The Chemistry of Natural Immunity

PERTINENT STATEMENTS ON OXIDATION

One would expect that the cell structure that controls compensatory reproduction and hypertrophy would be the same structure that plays the fundamental part in the functions of the cell. It appears that this is exactly the case for the site of energy production is really the surfaces of the nucleus granules or genes. The energy production by the nucleo-protein complex is therefore important to our subject. The distribution of the energy throughout the conduction, secretion, contractile, or reproductive mechanisms from the energy generator, the nucleus, is likewise important to our subject, and since we conclude cholestrol is essential to this function we must look into the changes it undergoes. Though the material thus introduced reaches far out into the subject of physiology, we will try to keep as straight a path as possible in describing their essential position in, and such of their processes that constitute immunity to toxic activity of various origins, and to demonstrate how when this immunity is exhausted, the malfunctions that constitute allergy come about. The main purpose is to show how the natural immunity mechanism may be restored and the infection or the allergy, be it simple as in asthma or

profound as in malignancy, may be overcome and normalcy again be established.

The fact that the cell nucleus is the site of oxidations for energy production has been recognized a long time. My own observations on this were made in connection with some experiments on the parathyroid glands twenty-five years ago when I found that various guanidine bases were excreted in the urine after parathyroidectomy, during and previous to the violent muscle activity of tetany. Because of the presence of guanidine in the guanine unit of nucleic acid and the general extensive nucleolysis and cytolysis that followed parathyroidectomy its excretion in the urine might have resulted from excessive activity and breakdown of the nucleic acid structure, and thus it gave suspicion of being an important unit in the oxidation mechanism. Now a days we know that guanidine plays an important part in the oxidation of ammonia, via citrullin arginin and ornithin. Its place too in creatine phosphoric acid is important for the phosphorization of adenylic acid; and adenylphosphate is essential to anærobic glycolysis. This was not known twenty-five years ago. Still it is not peculiar that one should have suspected the guanine sugar phosphoric acid nucleotide to belong to the energy producing mechanism for cell functions, and that it's contained guanidine therefore should be an important structural unit. Most important structural units are toxic when excessive in the blood stream; even calcium is. It is shed in large quantities after parathyroidectomy and also plays an essential role in sugar oxidation. However we must not think of the parathyroids as simple calcium guardians. It is generally thought that the blood calcium and the phosphate of the blood

bear a constant relation to each other. Their product in milligrams per hundred cc. of blood is about 36, so when the calcium excretion is raised the phosphate excretion drops and vice versa. But after parathyroidectomy both the calcium and the phosphate increase in the blood and are excreted in greatly increased amounts in the urine, so the situation is not simply a matter of deficient calcium retention. Indeed the calcium may increase in the blood after parathyroidectomy even to the extent of its toxic depressant action. All of the toxic substances secreted in large quantities during the early tetany stages while the kidneys are still functioning, can be washed out of the blood by various saline injections with relief of tetany, but they accumulate during the late stages when the kidneys cease functioning, when neither calcium solutions nor other solutions are able to allay the toxic state. Indeed then, calcium injections produce coma more quickly. At this stage the glomerulæ of the kidneys are completely shot by way of hemorrhagic degeneration. If the parathyroid glands simply controlled calcium metabolism the tetany could be completely controlled and none of these conditions would arise. The difficulty with the "total calcium function theorists" is that their parathyroidectomies were not complete and the unremoved tissue had a chance to undergo compensatory hypertrophy. Complete parathyroidectomy is always fatal. Calcium deficiency is controllable. This digression could be followed further. The various other toxic bases, histamine, decarboxylated arginin, and other bases which I have not yet had opportunity to identify, point to the most extreme demands for oxidation energy during tetany because these bases are decarboxylated tissue structures

that are sacrificed for even the little energy yielded by their decarboxylization. So even the parathyroid function has its influence upon the oxidation mechanism.

