APPENDIX

Amplifying Comments

Sugar Metabolism.

The highly efficient "smokeless" oxidation of sugar that leaves no traces of its existence by way of isolatable intermediaries, has been claimed by a number of brilliant biochemists. We believe it is the normal process and the others that are impeded enough to yield intermediaries are alternative paths provided to accommodate the need for vital energy production under the hindered circumstances that exist, such as anoxia, and injury. Isolation for study and the hindrances of the Warburg Chamber exemplify. In cancer a different hindrance exists. One resultant pathway has been ingeniously outlined by Krebs, but it has been erroneously accepted as the major process.

There are phenomena that suggest the "smokeless" process is one that is carried by a peroxide free radical, and the set-up may be as follows, but there is no real proof that the process is such. There is a strong confirmatory suggestion however in the competition offered by the amino groups of the oft used antibiotics, *which cause memory lapses,* periods of *suspended consciousness and the like,* that give rise to so many serious accidents. We therefore suggest that the F.M. especially of nervous tissue is provided with an activated amine group that condenses with the carbonyl group of fructose to form an azomethine bond, and that by an Amadori rearrangement this double bond passes to between C 2 and C 3. This of course mobilizes the hydrogen atom of C 4, and makes it subject to removal with free radical production, and in the presence of adequate oxygen, to peroxide free radical formation that carries the burning of the sugar to carbon dioxide and water. In the *absence of adequate oxygen* the sugar would split at this point to form lactic acid, or pyruvic acid. Catalysts that are required to facilitate this procedure are at hand, including the phosphorylases. Since we are unable to identify the "smokeless" process, we cannot tell how many such procedures there really are, and though we know much about the hydrolytic glycolysis system, for which we suggested a "hook-

up" in the text, we do not know the connections whereby the energy carriers give up their energy to the functional mechanism. Several processes including the fluorescence we suggested may operate here. In view of the vast deficit of fact we must consider all explanations as provisional. Since fructose is oxidized so much easier than glucose we offer the above suggestion as a possible course consistent with established chemistry. (See Chapter II and III).

References to the Literature

References to supporting contributions well known to biologists are not listed with their publications. The time only of the publication is given. This is because it is better for anyone not informed on such developments to consult one of the many fine text books on biochemistry and obtain a workable view of the subject. Our own references are given because they did not follow the beaten paths and are not included in such reviews. Fact is always preferred to hypothesis, but where facts are inadequate a given goal has no other path than by hypothesis, and this was our predicament. However our hypotheses are founded on fact and established chemical theory, and we did reach our goal, as the clinical achievements demonstrate.

Alkalinization of the bowel to normal pH for patients under treatment.

Since we look upon the amines developed in the colon by bacterial decarboxylation of amino acids as the vanguard of disease in an important degree, we have to suggest a means of normalizing the reaction of the colon contents to a normal of pH 8 where decarboxylation does not take place. To accomplish this without injuring the acid secreting cells of the gastric mucosa, we *suggest the use of several mild alkalies* during the meals, *three times a day.*

Notice is taken of the fact that iron in the ferrous state inhibits some of the more important decarboxylases in only a one percent solution, while hydrazine inhibits the four "co-decarboxylase enzymes" practically completely in a dilution of but one to a thousand. The ferrous iron excites no contrary

mutation, while the hydrazine does. However the early improvement secured would prove helpful were it not that in cancer *this reagent must excite a more vigorous neoplasia.* No doubt in the recent tuberculosis therapy this inhibition of decarboxylation is a most important factor in the early improvement, but with adverse germ mutations that are inevitable, it is better to not use the reagent. A simple procedure of securing a normal intestinal alkalinity is all that is needed, so we have prepared a capsule which can be dissolved in water and taken during the course of the meal. Several alkalies are taken as the citrates and carbonates. These are, besides a small dose of iron, and minute traces of copper and cobalt, tin and zinc, material doses of sodium, potassium, calcium, magnesium, and manganese. The stools should be examined as to reaction, which should be held at pH 8 to pH 8.5. The amounts of alkali may then be increased or reduced as needed.

