as it is used up in the tissues it is constantly replaced from the red cells. Normally, 100 c.c. of plasma contains only about 0.35 c.c. of oxygen in solution, the balance of the oxygen in the blood being combined with the hemoglobin; but it is possible by increasing the oxygen in the inspired air sufficiently to raise the oxygen in solution in the plasma to nearly 3 c.c. per 100 c.c. For example, if the oxygen in the alveolar air be raised to 36.4 per cent., that in the plasma will stand at 0.945 per cent., and if the alveolar oxygen be 86.7 per cent. that in the plasma will be 2.26 per cent. This is always assuming that the pulmonary epithelium is passive. Thus it is possible to increase the partial oxygen pressure in the plasma some seven times by merely raising the percentage of oxygen in the inspired air. After all, the red cells are merely carriers, and it is the oxygen in the plasma that directly feeds the tissues. "One well-known proof

[1] British Med. Jour., July 19, 1919, p. 69.

of this consists in replacing the blood in a frog with physiological saline solution and then subjecting the frog with the saline in its bloodvessels to an atmosphere of pure oxygen, when it will be found that the animal continues to absorb the normal amount of oxygen and exhale the normal amount of CO_2. It respires normally without any blood in the bloodvessels."[8] The plasma, like travellers during a strike of railway porters, may to a certain extent do its own carrying.

The effect of anoxemia on the vital tissues is drastic. If the oxygen pressure be low enough then these tissues quickly die; but short of this they may be fatally damaged, as is seen when after CO poisoning an individual may die, although all the CO has again been replaced with oxygen. It is thus important to remember that anoxemia, which clinically is usually shown by cyanosis, is a damaging condition, especially to the nervous and circulatory tissues, and hence should be relieved as quickly as possible, not only for the immediate relief given but also for the sake of the future life and health of these tissues. It has been recently pointed out by Meakins, Priestly and Haldane[9] that in many cases in which the respiration is shallow but rapid the patient is insufficiently ventilating his lungs, although breathing a great deal. Here a vicious circle is liable to be established, the anoxemia making the breathing shallow though rapid and the shallow breathing increasing the anoxemia. Rapid breathing often denotes an insufficient breathing just as a rapid heart may mean a weak heart. Cheyne-Stokes' breathing is a sign of a failing respiratory center and may usually be at least temporarily removed by inhalations of oxygen.

Thus from a clinical point of view, whenever a patient is cyanosed and usually whenever he is breathing very rapidly he is more or less in a state of anoxemia, and we should try to relieve this by increasing the percentage of oxygen in the air that he breathes. Haldane says, "Cyanosis may always be taken as an indication that oxygen inhalation should be considered." There are, of course, two kinds of cyanosis: (1) The leaden color of the skin often seen in acute respiratory conditions, when the oxyhemoglobin is reduced, and yet the veins are not overfull, and (2) the blue color of the mucous membranes, in which the veins are distended with this reduced blood. In this latter type venesection is often called for, followed, if necessary, by oxygen:

Methods of Giving Oxygen by Inhalation. I may say here in parenthesis that oxygen has been administered subcutaneously, intravenously and into the cavities of the body, but we are only now dealing with its use as an inhalant. Perhaps the commonest way of giving oxygen is to hold a funnel connected with the oxygen cylinder near to the face of the patient. This is a most unsatisfactory

[8] Macleod's Physiology, p. 378.

[9] Jour. Physiol., 1919, liii, 433.

way and scarcely deserves to be considered as oxygen administration at all. Meltzer has shown that it is not thus possible to raise the percentage of oxygen in the inhaled air by more than 2 per cent. Further, in a patient already short of breath the mere holding of a funnel close to his mouth and nose gives him a sensation of smothering, and he will often try in his agony to remove the apparatus. I have not used the Haldane apparatus, but it involves the placing of a mask over the patient's face, and hence has this objection, and Haldane himself says that the patient may try to remove it. The same objection applies to the apparatus of Leonard Hill. A much better method than this, and the one that we used most extensively overseas, was the giving of the oxygen through a soft rubber tube inserted into one nostril and held in position by a strip of strapping. This is a wasteful way of giving the gas, but very efficient, and the patient does not object. Its efficacy can be greatly increased if an attendant rhythmically closes the opposite nostril during each inspiration.[10]

