SCIENCE

VOL. LXI JUNE 5, 1925 No. 1588

CONTENTS

SCIENCE: A Weekly Journal devoted to the Advancement of Science, edited by J. McKeen Cattell and published every Friday by

THE SCIENCE PRESS

Lancaster, Pa. Garrison, N. Y.
New York City: Grand Central Terminal.
Annual Subscription, $6.00. Single Copies, 15 Cts.

SCIENCE is the official organ of the American Association for the Advancement of Science. Information regarding membership in the association may be secured from the office of the permanent secretary, in the Smithsonian Institution Building, Washington, D. C.

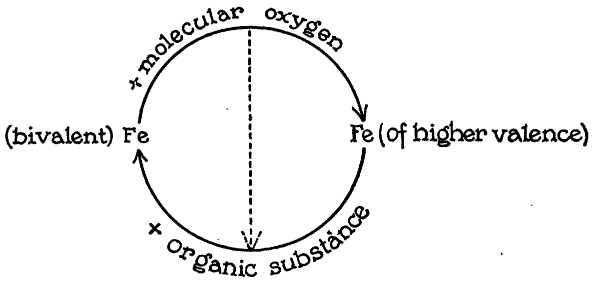
Entered as second-class matter July 18, 1923, at the Post Office at Lancaster, Pa., under the Act of March 8, 1879.

IRON, THE OXYGEN-CARRIER OF RESPIRATION-FERMENT[1]

THE idea that iron plays a part in the oxidation reactions of the living cell has appeared in a more or less definite form in the literature of the last fifty years. But since it was not possible to establish the idea and to differentiate it as correct from the false ideas which appeared at the same time, it was dropped and became worthless for science.

I

We maintain that in respiring cells there is a cycle of the form



In this cycle molecular oxygen reacts with bivalent iron, whereby iron in a higher state of oxidation is formed. The oxidized iron reacts with the organic substance and is again reduced to bivalent iron. Reactions in the direction of the dotted arrow do not occur; molecular oxygen never reacts directly with the organic substance.

According to this figure the organic substance is as little autoxidizable inside the cell as outside, the iron *alone* being autoxidizable. We know that iron can react with molecular oxygen in a test tube. Then, if our scheme is true, the problem of respiration ceases to exist, because it is solved if we are able to trace back the process of respiration to the reactions which occur in the test tube.

Not every form of bivalent iron reacts with molecular oxygen, and not every form of iron of higher valence reacts with organic substances. In order that iron may act catalytically according to our scheme, certain conditions with respect to the form in which the iron is present must be satisfied. It will be our problem to show that catalytically active forms of iron occur in living cells and in what way such forms of iron can be prepared by the chemist.

---

[1] Lecture delivered at the Rockefeller Institute for Medical Research, New York.

II

Our assertion assumes that every living cell contains iron and that life without iron is impossible.

Those who have cultivated cells know that this assumption is correct. Every nutrient medium must contain iron and the growth of the cells ceases when the iron is consumed. Although the necessity of iron for life was recognized by Eusèbe Gris sixty years ago, it has remained unexplained. The problem became more obscure when the fact was shown that iron does not take any part in the constitution of the organic molecule which occurs in the cell. The pure proteins, nucleic acids and chlorophylls do not contain iron.

The quantities of iron which occur in the cell are small. We have determined the iron content of different types of cells and found per gram of cell-substance one tenth to one hundredth of a milligram of iron. Do these small quantities of the element suffice to carry the oxygen which disappears during respiration?

To decide this question, we determine the respiration of cells, the iron content of which is known. If we assume that the oxygen transferred during respiration takes place exclusively according to our scheme, then the reactivity of the iron in the cell is obviously measured by the quotient

$$\frac{\text{oxygen consumption}}{\text{iron content} \times \text{times.}}$$

If we choose as units cubic millimeters of oxygen, milligrams of iron and hours, then our quotient becomes, for example:

For the unfertilized Strongylocentrotus-Egg at 20°	7,000
For the fertilized Strongylocentrotus-Egg at 20°	42,000
For the retina of mammals, the organ of higher animals which has the largest respiration, at 37°	100,000

Let us compare the reactivity of iron in the test tube with these figures. If, for example, we consider the oxidation of cystein to cystin, which is accelerated by iron salts, and determine how much oxygen 1 milligram of iron transfers per hour, when added to an aqueous solution of cystein, we find at 20° 120,000 cubic millimeters of oxygen and at 37° 400,000 cubic millimeters, that is, larger values than for the reactivity of iron in living cells.