Prolonged Silent Symbiosis

After vaccination against small pox the virus may maintain a prolonged absorption into the tissues or an integration with cutaneous tissue material either as a living virus or as a toxin which is able to produce tissue changes of a pox nature generally over the surface of the body when this toxin or virus is subjected to the immunological changes consequent to the carbonyl therapy of our text. Thus at the twenty-eighth week after the treatment has been given to certain cases of cancer, and the neoplasms have about completed their absorption, a general eruption of "small-pox" or vaccinia may show up, and then clear in three weeks, as the terminal phase of the recovery process. We have not had enough experience to master the details of this reaction, but it appears to fall in line with the rule we proposed that during the recovery the first symptoms to show up are the last symptoms of the pathogenesis, and the last symptoms to appear are the first of the pathogenesis. Thus we would place *vaccination* or a mild small pox infection as a causative agent in the development of the neoplasm, or one of the causative agents. It is probably held all this time absorbed or copolymerized with the collagenous material of the protective fibrosis, and being first to be laid down in this tissue, it is

the last to be broken down in the structure of the protective fiber, and is the one to show the monomeric or original form of the toxin before polymerizing through the successive phases that produce differing symptoms as the pathogenesis goes on. The last change in the toxin when we meet it, is its neoplastic property, and hence in the reversal of structure back toward the monomeric original form, the carcinogenic form is first to be lost and the cause of the cancer is thus removed, so it undergoes dissolution first. Any intermediate symptoms of the pathogenesis would show up in reverse order to their coming and disappear before the monomeric pox forming structure is reached. Thus while this is being set free from the absorbing or copolymerizing fibrosis it may produce the original symptoms of the infection before it is fully burned out of the way. We hold that it is fully burned out of the way since there are no cicatricial sequelae to the affair. Where we have given the carbonyl treatment to deep scars as from burns and in keloids, or following pox, this fibrosis has also cleared up to a remarkable degree, so we conclude that the scar is what we say, a protective copolymere or structure of collagenous material that adds the free radicals or highly polar unoxidized double bonds of the toxin of germ origin, or some incompletely burned tissue cell metabolite, or of a heat product, or an integrated virus.

The toxic fibrosis may predominate in a given tissue as the vascular walls and nerve nodes to produce a malignant hypertension with a systolic pressure holding stubbornly at 280 mms. Hg. Then twelve weeks after treatment a few days of reaction may duplicate the symptoms of an old malaria of several decades previously. The blood pressure is then found to be 140/80m ms. Hg. and remains so while the other symptoms are forgotten. A "silent" malaria was a factor in the fibrosis. It was the cause of the "essential" hypertension.

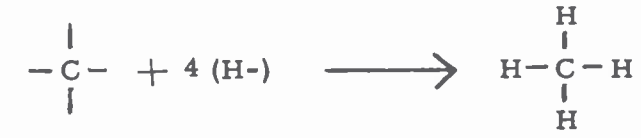
While vaccinia appears to form only the symbiotic type of integration, it may go lytic as would other less stabilized attenuated mutants, used as vaccines, when entering a favorable host. This may require hours or days. However certain viruses as Swine Pest virus are lytic only, and kill 100% of the pigs regularly in from 2 to 5 days. The state of union with the

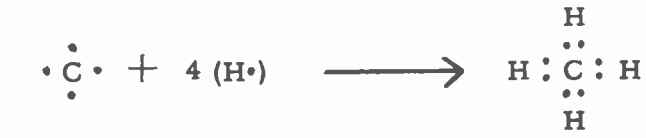
host cell however envolves the same atomic groups, as we have cured at times 100% of the treated pigs with one dose in from three to four days, even in the most virulent epidemics where the victims could not get up from the ground or eat or drink, and all untreated animals died in due course. The atomic unions are quite the same then no matter what form is taken or the state of the virulence. A twin or dimere status of the symbiotic virus holding unions as of Diagram V, (b), should be considered, as cleavage would favor change to the lytic type of action.

A Review of the Double Bond and the Free Radical

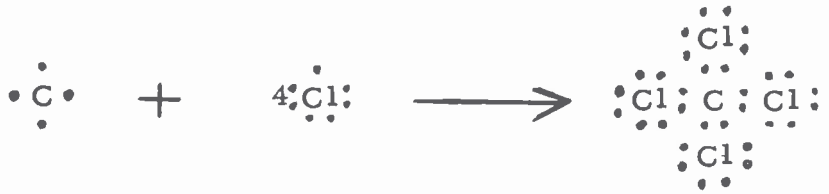
(1) Chemical Bonds:

The forces that hold atoms together to form molecules are called bonds. Each comprises a component or valence contributed by each atom. Up to 1859, when Kekule the renowned German chemist clarified the atom bonding system, progress was slow in establishing the structure of molecules. He proposed that the atom carbon holds four valences in all molecules, simple or complex, in which it takes part. Each valence he represented by a short line drawn out from the atom initial and joined to one from the other atom to represent the bond between them. This bond is termed the covalent bond for the reason just stated. It is made up of a pair of electrons shared by each atom. The following diagram illustrates (1) the Kekule formulae and (2) the electron formulae.

