THE OXIDATION MECHANISM

Much has been done in the study of the oxidations, but all is not yet learned. It seems pretty certain, however, that for any particular substance the course followed is determined by its structure and its environmental influences. Moreover, in larger molecules the differences in the various atomic groups will determine a correspondingly different oxidation course. Even the difference in the positions of similar atomic groups with reference to some other very active group will determine a different behavior in each.

In a system as complex as the living cell, one may only provisionally draw conclusions as to the events of the oxidation process from what one is able to observe in vitro experiments, and it is especially hazardous to use the behaviors of substances that do not exist in tissues as criteria. So complex indeed is the living system that one need never expect to exactly reproduce it in vitro to serve any experiment that might be designed. Therefore, the broadest field of possibilities must be selected from to lay out the most likely course of events; and these must all be checked most carefully by known data. Moreover, the rapidity of change in the intermediaries of oxidation of sugar and fats is so great that these substances need not be expected to patiently wait for isolations by any laboratory chemist. Where ærobic oxidation is concerned their order of instability is such that they have escaped detection. This moreover is the field of activity we are concerned with in matters of immunity. The

bodies we describe as intermediaries in ærobic oxidations possess an instability of exactly such an order and I have reasons to feel that what I shall propose here as the most likely mechanism is quite possibly correct.

In sugar all carbon atoms do not have the same values. We might say that quite remotely they all possess different values, and hence the well known optical isomerism is possible. However, certain carbon atoms, that of the carbonyl group and its alpha and beta neighbors, have especially important differences from the rest. Glucose and fructose, because of the difference in position of the carbonyl groups, have especially useful differences. Yet when the carbonyl groups are inactivated there may be sufficient similarity to permit quite uniform dehydrations to take place with the formation of a long unsaturated chain, straight or cyclic, quite able to be oxidized directly to carbon dioxide or simply leave a residue of formaldehyde or its peroxide. Inositol found in muscle may be related to a process such as this.

It is more probable that dehydration, peroxidation, and cleavage of the fructose and glucose molecules are accomplished between the carbon atoms in alpha and beta position to the carbonyl groups. This reaction is catalyzed by iodine. I may add that the same reaction takes place in the oxidation of fats. Both in the sugar and fatty acid so changed, the carbon atoms of the peroxide union yield to the splitting of the molecule and the production of two carbonyl groups. Thus from glucose, a two carbon and a four carbon chain aldehyde are formed; and from fructose one molecule of glyceric aldehyde and one of the aldehyde of glyceric acid are formed. From the four carbon chain two aldehyde molecules are formed. Likewise,

by repeating this procedure glyceric aldehyde may undergo the same change yielding formaldehyde and glyoxylic acid. By continued dehydrations, the glyceric aldehyde, the aldehyde of glyceric acid, the glyoxylic acid, and glycollic aldehyde that were formed are converted into ketenes and suboxides of carbon as pictured below. To indicate their metabolic relations we designate the internal anhydride of glyoxylic acid, O=C=C=O, as Glyoxylide, the internal anhydride of malonic acid, O=C=C=C=O, as Malonide, the ketene of glycollic aldehyde, H_2 C=C=O, is called ketene, and the ketene of lactic acid, H_2 C=C=C=O, is called Lactene or Malonene. We give the whole group the name "Ketenones," for we use them together in one solution for therapy purposes.

These unsaturated substances are extremely reactive in two directions because of the wealth of free valency they possess. They either take up peroxide oxygen and burn to carbon dioxide and water, or first enter a chain reaction, as such or as a peroxide, with suitable structures as pictured below before burning to carbon dioxide and water and at the same time inducing oxidation of the substance combined. They may add water reversing the process, reproducing sugar in any of its forms. It seems certain that the free valency of carbon atoms tends to activate oxygen to what I have called the "peroxide oxygen" state, in which it will combine free valent carbon. Hence, the more active are the free valences of the substance the greater is its catalytic power of activating oxygen. So the free valences of the very unstable unsaturated Glyoxylide, Malonide, and Ketenes with which we are dealing may induce a "peroxide state" of oxygen so actively that it will combine the lethargic free valences of un-

saturated carbon atoms of the large clumsy molecules of pathogenic coal tar products and similar bodies. When hydrolysis takes the place of the dehydrations and peroxidations described above, glycolaldehyde, glyceric aldehyde, and dihydroxyacetone intermediarily precede ketene and malonene. All five are active oxidation catalysts since their carbonyl groups are flanked with ethylene or hydroxyl, and not by amino groups.