This calculation shows that the iron content of a cell more than suffices to explain the oxygen consumption incident to respiration according to our assumption. The iron content of a cell is small to the quantitative chemist, but large for us in consideration of the reactivity of the element.

As is known, the living cell contains not only iron among the autoxidizable metals, but also copper, manganese and other metals. One might ask if it would not be better to write "heavy metal" instead of "iron" in our scheme. We do not do this, because we do not know if copper and manganese are necessary for life, and because, in comparison to their reactivity the quantities of these metals are small. According to Bertrand and Medigreceanu, 1 gram of cell substance contains one ten thousandth of a milligram of manganese, that is, the manganese content of a cell is a hundred to a thousand times smaller than the iron content. If the oxygen, which disappears during respiration, were carried by this amount of manganese, then the reactivity of the manganese in the cell would be ten million, greatly exceeding that which we find for the element in the test tube.

Therefore we confine our assumption explicitly to iron and consider its application to other heavy metals for the present as unfounded. There may be exceptions—one is reminded of the copper of the octopus and of the fact discovered by Henze that the ascidia contain vanadium—but such cases do not belong in a general theory of respiration.

III

According to our assumption, every substance which reacts with iron must interfere with oxygen transfer in the cell, provided that it penetrates the living cells and that its affinity for iron suffices to loosen the natural combinations with this element. Substances which react with iron are arsenious acid, hydrogen sulfide, prussic acid and such others as, when introduced into the cell, retard respiration.

We have studied the effect of prussic acid in greatest detail. Prussic acid is by no means a general ferment poison. Even one tenth normal prussic acid has no noticeable effect on hydrolyzing ferments. On the other hand, prussic acid in small concentrations has an effect on all those processes in which the combination and transfer of oxygen play a part, as for example, the assimilation of carbon dioxide, nitrate assimilation, the decomposition of hydrogen peroxide and respiration. These processes are retarded by prussic acid in concentrations of 1/10,000 to 1/100,000 normal. By direct measurement it can be shown that the cell takes very little prussic acid out of such a dilute solution, an amount which is very small compared with the weight of the cell.

Since a stoichiometrical relation must exist between the combined prussic acid and the substance with which it combines, it follows from what has been said that the cell contains a minute amount of some substance which is able on the one hand to transfer oxygen and on the other hand to react with prussic acid. Of all the substances which occur in the cell the only one which fulfills these conditions is iron. It is true that certain autoxidizable aldehydes can react with oxygen as well as prussic acid, but it is not known whether such aldehdyes are integral components of living cells.

IV

Until now we have presented a series of arguments in favor of our conception, namely, the necessity of iron for life, the large reactivity of iron, the specific effect of substances which react with iron, but we have presented no conclusive experiments. Is it possible to show directly that iron carries oxygen in the cell?

If the unfertilized eggs of Strongylocentrotus be centrifuged and shaken, the eggs dissolve and a liquid is obtained which respires as strongly as the intact eggs from which the liquid came. The liquid contains iron to the extent of some hundredths of a milligram per gram of cell substance. If iron is added to the liquid in such quantities as occur naturally in the egg substance, the oxygen consumption increases as does the increase in iron content. It is evident then that not only does the iron, when added to the cell substance, carry oxygen, but what is more significant, the oxygen consumption is proportional to the iron content of the cell substance.

This important experiment will be described more in detail. The respiration of the intact unfertilized eggs as well as their iron content is determined, and the reactivity of the iron calculated by dividing the respiration by the iron content. Then the eggs are dissolved, 1/100 milligram of iron is added to one gram of egg substance, and the increase in the oxygen consumption due to the iron is determined. From these figures the reactivity of the iron added is calculated. In both cases we find for the reactivity of the iron the value 7,000. This indicates that every milligram of iron, whether that of the intact egg or that which is added, carries the same quantity of oxygen per hour, that is, 7,000 cmm.

