CERTAIN ASPECTS OF BIOLOGICAL OXIDATION*

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The subject of oxidation presents one of the most fascinating themes in the entire domain of chemistry. The various views which have been held regarding the nature of combustion and oxidation have always exercised a profound influence on chemical thought and on biological science and medicine. Modern views regarding the nature of oxidation date from the work of Lavoisier, who observed that, in the process of oxidation, oxygen adds itself to the substance oxidized, and that the resulting one or more products weigh more than the original material by exactly the weight of oxygen required to effect the oxidation.

It is not within the scope of this lecture to recount the views which have been held regarding the mechanism of oxidation in general. It would also be quite futile to review the whole subject of vital oxidation in the time at our disposal. I shall therefore confine my remarks to a small part of the field in which I have been particularly interested for several years.

The subject of vital oxidation may be divided into the following phases:

1. The mechanism by which oxidative processes are brought about in living material.
2. The nature of the substances oxidized by living organisms.
3. The relation between oxidation within the body and the energy requirements of the organism.
4. The relation of oxidative processes to other chemical processes in the body.
5. The effect of various substances and of various conditions on vital oxidation.
6. The relation of vital oxidation to functional activity.

Notwithstanding the great interest connected with the first four phases of oxidation here enumerated, I shall have very little to say regarding them except as they bear directly on the last two phases.

It was recognized by Lavoisier that oxidation is constantly occurring in the body, and it was surmised that the body derives its heat from oxidation. Ever since the establishment of the principle of

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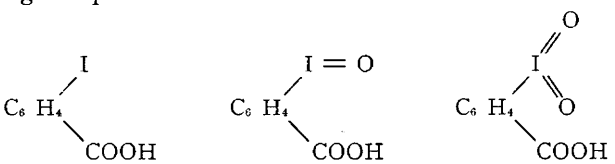
the conservation of energy, the body has been regarded as an engine which converts the latent chemical energy of foodstuffs by oxidation into heat, mechanical work and all the manifestations of life. Oxidation within the body was looked on for many years as quite similar to combustion outside the body. It is perfectly evident, however, that great differences exist between oxidation within and without the organism. Thus proteins, carbohydrates and fats are oxidized within the body at a temperature of 37° C., whereas it requires a far higher temperature to oxidize these substances in the air. In the attempts to explain this fact, the group of oxidizing enzymes, or oxidases, was discovered. Much work has been done to indicate the great differences between oxidation within and without the body. It has been shown that many substances which are readily oxidized outside the body are either very incompletely oxidized or not oxidized at all within the organism. Under this list may be classed carbon monoxid, oxalic acid, and many others. The selective oxidation of many organic substances in the body is another very remarkable characteristic of vital oxidation. Thus very slight changes in the structure of a substance may completely prevent its oxidation in the body. A great deal of work has been done on the relation of chemical constitution to the property of undergoing oxidation in the organism. I shall take occasion later to refer to another remarkable difference between oxidation within and without the body.

In 1901 Kastle and I[1] showed that certain of the organic peroxids give practically all of the reactions of certain oxidases widely distributed in living matter. We found, for instance, that benzoyl peroxid gives the well-known guaiacum reaction, and that the bluing of guaiacum by benzoyl peroxid can be inhibited by hydrocyanic acid in the same manner that this substance inhibits the bluing of guaiacum by the oxidases. On the basis of this work and on the presumption that the oxidases play a rôle in pathological as well as physiological processes, I was led to study the pharmacological action of benzoyl peroxid and also any therapeutic uses to which it might be put.[2] The substance proved to be markedly antiseptic and extremely useful in the treatment of local infection; in fact, its effect in local infection was so remarkable as to suggest that its beneficial effect could not be attributed entirely to its antiseptic action. This naturally suggested that the active oxygen contained in benzoyl peroxid had some peculiar effect on the tissues, increasing their resistance to infection. The nature of this increased resistance was not determined at that time. I shall refer to this again later. Benzoyl peroxid is but slightly soluble in water, so that its effect