The progress of the evolution of the oxidation mechanism, which, too, must undergo change with adaptation, should permit the operation of several contemporary mechanisms; namely, that being developed, that being discarded, and perhaps a middle course mostly in use. It is known that in the hepatectomized animal fructose is not used by the tissues, and glucose is used. Yet glycogen is split by the liver to fructose di-phosphate which is directly usable by the tissues. Fructose is not used as such and fructose di-phosphate is not known to circulate in the blood. However the white blood cells that have much to do in carrying material after a meal may manufacture or may well convey some precious fructose phosphate compound from the liver to the working cells where it is liberated under conditions of tissue activity. This consideration permits that a dehydrated hexose molecule be burned for energy production, and a demand upon white cells which may call them into hyperplasia when their work is handicapped. Thus we have employed a large dehydrated fructose phosphate and glucose phosphate molecule and their fully unsaturated derivatives in the leukemias, coronary thrombosis and cancer, and in the acute infections as poliomyelitis and in the chronic infections like tuberculosis and leprosy that excite a small round cell infiltration, with the most pleasing results. And since the deficiency involved is repaired by this procedure we believe our reasoning has been correct.

Finally, any deficiency in any of the accessories to

the oxidation process may contribute to the pathologies dependent upon impaired oxidation. Vitamins A, B, B_2, and D, Warburg's yellow pigment, ascorbic acid, cytochrome, adenylic acid, and the other co-enzymes must all be considered and made good wherever cell multiplication goes on beyond physiological control, or as we may say "allergically." However at the bottom of such conditions stands the toxic structure we will discuss later and this must be removed through a vigorous oxidation catalysis. It is even necessary to maintain the balance of mono-valent and di-valent cations necessary to correct the injury to dispersion of the cell colloids caused by physiological activity, such as happens in an extreme degree as a result to changes in complex substances in the development of tetany. Therefore calcium, magnesium, and potassium are required in correct amounts in various oxidation systems, to maintain a water in lipoid phase.

The other subject of importance to normal and allergic cell function is the conduction mechanism, for the energy produced on the surfaces of the chromatin material must be distributed to the functioning structures in amounts exactly required by the demand for each functional activity. Two facts are observable. Striations are seen under high magnification to lead from the surfaces of the chromatin material to the contractile, secretory, and impulse-conducting mechanisms. It is known that every nucleated cell contains sterols and only cells with organized nuclei do. Sterols are synthesized in the body. They are fluorescent substances that can absorb energy from exothermic reactions going on in their medium, whereby they enter a new state which can only be retained a very short period, the energy being immediately dissipated

as radiation or handed on to an absorbing chemical system of correct absorption and emission spectrum range and in which this energy is spent in activating its chemical processes. Moreover where molecules are attached or arranged end on end, as they are known to be in fibril formations, every condition exists to pass the energy absorbed by the first molecule on to each successive molecule until it can reach an appropriate acceptor for this energy, the functional structure. In cancer where the cholesterol chemistry is so badly upset that the blood concentrations may rise high very sharply or drop below the normal with equal speed most irregularly, it is evident that this substance is not efficiently occupying its place in the cell structure and is produced very irregularly. The ease of hydrogenation of bonds of "C-5," its sensitivity to radiation and the occurrence of several cis- and trans-isomeric forms about the saturated "carbon atom 5" and involving the active hydroxyl group, and also the readiness with which other cyclic and side chain carbon atoms may become unsaturated leaves it open to a great variety of changes under the influence of photo-active substances and agents, in an energy producing medium like the living cell. Changed structure may even promote altered molecular arrangement and destroy the straight fibrillar structure so that the energy is no longer conducted to the functional mechanism but remains in the nucleus to activate its function of cell division. Oxidations in the side chain lead to the formation of poisons resembling the heart poisons produced by some plants and animals. These changes need not take place, yet in view of the cachexia of cancer and the fact that sclerotic calcification cholestrol vascular changes are lessened by malignancy, the

study of cancer is not complete until all of the changes undergone by cholesterol are settled.