These experiments, which I carried out ten years ago, partially in cooperation with Otto Meyerhof, prove that our hypothesis is correct, at least in the case of the sea urchin's egg.

V

Instead of substantiating for other cases what we found in the case of the sea urchin's egg, we immediately proceeded to the problem of reproducing the same effects of iron in simple systems, which are free from the ballast of the cell substance.

The experiments which we now consider are model experiments, inasmuch as the conditions under which we work are simpler than in the case of the cell. Indeed, the experiments are to be considered more than model experiments, if the transfer of oxygen to the combustibles of the cell with the help of iron is successful. For then the natural process of oxygen transfer is not only imitated in the test tube, but the oxygen transfer in the test tube and in the cell is identical, the basis of the transfer in both cases being the change in valence of the iron.

It is not permitted in such experiments to use oxygen in an activated form, such as ozone, hydrogen peroxide or quinone. Activated oxygen, especially in the presence of iron, will attack, as shown by Fenton, Dakin and Neuberg, all organic molecules; but the point to be explained is why molecular oxygen inside of the cell behaves like activated oxygen outside of the cell. Respiration models with activated oxygen as oxidizing agent correspond to invertase models in which cane sugar is dissolved in concentrated hydrochloric acid.

We confine ourselves, then, strictly to molecular oxygen and investigate under what conditions the reaction between bivalent iron and molecular oxygen —the first phase of our cycle—takes place. It turns out that free ferrous ions practically do not react with molecular oxygen and hence can not transfer it. On the other hand, certain complex ferrous salts, when in solution, as well as certain solid iron compounds, react quickly with molecular oxygen. In this connection I should like to mention the interesting work of Baudisch. However, if amino acids or sugar are added to ferrous compounds which react quickly with oxygen, in general no transfer of oxygen takes place.[2] The absorption of oxygen by such mixtures ceases when the iron is oxidized. It is just as difficult to bring about the second phase of our cycle—the reaction between iron of higher valence and organic substance—as it is easy to bring about the first phase.

Obviously there are only certain specific and until now unknown compounds of iron which can act catalytically in the sense of our hypothesis. How such compounds are formed and what effects they produce will now be described.

VI

If pure crystallized hemin, an iron compound of pyrrol, is heated strongly to glowing, a black residue is obtained which after extraction with hot hydro-

---

[2] Recently H. A. Spoehr has observed that iron pyrophosphate is able to transfer oxygen to glucose with result that carbon dioxide is formed.

chloric acid contains, together with carbon, 3 per cent. nitrogen and as much iron. This charcoal acts as an oxidation catalyzer for amino acids. When added to an aqueous solution of amino acids and shaken with air or oxygen at body temperature, the oxygen is absorbed and carried to the amino acids. With leucine ammonia, carbon dioxide and valeric aldehyde are formed; with cystine ammonia, carbon dioxide and sulfuric acid, together with unknown products of the incomplete combustion. We have then a reaction between amino acids and oxygen, in which, as in the case of the combustion of proteins in the living cell, ammonia, carbon dioxide and sulfuric acid appear.

If we ask which constituents of the hemin charcoal are catalytically active here, then the same difficulty in principle arises as in the experiments with living cells. Given a mixture of different substances, we have to decide which constituents of the mixture cause the observed effect. In practice, however, we have the great advantage that we can prepare the catalytically active mixture artificially. In order to decide our question it is necessary merely to heat different substances to glowing and to compare the catalytic action of the charcoals formed with their chemical composition.