1. Kastle and Loevenhart: Am. Chem. Jour., 1901, xxvi, 539.
2. Loevenhart: Therap. Monatsch., 1905, p. 426.

on general infections could not be studied. In casting about for a substance soluble in water which might contain oxygen in a physiologically available form, and which could be injected intravenously, it was decided to make a careful pharmacological study of the sodium salts of iodbenzoic, iodosobenzoic and iodoxybenzoic acids. These acids, which were first prepared by Victor Meyer and his co-workers,[3] have the following composition:



Iodbenzoic acid contains no active oxygen. Iodosobenzoic acid contains 6.06 per cent. of active oxygen. Iodoxybenzoic acid contains 11.43 per cent. of active oxygen. By active oxygen I mean oxygen which in the chemical sense is very active outside the body and which in the compounds under consideration is the oxygen bound to the iodin.

Grove and I[4] sought to determine whether the oxygen contained in these substances is physiologically available, that is to say, whether the oxygen bound to iodin in these substances can be utilized by the organism for purposes of physiological oxidation. We found that the sodium salts of iodosobenzoic and iodoxybenzoic acids instantly oxidize hemoglobin to oxyhemoglobin. We found that sodium iodosobenzoate can furnish the oxygen for at least one peroxidase reaction. It was found that while neither blood nor sodium iodosobenzoate is capable of oxidizing phenolphthalin to phenolphthalein, together they are capable of effecting this oxidation. Dilute solutions of sodium iodosobenzoate and sodium iodoxybenzoate taste very much like solutions of hydrogen peroxid. All of these facts indicate that the oxygen which they contain is physiologically available.

Arkin showed that sodium iodosobenzoate and sodium iodoxybenzoate are from one hundred to two hundred times as highly bactericidal as sodium iodbenzoate on *Bacillus typhosus*.[5] This difference can be attributed only to the oxidizing action of the former substances. On intravenous injection it was found that sodium iodosobenzoate and iodoxybenzoate markedly depress the respiratory and vasomotor centers, whereas the iodbenzoate has no such effect. Therefore, the effects of the two former substances on these centers must be attributed to the physiologically active oxygen which they contain. It would thus appear

3. Meyer, Victor: Ber. d. deutsch. chem. Gesellsch., 1892, xxv, 2632; 1893, xxvi, 1354, 1727; 1894, xxvii, 1600.

4. Grove and Loevenhart: Jour. Pharmacol. and exper. Therap., 1911, iii, 101.

5. Arkin: Jour. Pharmacol. and exper. Therap., 1911, iii, 145.

that a substance which apparently increases oxidation within the respiratory and vasomotor centers, depresses them. It has been known for a long time that hydrocyanic acid is one of the most powerful stimulants of the respiratory center. It is also well known that hydrocyanic acid depresses vital oxidation. Therefore it seemed interesting to determine whether an antagonism existed between the action of hydrocyanic acid and iodosobenzoate. In order to determine this, cannulas were placed in both femoral veins of a cat. In the left femoral vein a solution of sodium iodosobenzoate was injected and its effect determined. After a short time sodium cyanid was injected into the right femoral vein, in order determine the effect of a given dose in the animal under experimentation. Then both substances were injected simultaneously into the opposite veins. The complete antagonism of the two substances in their action on the respiratory center was readily seen.[6] This further indicated that iodosobenzoate increased oxidation in the center, since it was capable of antagonizing a substance known to inhibit vital oxidation.

Eyster and I[7] showed that sodium iodosobenzoate, when perfused through the isolated mammalian heart, has a marked effect on the size of the beat even in very dilute solutions, whereas iodbenzoate has very much less action. We found that most of the active oxygen of the iodosobenzoate is removed from the solution on perfusing through the heart, and that the more vigorously the heart is beating the greater is the amount of oxygen taken up by the heart from this compound. Although iodoxybenzoate is apparently as active on the respiratory center as iodosobenzoate, it is much less active in alterating the activity of the isolated heart. The heart also takes up far less oxygen from a solution of iodoxybenzoate than from iodosobenzoate, which again clearly indicates that it is the active oxygen in these compounds which accounts for their pharmacological action. It is also very interesting as showing how futile it is to predict, from knowledge previously gained with one tissue, what effect a given oxidizing substance will have on another tissue. In fact, the longer one works at the problems of vital oxidation, the less willing he becomes to make predictions. The effect of any new factor or condition cannot be foretold. It must be ascertained by experiment.