Even though it is chemically possible to produce every known sex hormone from cholesterol, it would be difficult to prove that this is their parent substance in the body. I believe that it is and in the transformation the hydroxyl and unsaturated bonds of "C-5" remain, and the side chain of the five membered ring is oxidized away leaving a keto-group at "C-17." The keto- and hydroxy-groups may change position with hydrogen added at "C-17," producing a strongly œstrogenic substance with marked stimulating action on the growth of the genetalia of rats. If both positions are occupied by hydroxyls the effect is less on genetalia development, but stronger in changing the growth of the cock's comb. When both these positions are occupied by keto groups the effect on the growth of the genetalia is increased. The most active of all the male hormones has the keto group at position "C-3" and the hydroxyl group at position "C-17." With these shifts the position of the unsaturated bonds vary about "C-5." Although reduction of the keto group to hydroxyl increases activity in some respects, this may be referable to the easy oxidation of the keto group which may reduce its concentration in the blood before it gets to work on its chosen apparatus, whereas the hydroxy derivative on oxidation becomes a nascent active keto group at the site of its activity and is thus protected until it is used. Thus the comb is a special accessory sex organ adapted to one function only and oxidation of the hydroxyl groups is not adding much to its activity; whereas the genetalia have other work to do along the usual physiological lines and here the "keto" formed hormone should serve

more acceptibly. Possibly in this way the apparent inconsistency is made reasonable. At the same time not only the importance of the unsaturated bonds associated with "C-5" is emphasized, but also the carbonyl group which is able to mediate a chain reaction liberating energy according to the mechanism discussed later on. Except that the ring A becomes aromatic and photo-chemic activity is thus increased, the same situations hold for the follicular and corpus luteum hormones.

The vitamins of the D series, sterols closely allied to cholesterol, have essential physiological activity. Their photochemic significance and relation to calcium retention without parathyroid aid gives their sterol structure still more importance. This is especially true since calcium is necessary to the sugar oxidation mechanism. Through photochemic action the provitamin, ergosterol, is changed to a three ring system having three sets of conjugated double bonds between carbon atoms. The A ring is ruptured at "C-9," and the hydroxyl is retained at "C-3." An unsaturated carbon linkage is present in the side chain. Photochemic activity is therefore marked. There is no proof that the vitamin is not changed in the tissues by oxidation either at the hydroxyl or in the side chain to resemble a sex hormone more closely. The fact that only the structure with a free hydroxyl unprotected by an acetyl or glucoside union is active is significant in this direction. It is interesting too that the anti-rachitic and the calcium-fixing properties are separate, and the further products of irradiation of ergosterol, tachysterol, and toxysterol have no anti-rachitic properties like vitamin D, calciferol, although they are strong calcium fixing agents.

Substances of such essential and complex physiological behavior as the three sterol groups mentioned may well be related to other bodies of somewhat similar structure that possess profound influence on the chemistry of living tissues. Thus certain benzanthracenes and even simpler aromatic compounds which I believe inhibit the dehydration and peroxidation of hexoses are able to remove karyokinesis and cell division from the normal physiological control and place neoplasia in the category of allergies as I view them. This property is due to specific fluorescence to a large degree and also, I believe, to the ability to produce a carbonyl group that serves as the carrier of a chain reaction which will be described later.

The oxidation mechanism includes very definitely also both vitamins B_1 and B_2. Vitamin B_1 is a Thyol-pyrrol-pyrimidine derivative. Its molecule contains five unsaturated unions between carbon atoms. Its structure suggests possibility of being a pro-nucleic acid derivative, and its function is tied up with that of the nervous system. Its deficiency causes beri-beri, a disease showing peripheral neuritis and paralysis, suppressed heart action, and diminished oxidation with lactic acid accumulation in the brain. Pyruvic acid accumulates in the blood, and brain tissue slices use less oxygen than normal brain slices. Addition of the vitamin to the slices immediately raises the oxidations to normal and its administration to animals showing deficiency immediately corrects the total pathology. Thus this vitamin is definitely an oxidation agent. It may function thus directly by virtue of its several unsaturated unions between carbon atoms and between carbon and nitrogen atoms. It possesses an amino group that can very easily be replaced by an oxygen

atom thus producing a carbonyl group able to serve as an oxidation carrier. It may also serve the oxidation mechanism indirectly as a building unit for the production of nucleic acid.