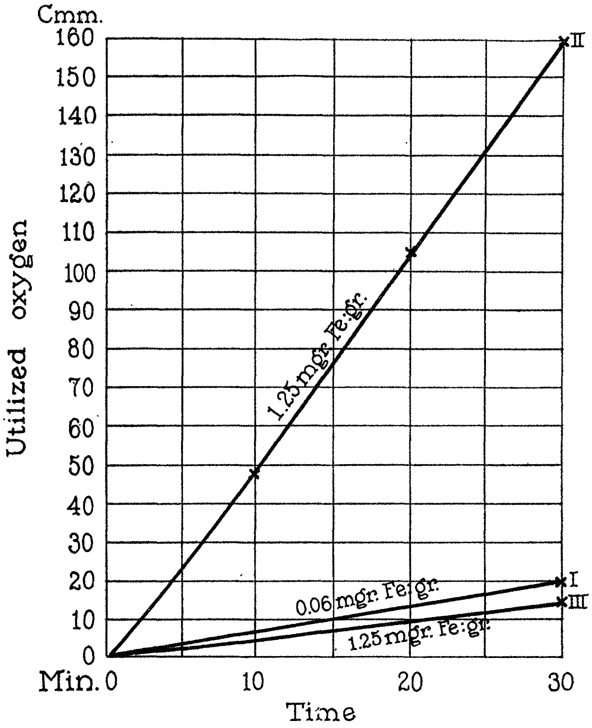
We have carried out experiments of this kind. In these it developed that charcoals having the catalytic effect of hemin charcoal are always formed when two conditions are satisfied, first, when the starting material contains non-volatile nitrogen, and second, when it contains iron. If suitable substances containing nitrogen are carefully purified so that they contain very little iron and then heated to glowing, weakly active charcoals are formed. If these be impregnated with iron salt and then heated to glowing, they become activated and attain the catalytic activity of hemin charcoal. The richer the charcoals are in iron, the more active they are, until the maximum of reactivity is reached at an iron content of some tenths of a milligram per gram of charcoal.

There is no activation if charcoals containing nitrogen with other metals or charcoals free from nitrogen are heated to glowing with iron. Hence, the catalytically active substance of hemin charcoal is iron, not iron in any form, but in combination with nitrogen.

We do not maintain that only iron can carry oxygen to amino acids: rather we have found that charcoals made from pure sucrose free from iron also possess a certain catalytic activity. However, this activity, which is due to the action of a carbon peroxide, is not to be compared in magnitude with the action of iron combined with nitrogen. The best charcoals free from iron which we obtained are 500 times weaker in action than hemin charcoal, so that at least 99.8 per cent. of the action of hemin charcoal must be due to iron.

VII

The catalytic action of iron combined with nitrogen, like the respiration of living cells, is retarded by prussic acid. One ten thousandth normal prussic acid markedly reduces the activity of hemin charcoal and of all other iron-nitrogen charcoals which we have prepared. One thousandth normal prussic acid causes the catalytic activity practically to disappear. I do not hesitate to see in this result a striking confirmation of our hypothesis.



A figure will make clear the main experiments. The abscissae represent time, the ordinates the transferred oxygen. In our example the amino acid, to which the oxygen is carried, is leucine, while the charcoals, which carry the oxygen, were prepared from an aniline dye rich in nitrogen. Curve 1 shows the transfer of oxygen by a charcoal which contains .06 mgr Fe per gram; curve 2 shows the transfer of oxygen by the same charcoal after its iron content had been increased to 1.25 mgr per gram by impregnation with iron salt and heating to glowing; curve 3 shows the transfer of oxygen by this charcoal rich in iron after adding 1/1000 mol prussic acid to a liter of solution. As is seen, the activity of the charcoal increases with its iron content and its action disappears completely under the influence of prussic acid.

VIII

As far as the activity of iron in its combination with nitrogen is concerned, we calculate it, as heretofore, by dividing the increase in oxygen consumption, which takes place when iron is added, by the amount of iron added. In the case represented by the figure, we find the value 12,000, which is approximately the reactivity of iron in the intact unfertilized sea urchin's egg, in other words the reactivity of iron combined with nitrogen is of the same order of magnitude as the reactivity of iron in the living cell.