The action of iodoso- and iodoxybenzoate on the circulation and respiration seemed so interesting that we determined to step aside from the original object of the investigation, namely, the quest of a substance for the treatment of general infection, long enough to determine the relation between physiological activity and changes in the rate of

6. Grove and Loevenhart: Jour. Pharmacol. and exper. Therap., 1911, iii, 131.
7. Eyster and Loevenhart: Jour. Pharmacol. and exper. Therap., 1913, v, 21.

oxidative processes. Strange to say, this question had never been carefully attacked as such, and the knowledge on the subject, which was more or less desultory, did not elucidate the problem satisfactorily. The reaction of the animal to asphyxia has been investigated for the last sixty years. Asphyxia is, however, a complicated condition. There exists both a lack of oxygen and an excess of carbon dioxid, and the relative parts played by these two factors in producing the symptoms of asphyxia have been the source of endless controversy. Furthermore, products of incomplete oxidation having an acid character arise during asphyxia, and to these the symptoms of asphyxia have also been ascribed in part. The striking symptoms of asphyxia, however produced, are the following: increase in the rate and depth of the respiration, rise of blood pressure, slowing of the pulse, cessation of respiration, general convulsions followed by paralysis, marked and progressive fall of blood pressure, death.

I cannot review the previous work on the subject of asphyxia, and must confine myself to recounting certain experiments which seem to us to demonstrate conclusively that the symptoms of asphyxia can be brought about by decreased oxidation. Gasser and I[8] produced decreased oxidation by methods which did not permit of any accumulation of carbon dioxid or of acid products in two ways:

1. By injecting sodium cyanid intravenously.

2. By injecting pure carbon monoxid into the trachea without interfering with the respiration in any way.

Artificial respiration was given when the natural respiration was depressed, thus preventing the accumulation of carbon dioxid. In the rabbit the injection of sodium cyanid into the jugular vein stimulates the respiratory center, on the average, within three to four seconds. Stewart[9] found that it requires 2.8 seconds for the blood to pass from the left jugular vein to the right carotid in the rabbit. Thus the latent period of stimulation of the respiratory center by sodium cyanid is practically the time required for the substance to reach the center. This extremely rapid action precludes all possibility of explaining the stimulation as due to excess of carbon dioxid or the accumulation of acid products. It proves beyond peradventure that the cells respond with stimulation to a decrease in their own oxidative processes directly. Similarly, the vasomotor and cardio-inhibitory centers are stimulated, but the latent period is longer than in the case of the respiratory center. The order of stimulation is, first, respiratory center, second, the vasomotor center and last, the cardio-inhibitory center. With carbon monoxid quite similar results were obtained, but a little longer time was

8. Gasser and Loevenhart: Jour. Pharmacol. and exper. Therap., 1914, v, 239.
9. Stewart: Jour. of Physiol., 1894, xv, 4.

required. Here the stimulation of the respiratory center occurs within six and one-half seconds. The extra time required to produce stimulation by carbon monoxid can readily be accounted for by the time required for the gas to be drawn into the lungs and pass through the endothelium into the blood. The difference between the action of carbon monoxid and hydrocyanic acid in these reactions is this: The carbon monoxid by combining with hemoglobin and forming carbon monoxid hemoglobin reduces the amount of oxygen which the cells receive, whereas hydrocyanic acid does not interfere with the supply of oxygen, but interferes with the consumption of oxygen by the tissues through its inhibiting action on the oxidases. This fact illustrates that *decreased oxidation may occur when the supply of oxygen is not diminished and that the term decreased oxidation is not synonymous with oxygen want. Oxygen want is but one means of producing decreased oxidation.* Every phase of the pharmacologic action of hydrocyanic acid and carbon monoxid can be explained on this basis. These results clearly prove that decreased oxidation leads first to increased functional activity or stimulation and later to depression.