(1) 

(2) 

One will note that each atom donates and also accepts an electron to make up the bond. In such a molecule, all of the electrons and nuclear charges are in the same atomic field and hence the molecule is non-polar, non-ionized and stable in structure. Carbon atoms have relatively little tendancy to give up or accept electrons and hence tend not to form ionic bonds. Carbon does more readily combine with other atoms by electron sharing, which envolves much less energy expenditure than ionization, and hence is most favorable for biological structures and processes. It is also preferable to silicon for purposes of organic life. Carbon also tends to form a stable octet with electron accepting atoms such as chlorine, thus:



Carbon also gains stability through its four electrons in the outer shell with little tendancy to gain or contribute electrons, standing as it does midway between the stable electron states of Neon and Helium and being very different in type.

The Covalent Double Bond envolves the sharing of four electrons by two atoms, two electrons being contributed by each atom. The bond is shorter and the bond energy values are greater than for the covalent single bond. However, the mobile electrons are not entirely satisfied and tend to make additions. This may be surmised from the fact that the C-C bond energy is 58.6 kcal. while in the C=C double bond it is 100 kcal. per molecule, thus leaving about 17 kcal. looking for "satisfaction". In symetrical molecules the electrons are symetrically disposed. Otherwise one terminal of the double bond would present more than the other and be partially polarized. The substituents determine the direction in which electrons are asymmetrically displaced. Thus carbonyl and nitro substituents tend to polarize the electrons in the opposite direction, and like halogen tend

to decrease the availability of electrons in the bond. On the other hand, alkyl, aryl, alkoxy and ester groups increase the density of the electrons in the bond and tend to make it more negative. The tendency and position of addition of radicals carrying relatively positive or negative charges is thus determined. While methyl substituents tend to displace the mobile electrons in the opposite direction to make the closer pole of the double bond more positive and more able to attract a negatively charged atom or group, the situation may be reversed in the presence of peroxide catalysts. This is worth noting since peroxide catalysis is quite universal in tissue chemistry.

Some covalent double bonds are polarized by the charges the constituent atoms normally carry. Thus in the carbonyl group the carbon atom has an electro-negativity of 2.5 in comparison with oxygen's 3.5 and will tend to attract electrons from a conjugated ethylenic linkage, as well as a negatively charged atom, while the oxygen would tend to add the more positively charged unit. In the azomethine double bond the carbon electronegativity is less than that of the nitrogen, being 2.5 and 3.0 respectively, so the carbon would tend to attract the more negative oxygen first in the oxidative cleavage of the bond. A carbonyl group as a terminal is thus assured. The nitrogen would also attract oxygen and separate as an oxide of that nitrogen.

Double bonds tend also to mobilize the hydrogen atom attached to the carbon atom in the alpha position thereto. This hydrogen atom tends to separate as a proton. Continuous oxidative breakdown is thus facilitated with production of a peroxide free radical as a chain carrier, or of a terminal carbonyl group with each step of cleavage when an efficient dehydrogenator is supplied.

(2) Free Radicals:

The double bond may make an addition at one pole so as to break one bond with the other pole. This produces an unpaired electron or free radical at the other pole which wants to satisfy its stable octet by adding another electron. Whether this free radical is neutrophilic or electrophilic will depend on

the electronic concentration at that position. Free radicals so formed will add to one pole of a double bond of the same type molecule or another and thus form a dimer which presents a free radical at the opposite pole. These continue with the additions until the polymeres or copolymeres formed are so large in molecular weight and so inert that they fail to make further additions. Thus the polymerization process starts out with an initiator addition and continues as a propagation phase until it terminates itself by the inert nature of the final product. The propagation phase may be halted by addition of an inert free radical in like manner and at any stage of its progress.

In free radical production, the fission of a covalent bond is "homolytic". That is, each resultant fragment possesses an odd electron. One may contrast this situation with "heterolytic" fission in which the pair of electrons go with one fragment leaving the other with an exposed nucleus (ionization). The former fragment is negative and is nucleophilic (an anion), while the latter is positively charged and is electrophilic (a cation). Such rupture of a covalent bond results when the attacking atom has an affinity for an electron pair or for an atomic nucleus. A cation attacks at the point of highest electron availability while the anion where the greatest paucity of electrons is offered. The energy envolved in ionic reactions is much greater than where free radicals are produced, since two electrons are moved instead of one. So the latter are adapted to biochemical processes pre-eminently.