Summarizing the results of the experiments with charcoal, we see that at body temperature and in neutral solution, with the help of iron, molecular oxygen can be carried to amino acids whereby ammonia, carbon dioxide and sulfuric acid appear as decomposition products. This reaction, like respiration in the living cell, is specifically retarded by prussic acid.

IX

When bivalent iron reacts with oxygen or when iron of higher valence reacts with the amino acids, then the driving forces are specific chemical forces. In the transfer of oxygen by hemin charcoal the general surface forces play an important part, together with the specific chemical forces, inasmuch as they bring the amino acid out of the solution on to the iron. Substances of the most dissimilar chemical properties, if they are adsorbed by the charcoal, can displace the amino acids from the charcoal. This displacing action of a substance is determined by the force with which the surface attracts the substance one which is proportional to the adsorption constant. The greater the adsorption constant, the greater is the displacing action, which proves that the general surface forces hold the amino acids and catalyzer together.

Physical chemistry has shown that chemical reactions can be accelerated by the action of general surface forces. Porcelain, quartz and other solids accelerate the reaction of hydrogen and oxygen to form water. The hydrogen and oxygen become more reactive under the influence of the surface forces, and we must assume the same in our case for the amino acids, the structure of which is loosened by the surface forces.

However, this loosening does not suffice to cause the amino acids and oxygen to react. Charcoals which contain neither iron nor carbon peroxide, even if they adsorb well, are catalytically completely inactive. A reaction takes place only when chemical forces are present together with surface forces.

Thus that peculiar combination of general surface forces and specific chemical forces arises which is characteristic of our model as well as of the living substance. Both systems react on the one hand like general surface catalysts, on the other hand like specific metal catalysts. The specific negative catalyst is prussic acid; the general negative catalysts are the narcotics.

X

If the idea of activation is carried far enough, then iron of higher valence plays the part of "activated" oxygen and the atoms of the loosened organic molecules are "activated" carbon, hydrogen, sulfur, etc. All the molecules which take part in the process of respiration are activated, the oxygen by chemical forces and the other molecules by general surface forces.

This conclusion shows that the former theories of respiration were partly correct and partly false. The theories of Moritz, Traube, Bach and Engler were correct in so far as they assumed an activation of oxygen, but false in so far as they overlooked the activation of the organic molecules. The theories of Pfeffer and Wieland were correct in so far as they assumed an activation of the organic molecules but false in so far as they denied the activation of the oxygen.

The most unsatisfactory element of the older theories of respiration was their vagueness. To say that a ferment activates the reacting substances is merely another expression for the fact that it acts. Invertase activates cane sugar; zymase activates dextrose.

The problem to be solved is not whether a ferment activates but in what way it activates. If we content ourselves with answering the first question, then we have an argument in a circle which explains respiration by means of activation and activation by means of the activating ferments.

XI

The iron of the hemin charcoal attacks with an appreciable velocity only a limited number of the many organic substances. Of the principal combustibles of the cell neither the sugar nor the fatty acids but only the amino acids are attacked. The selective action of our model seems more marked than that of the living cell.

On the other hand the combustion of carbohydrate and fat in the living cell is as much an iron catalysis as the combustion of amino acids. For the combustion of carbohydrate and fat in living cells is specifically retarded by prussic acid.

The contradiction disappears if we expand our assumptions with the hypothesis that of the three principal combustibles only the amino acids are attacked directly by iron, while the carbohydrates and fats do not react as such with the iron, but in the form of unknown derivatives. If this is true, then we must look for reactions, which are not oxidation reactions, but splittings or condensations, which take a part in respiration in so far as they make the attack of the iron possible. We have found a reaction of this kind in which sugar is changed into a reactive form.

If oxygen be passed through a neutral solution of fructose and sodium phosphate at body temperature, the oxygen disappears and the higher the phosphate concentration the quicker the disappearance. Fructose, when dissolved in other salt solutions, does not absorb oxygen, and other sugars, when dissolved in phosphate solutions, absorb very little oxygen in comparison with fructose. Thus a specific reaction between fructose and phosphate is concerned here, whereby a reactive substance is formed. This substance is not the much investigated hexose-phosphate-acid, which is stable in the presence of oxygen.