On the other hand the free valency disposes them to polymerization especially under several environmental conditions that are possibly exaggerated in living cells. When oxygen is not adequately supplied in excess and when thus a minor portion of their free valences are peroxidized, or when stable peroxides are present, polymerizations are not only free to take place, but under the influence of the peroxide present, are even accelerated, so that difficultly burned clumsy bodies are formed that further block the oxidation progress by being present adsorbed in the functional mechanisms of the cell and thus in the way, as it were. The withdrawal of free carbon valences from the field in this way reduces the activation of peroxide oxygen and so also poisons the oxidation mechanism.

It appears that a peroxide oxygen union with carbon either "in parallel" or "in series" disposes to an activation of the electrons of the carbon atoms of the group and by "resonance" also to an activation of the electrons of similarly positioned unsaturated carbon atoms of neighbor molecules because such free valences will unite with each other if oxygen is not available.

Environmental offenders such as excessive exposure to ultraviolet light, especially in the absence of adequate oxygen produces peroxides of various unsaturated bodies of large molecular weight that do not yield to easy oxidation. Thus derivatives of cholesterol, produced in the body by sun light, by bacterial action, by the action of peroxides in anæsthetics taken into the body or contacted in plant pollens or as coal-tar preparations, and also in many "aniline dye" products, form peroxides that polymerize and produce polymerizations of unsaturated metabolites with the significance mentioned here, or yield fluorescent substances that can transfer the energy of any stage of normal metabolism to any functional mechanism affected, and thus through fluorescence activate and force functional activity beyond physiological control. This I believe is the true mechanism of allergy.

Therefore, the unsaturated products of both sugar and fat metabolism as well as of other normal cell constituents may be diverted from their normal service by polymerization so as to cause disease, when the oxygen supply is inadequate to fully burn free valences, and when difficultly burned peroxides are present to help an abnormal polymerization along. Depletion of accessory catalysts like peroxidase and catalase disposes to this abnormal process.

In the oxidation of fats, one might propose that the hydroxyl of the carbonyl of fatty acid and the hydrogen of the alpha carbon atom are removed first, then hydrogen shift from the carbon atom in beta position to the carbonyl carbon takes place so that the ethylene group is formed by the alpha and beta positioned carbon atoms. Peroxidation here with subsequent split leaves two molecules with terminal car-

bonyl groups from which oxidation proceeds again. Thus is explained the well proven metabolic fact that two carbons at a time are removed from fatty acid in its oxidation, and so this scheme seems to fit not only the physiological facts, but to offer the basis of pathologic events exhibited in disease, no matter what direction it ultimately takes.

As age advances the vigor of the oxidations is progressively reduced. In plants the same phenomenon should be observed to follow the complexity in the terpene structures formed, that is, the failure of oxidations to compete with polymerization. In cancer cells the malignancy of the cell and its loss of oxidizing power run hand in hand in my experience and so too the presence of polymers is more notable. One is therefore tempted to conclude that old age changes will ultimately lead to neoplastic efforts in any cell.

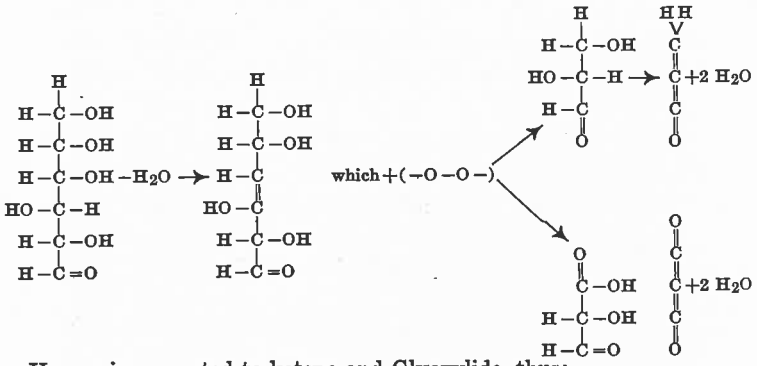
This very neoplastic effort of cell multiplication, mediated by fluorescent properties specifically affecting the particular mitotic mechanism of the cells that are envolved, offers them opportunity to adsorb from the blood stream and dilute the offending substance to a state of adsorption in which it is more readily oxidized by such oxidizing powers as still survive in the cells concerned. The tendency of a lipoid in water phase in cancer cells aids this detoxication of the blood. Most important and amazing of all, the dilution is directed toward conversion of the polymeres of intermediary unsaturated oxidation metabolites into their monomere, active catalytic form, which when restored should be able to reestablish the oxidation mechanism in the cell. Thus the crucial step in the causation of malignancy is directed toward the cure. Some day when the multiplication is rapid enough as

compared with the production of the toxic factor the evolutionary purpose of the whole effort will be realized, and an efficient oxidizing machine will be produced which should serve as a protection not only against malignancy, but also against all of its associated allergic expressions, old age changes, and the lowered resistance against infection. If this anticipated accomplishment of the race will also help the development of the fetus and give the infant the start we observe after treating an expectant mother with our Ketenones, then a better race will be brought into the world as well.