B_2 the anti-pellagra substance is probably a flavine derivative containing five double bonds and two carbonyl groups and a pentose attached to a meso-nitrogen atom in nucleotide fashion. Thus it resembles Warburg's yellow pigment, a hydrogen acceptor in the presence of dehydrogenase co-enzyme. If the structure so far suggested is correct this body too functions in the oxidation mechanism, which its carbonyl groups may serve as carriers.

Thus the vitamins fit into the body chemistry much like the hormones and may replace them in some respects, for instance, tachysterol parathyroid and suprarenal hormone are interchangeable in calcium fixing activity. Moreover, under natural living conditions where a man exercises and perspires in the sunlight, he manufactures his own ergosterol (which otherwise is only built up in fungi and fish), and he converts this substance into vitamin D, and its further calcium-fixing irradiation products. But excessive irradiation may contribute carcinogenic properties.

Other substances of the highest physiological importance are products of digestion of aging spermatozoa absorbed from the seminal vesicules. They improve the efficiency of muscle and nerve cell function. The amount of adenylic acid and other nuclein digestion products may not be large, but the efficiency, perhaps of some particular structure formed with the aging of the sperm is important to muscle quality, and to mental activity, and also to the oxidation mechanism in a way that improves immunity to infection.

The chemistry of these substances is unknown at present, but their importance will call for their full investigation some time.

That physiologically important metabolites may become dangerously toxic is observed in the behavior of acetyl-choline, which is produced at the nerve ending of the autonomic system during their function. This substance is highly active in a dose of one to ten million, and to it some are ascribing the cause of such vascular disease as coronary thrombosis and occlusion. It is known that acetyl-choline is formed constantly at the parasympathetic nerve endings, and in worried or the high-strung people there is some chance for its accumulation. However, this could not take place in anyone with an unimpeded oxidation mechanism. Choline has much to do with the oxidation of fats. That it prevents the conversion of amino acids and of sugars to fats under the influence of cholesterol, it seems there is sufficient evidence when the rest of the oxidation mechanism is normal. It does not aid the burning of aceto-acetic acid, but where the rest of the oxidation mechanism is sound, its presence favors the burning of fats or their precursors by another route. It is, therefore, an important link in the oxidation mechanism, but of course where the oxidation process is otherwise impaired we must assume that it not only fails to function and therefore accumulates or is formed in greater quantity for compensation than normally occurs; and worst of all it is not burned itself and produces its toxic effects. Thus one might well assume that it is a factor in coronary disease, much like cholesterol is in other vascular degenerations that are so well known. In fact they both accumulate where the normal catalysis of oxidation is broken, and there-

fore both coronary disease and atheromatous degeneration and arterial sclerosis depend upon one basic deficiency, a crippled oxidation catalysis. Toxic blood colloid jelling is a commanding factor. That this is true will be seen from the fact that recovery is promptly brought about by the oxidation catalysts discussed below. Moreover in advanced arterial sclerosis with tortuous nodulated pipe stem vessels recovery has been accomplished with full restoration to normal so far as symptomotology and palpation could reveal. Vascular normalcy is important to tissue function and obliterative vascular disease so often the cause of tissue degeneration that one might say that all disease shows its marks on the vascular system early or late. The infectious granulomata all start out with an obliterative endarteritis. Cancer does also, and cancer should be classified with the granulomata. They are all based upon toxic activity that destroys oxidation catalysis. They are all curable by restoration of the oxidation catalysis to normal or to better than normal. This holds also for Renaud's and Berger's diseases.

Through an over-active nervous system, therefore, in the presence of deficient oxidation catalysis, an accumulation of metabolites to toxic concentration, be it choline, neurine, cholesterol or some other, is possible whereby disease is produced in a similar way to that caused by disease germ poisons where the oxidation catalysis is insufficient to destroy them. The various allergies including cancer possess in this way an additional mechanism for being brought about and being maintained. Again let me repeat that the restoration of a vigorous oxidation catalysis removes the

offending substance, no matter what its origin may be, and thus establishes the basis for recovery.