The rate of oxidation of fructose in the presence of phosphate is large under suitable conditions; 0.3 per cent. of the fructose present at any time can be destroyed per hour.

Carbon dioxide is formed as a product of the reaction, and per molecule of oxygen used, one third of a molecule of carbon dioxide appears. Thus the oxidation is not complete, as in the case of living cells, but nevertheless yields in large quantities the physiological end product of carbohydrate combustion.

It is remarkable that till now this simple and important reaction has been overlooked. The reaction is important because we have here a partial combustion of carbohydrate in the test tube under the influence of a substance which is an integral part of living cells.

At first this case seems to contradict our assertion that not the organic substance but only the iron of the cell is autoxidizable. For is not the sugar affected in such a way through combination with phosphate that molecular oxygen attacks it? This is not true, but, as shown by Otto Meyerhof, the autoxidizable component of the system is here also a metal.

Meyerhof observed the following: If 1/1,000 mol of sodium pyrophosphate be added to a solution of fructose in N/2 phosphate there is a strong retardation of the oxidation. The same is the case if 1/10,000 prussic acid be added to the weakly alkaline solution. Both substances, pyrophosphate and prussic acid, are characterized in that they form stable, complex compounds with metals, and both cases are understandable if we assume that the fructose oxidation in a solution of phosphate is caused by the action of metals which are always present to a small extent in the laboratory reagents.

As a matter of fact, small quantities of copper, manganese and iron, when added to the fructose-phosphate mixture, strongly accelerate the oxidation. Meyerhof obtained the strongest action of the metals in a weakly alkaline solution and found, for example, that 1/100 milligram of copper, when added to 100 milligrams of fructose, accelerated the oxidation 140 per cent., and 1/100 milligram of iron 70 per cent.

Of course the degree of acceleration depends upon the purity of the fructose-phosphate mixture and would be infinitely great if we had solutions free from iron at our disposal. Under such conditions it is more appropriate to disregard the oxidation before the addition of metal and to consider only the increase in the oxygen absorption which takes place with the addition of metal. If we do this and divide the increase of oxygen consumption by the metal added, we obtain the reactivity of the metal in the system fructose-phosphate. We calculate from an example of Meyerhof for copper 20,000, and for iron 10,000, which is of the order of magnitude of the reactivity of iron found for living cells.

In summary, if inorganic phosphate and fructose are brought together in aqueous solution, a substance is formed which combines with iron, changing it into a catalytically active form. Iron in this form reacts quickly with molecular oxygen and the iron which is formed in a higher state of oxidation reacts quickly with the organic substance, being reduced again to bivalent iron.

This is the cycle of our scheme which here partially combusts the carbohydrate to carbon dioxide, a process which, like the combustion of carbohydrates in the living cell, is specifically retarded by prussic acid.

The significance of the system fructose-phosphate-iron lies in the fact that it is built up exclusively of substances which occur in the cell, and that here, as we must assume, one of the physiologically active forms of iron is present. In this respect the system is a better model than the charcoal model in which the combination of iron is not physiological. On the other hand, the surfaces are lacking in the fructose system, which necessitates high and non-physiological concentrations and makes it non-narcotizable.

XII

The problem of attacking fats by means of iron in the test-tube is for the most part still to be solved. Nevertheless, the little that has been done is of interest because one of the combinations of iron occurring in the cell—the combination with the SH group—plays a part here.

Thunberg found that iron salts accelerate the oxidation of aqueous lecithin suspensions. We have studied the reaction more closely and found that iron salts act similarly on linolenic acid, that the double bonds of the linolenic acid are attacked in the reaction and that the taking up of oxygen ceases when two of the three double bonds have disappeared. Thus the action of the iron is not strong and not to be compared with the action of iron on the fructose in our models; but still we have here a system which is built up exclusively of substances that occur in the cell.

Meyerhof found that in the system linolenic-acid-iron the iron can be replaced by the SH — group. Hopkins showed the same to be the case for the SH — group of the glutation which, according to his discovery, is quite a common constituent of living cells. So it seemed that the SH — group, like iron, can take up and carry oxygen, which contradicts our assertion that iron is the only autoxidizable component of the cell.