It is easy to see that when one dehydrogenator molecule can start a chain reaction that will increase in velocity with great speed and convert an enormous amount of substrate in short order, the concentration of the initiator need not be great. When acting on substances in solution, a minimum concentration as 1×10^{-12} will suffice. Such a solution still carries many millions of molecules where but one is required theoretically. When the reagent must initiate the reaction separately in a number of tissue cells, even though one molecule per tissue cell may suffice, the number of tissue cells must be considered and so the solution must be adequately concentrated or dilute as you please. Physiological reactions are of this order and that

speaks for their free radical and chain characters. Thus acetylcholine is found to renew contractions in surviving guinea pig intestine muscle in dilutions of one part to a thousand million of water. (Paul Karrer, Organic Chemistry, 3rd edition, 1947, p. 239). In this instance the hormone itself becomes the free radical. The quinones may offer free radical resonance hybrids which initiate reactions in equally high dilutions, and besides, the quinone carbonyl group may serve as a dehydrogenator and produce a free radical in the substrate from which the reaction is propagated. For example; Echinochrome A, the pentahydroxyl quinone of beta-ethylnaphthalene, produced in the ovary and egg of the Sea Urchin is able to motilize sperm cells in dilutions as high as one part to 2×10^9 parts of water. (Kuhn and Wallenfels 1939—Fieser & Fieser, Organic Chemistry, 1944 edition, pages 752-753). Likewise Crosin, whose dehydrogenator carbonyl group is activated by conjugation with an ethylene linkage, was shown by Kuhn and Moewus (1938-1940) to activate the gametes of certain algae in like high dilutions where but one molecule of the reagent served each sex cell. Benzoquinone has shown therapeutic effect in high dilution.

Diphenoquinone offers resonance hybrid free radicals in solution. When going into solution under correct conditions, an apple greenish yellow color is at first produced by diphenoquinone. This color lasts a few hours before turning to yellow and then becoming colorless as its polymeres separate out. The color may last as long as seven hours during which period it is therapeutically active, but after it becomes colorless it is inactive. The rich quota of resonance hybrids serve as chain initiating free radicals.

For this reason and because its highly activated carbonyl groups are such efficient dehydrogenators, its ability to initiate oxidation chains in high dilutions would be anticipated. Observations have shown that doses of a fraction of a microgram are sufficient to cure well established Hog Cholera in four days. To accomplish this, the amount of virus and toxin that had to be converted into peroxide free radical (Antitoxin State of Structure) to progagate the reaction was quite large. It was evident in the clinical symptoms that the rate of turnover in-

creased rapidly as the hours passed. In the treatment of Rabies, a small fraction of a microgram of a compound presenting serially arranged carbonyl groups with free radical terminals demonstrated the same conversion power. Molecular oxygen is necessary to the production of the "antitoxin" state of structure we referred to as early as 1924. It is the carrier of the oxidation chain so long as toxin is present, and thereafter persists as the "immune body" we referred to in "Cancer and its Allied Diseases" 1926. How this carrier is stabilized until new substrate arrives and how it is activated to again convert substrate is a matter of conjecture. Clinically and in animals we find it behaves that way, but the mechanisms are obscure still. A dimerization as when triphenylmethyl is converted to hexaphenylethane could be the case, or adsorption of the free radical into some colloidal structure, or perhaps the resonance hybrids discussed below. The subject is worth investigation.

The greenish yellow to pure yellow color of diphenoquinone, when under going solution in water, recalls the yellow color of triphenylmethyl which the writer observed while enjoying the courtesy of working in Prof. Gomberg's personal laboratory, just seven years after that wonderful gentleman and chemist demonstrated the free radical beyond any doubt. He found that his free radical gave the same absorption in the visible spectrum that quinoid structures show, as benzoquinone for example. This fact helped him work out the resonance hybrids, nine in number, that added to the stability of the structure. Because of this resonance triphenylmethyl as a free radical tends to show more stability than when dimerized to form hexaphenylethane. That is its resonance tends to weaken the C - C bond (70-80 kcal) which compensates for the energy needed to break the bond. The increase in entropy gained by the wandering of the lone electron of a free radical in this way should prove very instructive in considering the phenomena of the long persisting immunity. The lone electron in this capacity also determines the color characteristics and makes the molecule paramagnetic, both properties serving in their detection and measurements.