The effect of reducing oxidation in these centers depends on three factors: first, on the extent to which the oxidative processes are reduced; second, the suddenness with which they are reduced; third, the condition of the centers.[10] If oxidation is reduced below a certain level, stimulation will not be observed. The more suddenly the rate of oxidation is reduced, the greater will be the stimulation. If the reduction of the rate of oxidation is very slow no stage of stimulation will be noted, as the irritability of the cells will then decrease faster than the stimulus increases. Finally, the better the condition of the center the more readily is the stage of stimulation demonstrable and conversely, the poorer the condition of the center the more difficult it is to elicit a stage of stimulation. To summarize, then, we have found that a depression in the rate of oxidative processes in the medullary centers leads primarily to stimulation, whereas our work on iodosobenzoate and iodoxybenzoate showed that an increase in the rate of oxidative processes causes decreased activity or depression. In other words, the functional activity varies inversely with changes in the rate of oxidative processes. We[11] have attempted to form some conception which would account for this inverse relationship between functional activity and changes in the rate of oxygen utilization by the cell. Verzár,[12] working on the gaseous metabolism of muscle, and Barcroft and Piper[13] on the

10. Loevenhart: Arch. f. d. ges. Physiol. (Pflüger's), 1913, cl, 379.
11. Gasser and Loevenhart: Jour. of Pharmacol. and exper. Therap., 1914, v, 239.
12. Verzár: Jour. Physiol., 1912, xliv, 243.
13. Barcroft and Piper: Jour. of Physiol., 1912, xliv, 359.

gaseous metabolism of the submaxillary gland, have shown that the period of increased utilization of oxygen outlasts by several minutes the period of increased functional activity following stimulation. Barcroft and Piper found that following certain forms of stimulation, maximum utilization of oxygen occurs when the saliva almost ceased to flow. They say: "Probably therefore gland, like muscle, is a mechanism in which oxidation serves to replenish a store of potential energy which is liberated in the act of secretion." It would seem that we have two sets of processes going on within cells, one of which requires the acquisition of oxygen from without the cell. Since the cell continues to fix oxygen at a greatly increased rate for a time after functional activity has ceased and since heat continues to be liberated after the contraction of a muscle as shown by A. V. Hill[14] it would seem that the fixation of oxygen by the cell must be the beginning of a series of oxidations. Let us designate this phase of oxidation within the cell as the R processes, since R will suggest rest and recovery. The essential feature of the R processes is that they require oxygen from without the cell. From our point of view functional activity is the external manifestation of a set of chemical reactions occurring within the cell. Since energy is liberated during functional activity we must assume that these processes are also oxidative at least in part. Let us designate the processes of which function is the external expression as A processes, since A will suggest activity. We conceive that neither the A nor the R processes are ever in complete abeyance during life but that their relative intensity determines the relative state of activity of the cell.

The work with iodosobenzoate and iodoxybenzoate indicates that a stimulation of the R processes (oxygen fixation) retards the A processes and depression results. On the other hand, if the R processes are depressed, as by the use of carbon monoxid or sodium cyanid, it would seem that the cell must derive its energy from the A processes and increased functional activity must result. This is the only conception we have been able to form to account for the reciprocal relationship of oxygen fixation and functional activity. We know that an increase in the A processes entails an increase in the R processes, but since the latter outlast the former it would appear that the R processes lag behind. Since recuperation apparently does not occur under anesthesia, it would follow that both the A and the R processes are depressed in this state. Our work indicates also that when the R processes fall below a certain level, all functional activity ceases, or, in other words, the A processes cease. According to our point of view, the stimulating action of carbon dioxid is due to its power to depress the R processes

14. Hill, A. V.: Jour. Physiol., 1913, xlvi, 28.

just as hydrocyanic acid does. We believe that under physiological conditions the oxidative processes and therefore the functional activity of the respiratory center are conditioned by the carbon dioxid tension and not by the oxygen tension. This follows from the work of Haldane and his co-workers.

We have recently turned our attention to another phase of the proposition that decreased oxidation primarily stimulates cells. The previous work showed that the cells of the respiratory center are apparently more sensitive to alteration in the rate of their oxidative processes than any cells in the body, and respond most readily with stimulation to a decrease in their oxidative processes. This is what we should expect, since the respiratory center, by controlling the entrance of oxygen into the body and the exit of carbon dioxid, really controls one of the fundamental conditions for tissue oxidation. From the lungs to the tissues the oxygen must be carried by the hemoglobin. Since the red blood corpuscles and hemoglobin are produced by the red bone-marrow, it is obvious that the red bone-marrow supplements the action of the respiratory center in supplying the tissues with oxygen.