The contradiction becomes even stronger if we add that, according to Mathews and Walker, the autoxidation of cystein is retarded by prussic acid. When Mathews and Walker added prussic acid to a neutral cystein-solution the oxygen absorption ceased. According to this it seemed that the SH — group, like iron, not only carries oxygen, but also, like iron, is inactivated by prussic acid, which contradicts our assertion that prussic acid effects the absorption of oxygen only in that it combines with iron.

If we consider the experiments of Mathews and Walker more closely, we hit upon a difficulty. If prussic acid inactivates the SH — group, then it must combine with it, and the amount of prussic acid must be stoichiometrically related to and of the same order of magnitude as the amount of cystein which it inactivates. However, the figures of Mathews and Walker show that one molecule of prussic acid inactivates 1,000 and more molecules of cystein. As this is contradictory to the laws of chemistry, we have taken the stand that the autoxidation of cystein is in reality not an autoxidation, but is due to the action of traces of catalytically active metals, which, under the experimental conditions of Mathews and Walker, must have always been present as impurities in their solutions.

In order to test this we worked out a method of purification for cystein, carried out our experiments in quartz instead of glass vessels, and, which was no doubt the vital point, prepared the alkali for the neutralization of the cystein-chlorhydrate by distillation in quartz vessels. It thereby developed that the oxygen absorption by the cystein solutions became less and less as the purity of the solutions increased. While the purest preparations of Mathews and Walker were one half oxidized in a few hours when shaken with air, 14 days were necessary in our best experiments to oxidize half the cystein under otherwise similar conditions. If we added iron to these preparations they assumed the properties of the preparations described by Mathews and Walker.

What held up a true knowledge of the facts so long was that one was not accustomed to deal with the quantities of iron which are active in the cystein catalysis. Some 1/100,000 mgr of iron when added to 10 cc of a solution of cystein cause a large and easily measured absorption of oxygen, while it is hardly possible to test for iron at such dilutions with the customary reagents.

In summary, cystein free from metal does not react with molecular oxygen and therefore can not carry it. In solutions containing metal, it is the metal which carries the oxygen and this transfer of oxygen, like the other metal-catalyses, is retarded by prussic acid. This case, which at first seemed to be irreconcilably opposed to our views, becomes, on closer examination, a very simple and striking argument for the truth of our theory.

Our experiments do not indicate that the SH — group is insignificant for respiration; rather they show wherein it is significant. By combining with the SH — group iron attains a reactivity which is greater than that of any of the known combinations. Iron, combined with the SH — group of cystein, reacts ten times as fast as the iron in charcoals containing nitrogen or the iron in the fructose-phosphate mixture.

XIII

If we survey the three models discussed—hemin charcoal-amino acids, fructose-phosphate and cystein-linolenic-acid—and compare the effects of iron, we recognize that in each the combination of iron has a decisive influence upon its action. Iron combined with the nitrogen of the charcoal attacks neither the fatty acids nor sugar, but only the amino acids. Iron combined with fructose-phosphate attacks neither amino acids nor fatty acids but only sugar and of these only fructose with an appreciable velocity, so that it would not be difficult with the help of this artificial system to separate fructose from galactose as completely as with the help of fermenting yeast cells. Iron, combined with the SH — group, attacks neither amino acids nor sugar, but only fatty acids and of these only the unsaturated ones.

This contrast shows upon what the specific action of respiration depends. To be sure, it is always the same atom which takes up the oxygen and transfers it, and it is always the same process—the change in valence—which is the basis of the oxidation, but whether and how quickly this change of valence takes place depends upon how the iron is combined. Therewith the specific action is explained so far as it is possible in the present stage of physical chemistry. Why iron in the one combination reacts quickly, and in the other combination slowly, we can not explain any more than we can explain the velocity of any chemical reaction. The mechanism of chemical reactions is unknown.