(3) Photoactivity:

Nitric oxide permanently presents a free radical stabilized as a covalent bond carrying three electrons. It can block chain reactions carried by free radicals. All oxides of nitrogen offer the same predicament; thus when nitrous oxide is used as an anaesthetic, it has sharply reversed many a splendid recovery course. This fact throws light on the nature of the recovery mechanism, indicating that it is a chain process carried by free radicals. Another experience is the blocking of the recovery course by substances carrying highly polarized double bonds. Substances in coffee, tea, in motor exhausts and paint solvents are of that nature. Substances that release hydrogen easily may reduce the free radical chain carrier and inactivate it so as to bring an end to the propagation of the reaction. If, however, the hydrogen donor is itself converted to a free radical and oxygen is at hand the oxidation chain may progress. Hindering substances are those with sulphidryl groups. The hydrogen is released to inactivate the carrier free radical and two dehydrogenated sulphur radicals will unite as a dimer, terminating the process. Free radicals act like cations preferring to attack positions of high electron density. Halogen anions and halogen free radicals thus act differently as the anion is nucleophilic (basophilic). This difference should be remembered in the interpretation of biochemical events and in the preparation of therapeutic agents.

Covalent bonds are split by light waves quite specifically. It takes more energy for this cleavage than when produced chemically or by heat since the atoms are activated by light in addition to the cleavage of the bond. The activation may be translational and result in more effective reactivity through increased collisions or it may be internal with transition of a valency electron from one quantum orbit to another, thus a new binding energy is obtained. In this excited state the molecule vibrates, and if the energy is sufficient, a dissociation into fragments may occur. When the energy is not sufficient, a rearrangement of atoms within the molecule may happen or a new electronic configuration may result. The reactivity is thus altered.

A molecule that has absorbed radiant energy is capable of fluorescense, that is the emission of this energy (somewhat degraded) as radiation almost immediately (10^{-8} sec.) after its reception, unless the energy has been used in some other way as by collision with a particle that can use the exact energy quantum that the activated molecule is carrying. This specificity is important to our photosensitization theory of carcinogenesis (Koch, Natural Immunity, 1934, 1936, 1939). The gas phase is ideal for emission as irradiation, as the closer the molecules are together and the denser the medium, the greater the opportunity for inactivating collisions. Such inactivation by collision is a very specific affair and only molecules of a particular molecular species can accept the energy available and become activated thereby. Particles that can quench fluorescense in this way gain the energy as internal energy and not as translational energy. This type of activation is termed photosensitization. Such energy may bring about dissociation of covalent bonds and produce free radicals that bring about activation of reactions that mediate the cycle of nucleoprotein construction and cleavage of viral and neoplastic propagation. Once the free radical is formed, whether by light energy or in some chemical way discussed earlier, its deportment follows the known behaviors of free radicals. The initiation of carcinogenesis need not be by irradiation, though the processes of photosensitization depending on the energy passed internally through collisions can produce free radicals and the ultimate effect is the same as if from irradiation.

Oxidative Cleavage of Viral-Host Cell Integrate

Let the host cell and its functional carbonyl group (FCG) and the activating ethylene linkage be represented by

$$\text{(Host C)}\ -\overset{\overset{\text{H}}{|}}{\underset{\underset{\text{H}}{|}}{\text{C}}}-\overset{\overset{\text{H}}{|}}{\underset{\underset{\text{(b)}}{|}}{\text{C}}}=\overset{\overset{\text{H}}{|}}{\underset{\underset{\text{(c)}}{|}}{\text{C}}}-\overset{\overset{\text{H}}{|}}{\underset{\underset{\text{(d)}}{|}}{\text{C}}}=\text{O}$$

and the virus by

$$\text{(VR)}\ -\overset{\overset{\text{H}}{|}}{\underset{\underset{\text{H}}{|}}{\text{C}}}-\overset{\overset{\text{H}}{|}}{\underset{\underset{\text{(a)}}{|}}{\text{C}}}=\overset{\overset{\text{H}}{|}}{\underset{\underset{\text{(e)}}{|}}{\text{C}}}-\overset{\overset{\text{H}}{|}}{\underset{\underset{\text{(f)}}{|}}{\text{C}}}-\text{R}$$