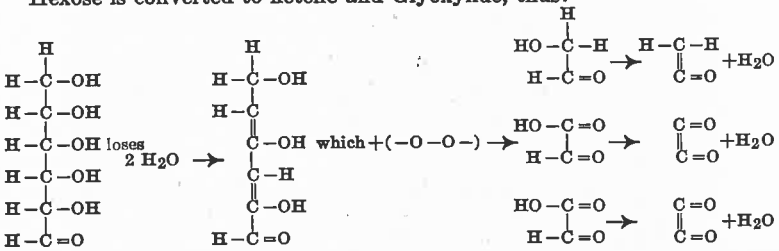
Here too is a guide to the active therapy to be enlisted and we shall see later on how dilution of the specific polymers concerned yield the active monomers needed to restore a normal oxidation catalysis and recovery.

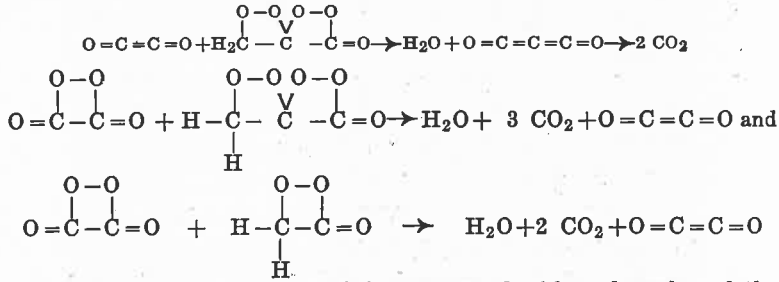
Formaldehyde might be grouped with the ketenes in our scheme of the oxidations in spite of its possession of but one carbon atom. It serves as the carrier of a chain reaction which any of the ketenes may mediate, and it also serves as the starting point for the synthesis of ketene, of lactic acid, and even of hexose and glycogen. This is possible because of the ease of union of two molecules by dehydration that forms double bonds between carbon atoms, able to take up oxygen and burn to formaldehyde and carbon dioxide on the one hand, or on the other, to take up water as the condensations are made and thus to produce the hydrated molecules lactic acid, hexose and glycogen.

Under proper conditions, two molecules of formaldehyde may condense to form glycolaldehyde, and three may form dihdroxyacetone and glyceric aldehyde. Three molecules of glycolaldehyde may condense to



Hexose is converted to ketene and Glyoxylide, thus:

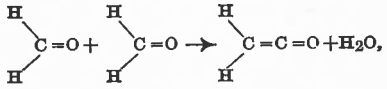


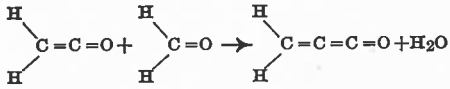


Thus the carrier O=C=C=O is regenerated with each cycle and the products are water and carbon dioxide, the reactants being fully burned.

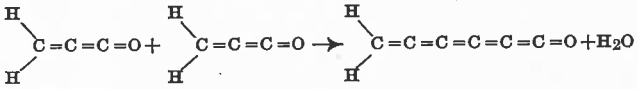
In like manner the internal anhydride of malonic acid O=C=C=C=O mediates the same combustions forming the carrier glyoxylide and the same resultants, carbon dioxide and water.

form glucose, and two of glyceric aldehyde may form fructose, as may also occur in plants. I have found these intermediaries to be strong oxidation catalysts

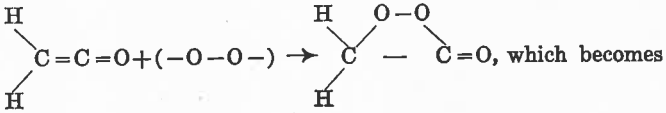


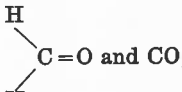


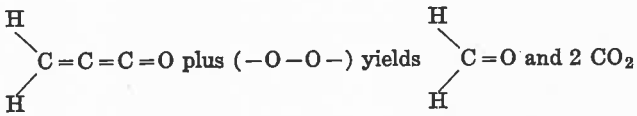
The Malonene or Lactene so formed by adding 2 H_2O becomes lactic acid.



The Hexylene so formed by addition of five molecules of water becomes hexose, (glucose). Ketenes add oxygen and yield CO_2 and formaldehyde.







within the body, able to remove the basis of otherwise incurable disease by correcting an existing deficiency, and I therefore assign to them all an important place in aerobic glycolysis, and natural immunity.