The oxidation mechanism is also influenced by the glands of internal secretion. They all play a part in conserving or stimulating fuel and oxygen usage in a variety of complicated ways which adapts their service perfectly to the most specifically differentiated requirements. For their best co-ordination they are placed under the control of the central nervous system. Under normal conditions this is a wise provision, but it lays the gland system open to allergic interference through the nervous system. Since they mutually antagonize or reinforce each other's activity, allergic hyperactivity of a part of the nerve center may excite or inhibit one or more gland activities and produce profound changes such as diabetes, toxic goitre, or any of the other well known or obscure endocrine disturbances. Fortunately allergic activity of nervous tissue (for example, as expressed by shingles, or even certain forms of mental imbalance and inhibited development) is readily corrected by the measures we propose farther along, and thus the most profound endocrine disease has yielded very promptly and permanently to this treatment. Such prompt response could only follow the correction of an allergic state for it takes place sooner than tissue regeneration of any gland could be accomplished. However, the nerve or the gland tissue development that follows the removal of oxidation inhibition has been observed to take place with remarkable speed; for instance, the descent and development of the testes in young adults, and the gain of normal painless menstruation cycles in young females, the restoration of thyroid and

pituitary function, and the improvement in mentality of imbeciles and idiots.

An experiment that shows the control exercised by the central nervous system over endocrine function is that where the circulation from one dog (B) was sent through the brain of another (A) whose brain was otherwise not receiving blood from his body, nor was the blood of the donor animal (B) circulating through A's body. When the blood sugar was increased in B's blood flowing through A's brain, tests of his (A's) systematic blood showed a drop in blood sugar and when the blood sugar in B's blood was decreased, A's systematic blood showed a rise in sugar. It is known, too, that gastric ulcer develops mostly in those who have suffered some form of nerve exhaustion or other change in the central nervous system. A mental or a nervous influence is a factor in many allergic disturbances. Adjunct to the brain control, the pituitary exercises hormone control over the other ductless glands, and allergic activity of any of its functions like allergy of any of the endocrines demonstrates characteristic disease.

The chemical structures of the hormones so far isolated and producible synthetically possess strong photochemic possibilities and both adrenalin and thyroxin contain hydroxyl groups in their aromatic rings that can easily oxidize to keto groups. The sex hormones have already been discussed from this standpoint.

There are several metabolites that may also share oxidation function; one, so well known in connection with allergy, histamine, deserve a word. Its imidazol ring, when present in the normal amino-acid histidine, plays an important harmless role. Simple

decarboxylization of this amino-acid gives the molecule very toxic properties and the ability to produce allergic necrosis. The mechanism is not understood; conjecture leads to the photochemic properties resident in the unsaturated groups of the imidazol ring which in the decarboxylated molecule may exactly annul the vital activity of its parent substance. The instance is valuable in emphasizing the profound effect so slight a change as the loss of a carboxyl group may cause. Since a tissue hampered by poor oxygen supply or poor oxidation catalysis will sacrifice its vital structural elements, amino-acids, for the energy secured by decarboxylization as my parathyroid studies have shown, allergic necrosis may thus depend upon a crippled oxidation mechanism.

The tissue slice method has facilitated the study of the oxidation mechanism in a most gratifying way and the facts so far revealed in the mechanisms of anærobic glycolysis are quite illuminating. However, the normal oxidation mechanism as conducted in the body with adequate oxygen supply must indeed be entirely different. One fact, the presence of free phosphoric acid, settles the matter. The system of sugar oxidation proposed later is very different from the usual conceptions. It was worked out over twenty-five years ago, long before any of the co-enzyme systems were established. The scheme is not intended to exclude any accessory to the mechanism but to fit in the general procedure the best it may.