Paul Bert[15] thirty-six years ago showed that the oxygen carrying power of the blood increases at high altitudes. He explained this as due to a reaction of the organism to accommodate itself to the decreased pressure of oxygen in the atmosphere. The facts brought out by Bert as well as his explanation of the blood changes have been the subject of much controversy. The majority of investigators, however, have agreed with Bert that there is an increase in erythrocytes and hemoglobin at high altitude. I cannot review the views which have been held regarding these phenomena, but will merely enumerate some of them. 1. The increase is insignificant. 2. The erythrocytes and hemoglobin always increase proportionately and the increase is due to concentration of the blood either by loss of water from the body through evaporation or by the passage of plasma from the blood to the tissues. Again, the blood changes have been attributed to various physical factors such as (1) a displacement of the diaphragm upward and an alteration in the pulmonary circulation, (2) lessened vital capacity of the lungs at reduced pressure, etc. There are obviously many factors which may play a rôle in the effect of reduced atmospheric pressure on the blood. From our point of view, the increase in the hemoglobin and red blood corpuscles is probably due to a stimulation of the bone-marrow by decreased oxidation within the bone-marrow itself.

I should like to describe briefly the apparatus which Mr. A. C. Kolls and I have devised in order to attack this problem.[16] This apparatus

15. Bert, Paul: La pression barométrique, 1878, p. 1108; Compt. rend. Acad., 1882, xciv, 805.

16. A description of this apparatus will soon be published.

was devised for the purpose of keeping animals in an atmosphere of reduced oxygen tension and at the same time to maintain them at the normal atmospheric pressure and thereby exclude all of the physical factors of high altitude. It consists of a respiratory chamber, the air of which is kept at a constant composition. The arrangement for absorbing carbon dioxid and water which the animal produces is that devised by Professor Benedict,[17] and the oxygen supply is automatically controlled by a mechanism quite similar to that used in Professor Lusk's laboratory and described by Williams.[18] We have introduced certain modifications which greatly facilitate the work that we have in hand. The results which Mr. H. C. Dallwig, Mr. A. C. Kolls and I have obtained with this apparatus may be indicated by citing two or three experiments out of a large number.[19]

I. REDUCED OXYGEN EXPERIMENT

Rabbits 4 and 5

Length of experiment.....132 hours
Average oxygen tension.....11.98 per cent.
Average carbon dioxid..... 0.08 per cent.
Average per cent. humidity.... { Inside 33 per cent. / Outside 33 per cent.

	Hemoglobin G. per 100 c.c.	Erythrocytes
No. 4—Before experiment.....	13.98	6,678,000
After 132 hours.....	16.97 (+ 21.4)	8,417,000 (+ 26)
No. 5—Before experiment	14.39	8,384,000
After 132 hours.....	17.43 (+ 21)	8,490,000 (+ 1.3)

II. CONTROL EXPERIMENT

Rabbits 9, 10 and 11

Length of experiment.....167.5 hours
Average oxygen tension .....20.9 per cent.
Average carbon dioxid tension..... 0.21 per cent.

Weight
No. 9 (albino) Before control 852 gm. After 970 gm. (+ 118 gm.)
No. 10 (albino) Before control 861 gm. After 935 gm. (+ 74 gm.)
No. 11 (albino) Before control 790 gm. After 898 gm. (+108 gm.)

	Hemoglobin G. per 100 c.c.	Erythrocytes
No. 9—Before control	10.9	5,293,000
After control	11.58 (+ 6.2)	5,772,000 (+ 9)
No. 10—Before control	13.1	6,389,000
After control	13.74 (+ 4.9)	6,512,000 (+ 1.9)
No. 11—Before control	12.66	6,152,000
After control	11.54 (— 8.8)	5,827,000 (— 5.3)

17. Benedict: Deutsch. Arch. f. klin. Med., 1912, cvii, 156.
18. Williams: Jour. Biol. Chem., 1912, xii, 317.
19. A complete account of these experiments will soon be published.