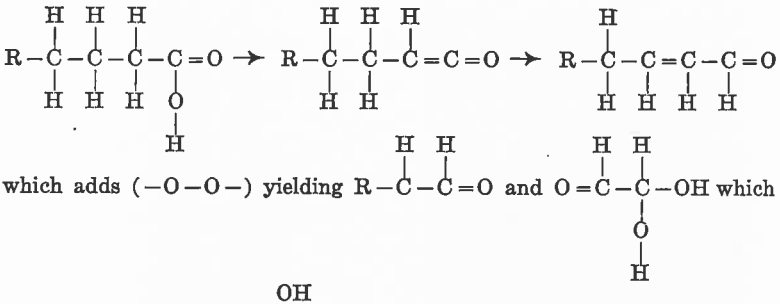
Ketene or Lactene by condensing with lactic acid either before or after dehydration and peroxidation leads to the production of formaldehyde, water, and

carbon dioxide. The dehydrated product of condensation on the other hand may add water to become a pentose or hexose.

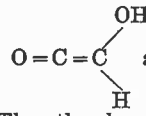
Thus energy may be yielded or utilized by the unsaturated carbon chains by oxidation or hydration, and carbon dioxide or sugar produced. The formaldehyde or ketene formed in the first reaction may also be burned or carry another cycle as the conditions determine. Fatty acid may dehydrate and then undergo hydrogen shift yielding double bonds between the alpha and beta carbon atoms which may add peroxide oxygen and split off a two carbon atom chain glyoxal leaving the long chain with a carbonyl group at which oxidation commences the same series of events.

The procedure outlined gains probability because the intermediaries in ærobic glycolysis have never been isolated and thus must share the same order of instability as the substances of the scheme presented here. Hence the peroxides described could never be detected, nor have peroxides been found in the body in view of the fact that peroxidase is well distributed in the tissues. Furthermore, oxidation of the substances here described as paralyzable by such substances as the quinones and dihydroxy-aromatic compounds, which prevent peroxidation of free valences.

The amino group definitely antagonizes oxidation boosting by the carbonyl group. It protects protein amino acids from oxidation. Thus when the amino group is removed from glycine, glycolaldehyde remains to favor oxidation, and when carboxyl is removed from histidine, the lethal inhibitor histamine remains. Acquired immunity then depends upon proteolysis and desamidation to liberate carbonyl activity.



which adds (−O−O−) yielding and which

dehydrates to  and yields on peroxidation, formic acid and carbon dioxide.Thus the chemical basis for oxidation of fats is provided by this system.

The anti-oxidation effects of carcinogenic bodies exhibited in the animal body and observed in isolated tissues by Pourbaix in Maisin's laboratory should possibly be explained as a quinone activity. Commercially the phenomenon is employed to suppress polymerization of unsaturated substances, because the polymerization is catalysed by traces of peroxides, and the aromatic dihydroxy bodies and quinones prevent the production of the peroxides. These facts support my contention that the carcinogenic agents act as quinones and that the normal oxidation process is a peroxidation of unsaturated groups.

Also the desaturated six carbon chains, the phosphorated hexoses, the adenylic nicotinic acid co-enzyme system, and creatine phosphoric acid all play important roles in maintaining a complete oxidation mechanism and are essential to recovery be the disease a leukemia, an infection, some form of allergy, or cancer.

There are probably many more accessory oxidation

agents than the hormones and vitamines mentioned so far. Each has its specific work of limited scope but none appear to be able to accomplish this special work without the support of the general catalysts of sugar oxidation we have described here. This is evident in the fact that serious hormone deficiency, endocrine gland abnormality, and vitamine deficiency on a diet that is not seriously inadequate can be changed to normal by the use of the unsaturated ketones have introduced. From what has been said above it should appear that they play a fundamental role in both plant and animal oxidations, and were it not for their great instability evidence of their existence in alcohol producing plants, the yeasts and moulds, should be forthcoming. The weak immunizing properties of yeast extracts may be attributed to them as well as to various oxidation coenzymes like adenylic and nicotinic acids.

It is interesting that the co-enzymes of oxidation contain carbon and nitrogen atoms joined by double bonds. I should interpret them as having a negative catalytic effect protective against destruction of the co-enzyme nucleus, for these groups both in guanidine and in the imidazol ring may practically completely annul oxidation in very small dosage and bring about rapid tissue death. One means is by inactivating peroxidase and catalase, and thus the decarboxylation of creatine and histidine by tissues forced to secure energy anaerobicolly compares with the primitive toxic mechanism of bacteria that produce methyl guanidine and histamine from creatine and histidine in colon putrefaction. Since the imide group serves as oxidation carrier in arginine in the oxidation of ammonia decarboxylation may negate the catalysis.