One must not forget the ease with which some aromatic hydroxyl compounds change to quinones, or even exist as both forms in equilibrium in solution and in the solid state. Since as we will describe, the quinone group can conduct chain reactions and liberate

energy quite perpetually, and through its fluorescent properties this group is like other unsaturated unions between atoms and can appropriate exothermic energy evolved in its environment and either use it for activation of its own chemical processes, or hand the energy on to a suitable acceptor that can so use it, we have in these properties all that is necessary to make a virus of a suitably constructed molecule.

The change of hydroxyl to quinone in the sterols is also accompanied by changes in isomerism and as we have seen definite alterations in the growth promoting properties follow. The stigmasterols, the sterols occurring in plants, must also function with the genes for differentiated activities and for reproduction, and most likely, as I have suggested, in the distribution of the energy generated at the nuclear surfaces. Changes in structure of the type under discussion, other than takes place in normal metabolism, must pervert function and therefore both the plant and animal foods submitted to chemical activities in preserving processes of modern civilization, or through the action of drugs and anæsthetics taken into the body should be investigated as possible causes at the bottom of the cancer situation.

Through irradiation by sunlight, X-rays or ultraviolet light or by chemical activity the production of double bonds and the shifting of those present to produce isomers not normally present, the normal oxidation and conducting functions we assign to cholestrol may well be lost to be replaced by catalytic peroxidation activities such as the terpenes carry on. Thus one molecule of altered cholesterol adsorbed in chromatin becomes the energy generator that is in position to force the chemistry of cell division of neoplasia. The

cholesterol changed by irradiation and oxygen has also some opportunity to take on quinone structure and become a catalyst for energy production by the method to be described later, which energy in like manner must force cell division. Polymerization of unsaturated derivatives of cholesterol and from sugars offers a group of substances not yet known to exist but which must not be forgotten in cancer research, and the stigmasterol peroxides in ether extract of wheat germ oil showing carcinogenic behavior must be examined from that standpoint too. Twenty-five years ago when this work was started the chemistry of the sterols was almost a blank page, so the chemical properties thought essential to carcinogenic activity could not be identified with them, and indeed they need not be the only important materials of this class. That there are plenty others should have become evident from this survey.

It might be argued that all substances that have to do with energy production and energy distribution are of sugar origin, though greatly modified, or carry sugar in their structures. Among them ascorbic acid deserves a word. It is definitely of sugar origin, derived by oxidation of two carbon atoms. The reduced form carries an unsaturated union between the second and third carbon atoms. The oxidized form carries a chain of three keto groups, two of them hydrated. It is able therefore to carry an oxidation chain reaction, and has definite photochemic properties. Since it is so easily destructible it is able to serve in a minor way in the immunity against infection and against cancer as described below, and the reason for the feebleness of ascorbic acid as compared with each of the various Ketenones we use for this purpose is observable

on comparison. These reagents were put into use a quarter of a century ago. It is, therefore, a matter of the greatest satisfaction that the chemistry of vitamin C, so recently contributed, is confirmatory to our thesis.

With this general survey of free valency activities as an introduction we may go on to the changes in catalysis we ascribe to the causation and correction of lost natural immunity.

The study of allergy and immunity as here presented proceeds on the basis of the established experience of physiochemistry and physiology with the aid of a working hypothesis and clinical observations. It identifies a defect in oxidation catalysis as a fundamental feature in the causation of disease, without which secondary causes should not find support.

The treatment outlined follows as a logical development and since it removes a primary cause, the many disease manifestations that characterize the activity of dependent secondary causes cease to exist where it operates. The pathogenic feature is traced to the specific physiochemical properties resident in atomic free valency existing in appropriately constructed molecules. Thus in one chemical property general to a large number of chemical compounds, highly specific photochemic activity is recognized because of the special architecture of the molecule concerned. The unit of atomic arrangement fundamental to specific pathogenesis within a large clinical field is the subject of our thesis therefore; and it is discussed here as concisely as possible. The work was started about twenty-five years ago. The first divisional report was made in the Medical Record of New York in October, 1920.