III. REDUCED OXYGEN EXPERIMENT

Rabbits 9, 10 and 11

Length of experiment.....147 hours
Average oxygen tension .....10.98 per cent.
Average carbon dioxid tension..... 0.19 per cent.

Weight
No. 9—Before experiment 970 gm. After 1,060 gm. (+ 90 gm.)
No. 10—Before experiment 935 gm. After 1,070 gm. (+ 135 gm.)
No. 11—Before experiment 898 gm. After 973 gm. (+ 75 gm.)

	Hemoglobin G. per 100 c.c.	Erythrocytes
No. 9—Before experiment	11.58	5,772,000
After experiment	15.68 (+ 35.4)	7,544,000 (+ 30.7)
2 days after	16.70 (+ 44.2)	7,707,000 (+ 33.5)
10 days after	15.26 (+ 31.8)	7,442,000 (+ 28.9)
23 days after	11.8 (+ 1.9)	6,000,000 (+ 3.9)
No. 10—Before experiment	13.74	6,512,000
After experiment	16.38 (+ 19.2)	7,301,000 (+ 12.1)
2 days after	15.82 (+ 15.1)	7,186,000 (+ 10.3)
10 days after	16.76 (+ 22)	7,635,000 (+ 17.2)
23 days after	15.77 (+ 14.8)	7,533,000 (+ 15.7)
No. 11—Before experiment	11.54	5,827,000
After experiment	17.02 (+ 47.5)	7,266,000 (+ 24.7)
2 days after	14.70 (+ 27.4)	7,200,000 (+ 23.6)
10 days after	14.83 (+ 28.5)	6,918,000 (+ 18.7)
23 days after	14.47 (+ 25.4)	6,872,000 (+ 17.9)

IV. REDUCED OXYGEN EXPERIMENT

Rabbits 15 and 16

Length of experiment.....260.5 hours
Average oxygen tension .....10.6 per cent.
Average carbon dioxid tension..... 0.2 per cent.

Weight
No. 15—(Gray and white)—
Before experiment, 1,050 gm. After 1,130 gm. (+ 80 gm.)
No. 16—(Albino)—
Before experiment, 1,010 gm. After 1,150 gm. (+ 140 gm.)

	Hemoglobin G. per 100 c.c.	Erythrocytes
No. 15—Before experiment	10.6	5,376,000
3 days' run	13.32 (+ 25.7)	5,920,000 (+ 10.10)
6 days' run	16.76 (+ 58.1)	6,620,000 (+ 23.1)
11 days' run	15.92 (+ 50.2)	5,715,000 (+ 6.3)
No. 16—Before experiment	11.16	5,952,000
3 days' run	12.28 (+ 10)	6,075,000 (+ 2.1)
6 days' run	14.96 (+ 34)	7,018,000 (+ 17.9)
11 days' run	15.26 (+ 36.7)	6,850,000 (+ 15.1)

We have obtained many equally striking increases in other experiments. It is noteworthy that in Rabbit 5 the large increase in hemoglobin was not accompanied by a decided increase in the red blood cor-

puscles, showing clearly that the results could not be due to increased concentration of the blood, in which case the red blood corpuscles and hemoglobin would have increased proportionately. Blood smears stained with Jenner stain showed a large number of basophilic macrocytes. The blood smear also left no doubt that we were here dealing with a stimulation of the bone marrow. The animals which we have used fall into four groups:

1. Those which show an increase in both the hemoglobin and red blood corpuscles.

2. Those which show an increase in the hemoglobin without an increase in the corpuscles.

3. Those showing an increase in the corpuscles with no change in the hemoglobin.

4. Those showing little or no increase in either the red corpuscles or hemoglobin. The percentage of refractory animals (Group 4) is quite small.