A third way of giving oxygen is by the use of the oxygen chamber. I saw this method last year at Cambridge, where Dr. Barcroft and his assistants were experimenting with it. They had three chambers in use. These were made specially for the treatment of late gassed cases, but as the Armistice had come before many soldier patients had been treated they were continuing the work on other conditions. The oxygen content of the atmosphere in the chambers was maintained at 40 to 50 per cent., any excess of CO_2 and moisture being removed by suitable agents. The patients were kept in the chambers from 5 P.M. until 10 A.M. next day for five consecutive days. Great improvement in their condition was evidenced by the removal of the nocturnal dyspnea, from which they nearly all suffered, by a greater capacity for physical work during the day and by the removal of the polycythemia, which was usually present. Several British hospitals have had such oxygen chambers erected as part of their equipment, notably at Guy's and at Stoke-on-Trent, and hope is held that many patients will be much benefited by their use. I would like to see one in Toronto.

The last method that I will describe is that of Dr. Meltzer, of the Rockefeller Institute. The apparatus consists of a hollow tongue depressor which is placed in the patient's mouth and is connected with a gas bag filled from an oxygen cylinder. A valve is so placed that during inspiration the oxygen under pressure from the elastic walls of the bag enters the patient's mouth, while during expiration the oxygen flow is checked and a large opening appears near the valve through which the patient exhales. This valve is worked rhythmi-

[10] Using this method with Professor Macleod, we found that his alveolar oxygen was raised to over 20 per cent. when the tube was in one nostril and the other nostril left open, while when the other nostril was rhythmically closed during each inspiration the oxygen in the expired air rose to 59.9 per cent.

cally by the thumb of the operator. By this arrangement the oxygen enters the air-passages under pressure during inspiration, while during expiration no resistance to the outflow of air occurs. Meltzer says[11] that Dr. A. L. Meyer, of the Rockefeller Institute, found that after he had been thus insufflated for eight minutes his expired air consisted of nearly pure oxygen, the nitrogen of the atmosphere being displaced by this gas. Professor Macleod and I tried this on him, and the analysis of his alveolar air after nine minutes' insufflation showed a percentage of oxygen of 34.6 instead of the normal of 16.5, and when we repeated the experiment, with the nose clamped so that he breathed entirely through the apparatus, the percentage of oxygen in the expired air rose to 86.7 per cent., which practically confirms Dr. Meyer's findings. Now, as before stated, a rise of the oxygen pressure in the alveolar air to 36.4 per cent. means a corresponding rise in the oxygen in the plasma to 0.945 per cent., and if the oxygen in the alveolar air stands at 86.7 then that in the plasma will be 2–26, or seven times the normal. The hemoglobin in a healthy man is already nearly saturated with oxygen and will, hence, not take up little more when it is offered to it through the raising of the percentage in the alveolar air. In fact, as already said, the inhalation of oxygen by the resting normal individual produces no results. The pulse-rate, respiration and blood-pressure remain unaltered and the individual has no subjective sensations. But in anoxemia the hemoglobin is not saturated, and in such cases we cannot only raise the oxygen percentage in the blood plasma, but also in the red blood cells, and hence the cyanosis tends to disappear.

Coming now to actual experience in the therapeutic use of oxygen I think that if it be properly given there is no doubt of its value in suitable cases. I say properly given, for if the administration consists in merely holding a funnel connected with the oxygen tank in front of the patient's face then the results will naturally be *nil*. As already said, in this way one cannot raise the oxygen in the alveolar air by more than 2 per cent., and, further, the patient probably objects to the apparatus, which interferes with his normal breathing. When the oxygen is given by the tube in a nostril great relief can usually be given. During the epidemic of influenza and pneumonia in England last year I frequently saw military patients who were breathing badly and cyanosed (even although being treated in the open air) improve visibly in a few minutes under this form of administration. Not only does the cyanosis lessen or disappear and the breathing tend to become slower and deeper, but again and again have I heard the patients express their great satisfaction at the relief given, and in such a definite disease as pneumonia the subjective improvement is of much significance and value. In some cases the cyanosis

[11] The Therapeutic Value of Oral Rhythmic Insufflation of Oxygen, Jour. Am. Med. Assn., October 6, 1917.

is relieved and yet the breathing remains rapid, while in others the opposite is the case; but in most instances the cyanosis is lessened and the respiration slows. Thus in a patient insufflated recently by the Meltzer method the respiration fell from 32 to 18 and the slight cyanosis from which he suffered remained practically unaltered. Professor Hoover has called attention to the frequent dissociation of the anoxemia and cyanosis,[12] but it would serve no useful purpose here to go into details in regard to it. If the pneumonic patient is having much pleuritic pain he will often say that the oxygen has relieved it. I presume that the slowing of the breathing accounts for this.