XIV

If we ask ourselves in conclusion: "What is the respiration ferment?" the answer depends upon how far we carry the idea of respiration. If we confine it to the oxidation process, then the respiration ferment is the sum of all the catalytically active iron compounds which occur in the cell. If we consider as a part of respiration reactions in which, as in the reaction between fructose and phosphate, specific affinities for iron arise, then all substances which, by a splitting or condensation, allow iron to combine, are also constituents of the respiration ferment. Whether we comprehend the idea of respiration in a narrow or broad sense, iron will always maintain its central position as the oxygen-carrying component of the respiration ferment. For oxidation is that process by means of which respiration is differentiated from the other ferment-reactions and in which the purpose of respiration, the production of energy, is fulfilled.

OTTO WARBURG

BERLIN-DAHLEM
GERMANY

JOHN MUIR, NATURALIST AND POET

OF the naturalist-poets of our time, two stand out above the others, the writings of both permeated with a lofty optimism—Burroughs and Muir. John Burroughs "accepted the universe" with an eye on the unresting masses who, tormented by one another and with no time nor energy to look upward, find this world empty and meaningless like themselves.

John Muir went deeper than this, "treading the crust of the earth in adoration." He found "the love of wildness ever sounding in his ears," a world in which beauty, grandeur and fitness were always within the reach of men and where most of the disillusionment and misery of human kind were chiefly self-inflicted. "Freshness and beauty are everywhere," he writes; "flowers are born every hour, living sunlight is poured over all and every thing and creature is glad. Our world is indeed a beautiful one and . . . I would hardly accept a free ticket to the moon or to Venus or any other world for fear it might not be as fraught with the glory of the Creator as our own."

"The Life and Letters of John Muir," as prepared by his younger friend, Professor William Badé, gives an illuminating record of the thoughts and activities of one of the finest and rarest of men. Muir was great as an explorer and investigator. His studies of mountains and glaciers give him a high rank as an interpreter of phenomena. His sympathetic record of trees and beasts places him with the most intense of nature lovers. His exquisite choice of langauge, noticeable in letters and essays alike, has nowhere a touch of the artificiality of those who give nature their patronizing but ignorant approval. His warm friendships and freedom from bitterness display the fine mettle of his character.

In two plump volumes, as a labor of love, Professor Badé gives us a clear insight into Muir and his ways. Born at Dunbar, Scotland, on April 21, 1838, he came early to Wisconsin, where he entered the state university. He went thence to Indianapolis, intending to become a mechanical inventor. But his love for nature carried him out of the shops and set him on a thousand-mile tramp to the gulf. Still later he sought the greater wildness of the high Sierras. Here he became a shepherd in the foothills, but soon forsook the sheep, "hoofed locusts," he called them from their ruthless raids on forest vegetation. For years he devoted himself to the Yosemite Valley, its geology and its grandeur, modestly describing its scenery in letters to his friends, and later as his fame spread eastward, in many magazines. One of his finest essays, the best bird biography in existence, relates to the water-ouzel as seen at East Lake in the Kings' River Canyon. After emerging from the Yosemite, Muir retired to his farm at Martinez and devoted himself to writing. He interrupted this work with frequent rushes to the Sierras, Alaska, Australia and the ends of the earth. His later years were devoted to the efforts for the protection of the Yosemite and other like glacier-worn valleys which he called collectively "Yosemites," not forgetting their giant forests. "However man might slight these," he said, "God must be proud of them for they were the finest He ever planted."

In these efforts he was mainly successful, but not in the case of the noble Hetch-Hetchy Canyon of the Tuolumne, which he saw to his great grief condemned as a water supply to San Francisco.

Muir always refused to lecture, but to small circles he was a brilliant conversationalist. His general attitude appears in an answer to the assertion that "the world was made for man," a notion derived from "the huckster appraisement of Nature." "Certainly not," said Muir. "No dogma taught . . . forms so insuperable an obstacle to a right understanding of the relation which human culture shows to wildness. Every animal, plant or crystal controverts it in the plainest terms. Yet it is taught from century to century as something ever new and precious, and in the resulting darkness the enormous conceit is allowed to go unchallenged."

STANFORD UNIVERSITY DAVID STARR JORDAN