An increase in the carbon dioxid in the atmosphere of the chamber with the normal oxygen concentration produces relatively little effect on the blood count in comparison with atmospheres poor in oxygen. We have some indication, however, that increased carbon dioxid here, as in the case of the respiratory center may stimulate the bone-marrow. In the case of the bone-marrow, however, the stimulation is slight whereas it acts powerfully on the respiratory center. It is interesting then that the respiratory center and the bone-marrow conduct themselves alike with regard to alteration in their own oxidative processes, since these two tissues provide the primary conditions for tissue oxidation. The work is interesting further in connection with polycythemia as observed clinically. It would seem that we might expect to find polycythemia in any chronic respiratory or circulatory condition which would result in the bone-marrow's receiving an insufficient supply of oxygen. In some of our experiments we have allowed animals to remain in the box at the normal oxygen concentration, and under these conditions, no increase in the red blood corpuscles and hemoglobin was noted. We have made certain observations in the box on the oxygen concentration required for a continuance of life, and compared with this the oxygen concentration required to support the flame of various combustible materials. It was shown by Clowes[20] that various combustible gases and liquids would burn only at definite minimum oxygen concentrations. We have confirmed certain phases of Clowes' work. Alcohol ceases to burn when the oxygen concentration falls to 15 per cent. The Madison illuminating gas ceases to burn in an oxygen con-

20. Clowes and Redwood: Proc. Royal Soc. London, 1894, lvi, 2.

centration of about 13 per cent. At about this point a flaming pledget of cotton saturated with ether is extinguished. The hydrogen flame is extinguished at about 6.6 per cent. oxygen. Below this point no combustible substances which we have studied will produce a flame. Animals continue to live, however, in an oxygen concentration far below this point. Thus we have found it necessary in order to produce alarming symptoms and death in rabbits to reduce the oxygen to between 3 and 3.5 per cent. This brings out one of the most striking differences between vital oxidation and ordinary combustion. If the atmosphere of the earth should become altered so as to contain only one-half the amount of oxygen, animal life would not be interfered with in any way, but it would be impossible to run a locomotive or to burn illuminating gas, and many of the substances which we consider dangerously inflammable would be as non-inflammable as water.

To return for a moment, before closing, to the original subject of the effect of physiologically active oxygen on inflammation and on immunity processes, I should like to refer briefly to two pieces of work. Prof. L. Hektoen[21] has investigated the effect of iodosobenzoate and iodoxybenzoate on certain immunity reactions. He injected these substances intravenously in dogs and found that they greatly increase the production of specific hemolysin following a single injection of 10 per cent. suspension of goat blood. The results were striking. The increase in hemolysin in the animals receiving the treatment was from 12 to 60 times as great as in the control animals. Iodbenzoate without active oxygen is without effect. Whether physiologically active oxygen will similarly stimulate the production of other immune bodies remains to be determined by further experiment. It is sufficiently obvious that if we could similarly increase the production of diphtheria antitoxin, it would be of great value.

Dr. S. Amberg and his co-workers[22] in a series of investigations have shown that iodosobenzoate and iodoxybenzoate injected intravenously or intraperitoneally have the power of markedly inhibiting the local inflammatory reaction as produced by mustard oil or bacterial toxins injected intracutaneously or instilled into the conjunctival sac, whereas iodbenzoate, possessing no physiologically active oxygen, is entirely without effect. The results are very striking indeed.

Many attempts of an unscientific character have been made to use oxygen in some form such as ozone, compressed air, etc., in the treatment of disease. I need only refer to the extensive and disastrous use of potassium chlorate internally which was in vogue for many years.

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21. Hektoen, L.: Tr. Chicago Pathological Soc., 1911, viii, 138.

22. Jour. Pharmacol. and exper. Therap., 1912, iii, 223; Jour. Am. Med. Assn., 1912, lix, 1598; Ztschr. f. d. ges. exper. Med., 1913, ii, 19, and oral communication.

It was supposed that since it is a very strong oxidizing agent outside the body that it would facilitate oxidation within the organism. This substance, however, does not lose its oxygen in the body, but is excreted unchanged in the urine. Dr. Abraham Jacobi[23] pointed out the great danger attendant on its use internally. The investigations which I have reviewed indicate that at some future time we may find important therapeutic applications of the results of studies in vital oxidation, but we hope that the next attempt will be founded on a basis of fact and will be subjected to careful scientific scrutiny before it is given to the profession.

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23. Jacobi, Abraham: Tr. Med. Soc., New York, 1879, p. 365.