It may be objected that oxygen insufflation is only symptomatic treatment and that the patient will soon relapse, but very often he may not do so for hours or not at all, and the treatment can always be repeated as required. As Haldane says: "It may be argued that such measures as the administration of oxygen are at the best only palliative, and of no use, since they do not remove the cause of the pathological conditions. As a physiologist I cannot agree with this reasoning. The living body is no machine, but constantly tending to maintain or to revert to the normal, and the respite afforded by such measures as the temporary administration of oxygen is not wasted but utilized for recuperation." It is pleasant to read such belief in the *vis medicatrix naturæ* from such an authority. Meltzer thinks that many patients have the power of storing oxygen in their tissues. This is not, I believe, accepted by physiologists, but the fact remains that the improvement after oxygen insufflation is usually very persistent.

In conclusion, it may be urged that oxygen should be employed in all serious cases of anoxemia and that its administration should not be delayed and only used as a *dernier ressort*, but should be employed early, before the vital tissues have been much damaged by the want of oxygen.

Conclusions. 1. Oxygen is of value whenever a state of anoxemia exists. This is universally recognized in cases of mountain sickness and sickness from high flying, and in poisoning by CO, nitrites and arseniuretted hydrogen and also in the effects of enemy gas.

2. For the same reasons oxygen should be tried in all cases of cyanosis, and also in acute respiratory conditions, such as pneumonia, when anoxemia threatens.

3. The ordinary method of giving oxygen by holding a funnel connected with the oxygen cylinder near the face of the patient is practically useless.

4. A better method than this is to give the gas through a rubber tube inserted into one nostril, and this may be made more effectual if the opposite nostril be rhythmically compressed during inspiration, the mouth, of course, being kept closed.

[12] Jour. Am. Med. Assn., September 14, 1918, p. 880.

5. The oxygen chamber is a very effectual way of giving oxygen, especially in chronic cases, but it involves much expense and care.

6. An extremely useful and effectual appliance for the administration of oxygen is Meltzer's apparatus for oral insufflation.

NOTE.—In the *British Medical Journal* March 6, 1920, Dr. J. C. Meakins shows that the arterial blood of the normal individual is nearly 5 per cent. "undersaturated" with oxygen, while in pneumonia the "undersaturation" may amount to nearly 18 per cent. By giving oxygen with the Haldane apparatus he was able to reduce the degree of undersaturation in the normal by one-half and in the pneumonic individual to just over 3 per cent. In other words, by the use of the method he increased the oxygen content of the blood of the cyanosed pneumonic person to above that of the normal individual. No better evidence than this could be needed of the value of oxygen inhalation in anoxemia.

A CASE OF SPLENOMEGALY WITH POLYMORPHONUCLEAR NEUTROPHIL HYPERLEUKOCYTOSIS.

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IN the November number, 1919, of this JOURNAL, p. 618, Dr. H. Z. Giffin, of the Mayo Clinic, presented a case of "Persistent Eosinophilia with Hyperleukocytosis and Splenomegaly." As soon as this article appeared I immediately recalled a patient we had treated with curiously corresponding findings: a very large spleen; a very high leukocyte count markedly increasing after splenectomy; a gradual decrease in number thereafter, with marked constitutional improvement. Comparing the two cases the most striking difference appeared in the type of the leukocytes: Giffen's case presented marked and persistent eosinophilia; in our case there was an overwhelming preponderance of mature polymorphonuclear neutrophils. It is suggested to the reader that Giffin's article be reviewed in order to compare the two reports. His thorough search of the literature dealt largely with eosinophil leukocyte increase. It is notable, however, that he found in a thorough search of the literature little at all comparable with his case. I wish to present the following data, acknowledging that I have not consulted the Surgeon-General's Library nor made a thorough review of the literature; but that portion immediately available has shown nothing corresponding whatever except Giffin's report.

CASE HISTORY.—C. D., aged fifty-eight years; female; married; two daughters living and well. She was first seen November 21, 1917.

Family History. Negative.