or by a chain of its polymeres. During hypoxia a free radical formed by dehydrogenation at (a) would add to the functional carbonyl group's activating double bond at (c) while the Hydrolytic Glycolysis System (HGS) would add at (b). Energy from the HGS could then pass to the virus. By further dehydrogenation during hypoxia other viral units could add to the terminal viral unit before or after integration with the host cell, at poles (d) or (e). No matter how many units would form the chain, the terminal unit would possess a double bond with a mobile hydrogen atom placed alpha thereto. When this hydrogen atom is withdrawn in the presence of oxygen, a peroxide free radical is produced, which causes cleavage with a terminal carbonyl group at (d). The double bond of this carbonyl group activates the hydrogen atom at (a), and so in the presence of a dehydrogenator and oxygen a peroxide free radical is formed here, and cleavage follows producing a terminal carbonyl group again. The process is repeated until the position alpha to the functional carbonyl group is reached. In this way, a carbonyl group becomes conjugated with the FCG replacing the ethylene linkage that activated the FCG formerly. Since the carbonyl group is a better electron doner than the ethylene linkage, the FCG is activated to a higher O/R potential than formerly, and becomes a more efficient dehydrogenator. Moreover, the carbonyl group does not add a dehydrogenated viral unit readily as did the ethylene linkage, and integration of the virus with the host cell is less able to take place. Hence an immunity against integration of the virus with the host cell is secured. This may be the explanation of the immunity observed in the patients that have recovered by the use of this type of therapeutic reagent.

It is seen that the virus is burned off bit by bit and the energy produced can pass over to the host cell and support its reconstruction. The same energy taken from the host cell to form the viral proprogeny is now returned to support host cell reconstruction. In this instance, however, the energy passed to the host cell is of higher order than that received by the virus from hydrolytic processes and is more suited to mitochondria synthesis in the host cell. Some such explanation is necessary, since after the treatment of paralytic viral infections as Rabies, Paralytic Polio or Paralytic Dog Distemper the vegetating virus

disappears, and the host cell is found to be no longer paralysed, but functioning normally. Its functional mechanism must have been restored during the destruction of the integrated virus and its proprogeny. The energy for such rapid reconstruction, 12 to 84 hours, is evidently provided by the orderly oxidation of the virus-progeny complex.

The other type of integration, where the functional carbonyl group is condensed with the amine group of the pathogen to form an azomethine linkage, offers the same type of bit by bit oxidative separation, with energy passing over the azomethine bridge to the host cell to support its reconstruction. On the other hand, the pathogen can be oxidized off at the azomethine linkage leaving the host cell with its carbonyl group free and restored, while the virus or other pathogen loses its pathogenic amine group. In this instance the FCG is still activated by its ethylene linkage.

What has been said with regard to viral integration with the host cell appears to apply also to other pathogens including pure hydrocarbon and amine containing carcinogens.

Mitotic Poisons

The attempt to strike at the center of the cancer problem via antimitotic poisons has revealed much that supports our thesis that the mitotic changes of cancer are secondary. The first observations started early in the past decade and have been increasing world-wide ever since. Dr. Biesele of the Sloan-Kettering Foundation gives a review of the antimitotic agents studied so far (Mitotic Poisons and the Cancer Problem, Elsevier, 1958) which he classifies as poisons of mitosis. We observe two types of agents here: one of the antibiotic type presenting a toxic amine group, and the other presenting an activated carbonyl group that regulates mitosis without injuring either the participants or activities of the process. Attention is directed toward Benzoquinone and Maleic acid which this writer used clinically with corrective results that were permanent, several decades ago. These are given a premitotic position of action by Biesele which one would prefer to classify as extra-mitotic. The whole review

supports the principles of our thesis, although the interpretations are different from our own in many respects.

On page 31 it is reported that "The threshold of mitotic inhibition on chick fibroblast cultures by benzoquinone was 10^{-9} (Meier and Schar, 1947), or 0.001 ug/ml, the same as for Colchicine". "The mitosis inhibition caused by some quinones and by maleic acid has paralleled their uptake of sulphydryl." (P. 33) This shows, in line with our thesis, that the action depends upon the activation of the carbonyl group as recipient of electrons from its conjugated double bonds, and that a physiological rather than a toxic action is to be expected, a dehydrogenating power that can initiate chain oxidation. Our diet has accordingly eliminated sulphides and sulphydryl. Lettre's suggestion, that quinone blocked sulphydryl compounds to inhibit mitosis, Biesele finds inadequate as other antimitotics are effective without blocking sulphydryl action. However, the oxidation catalysis of activated carbonyl is overlooked by all students of the problem.

On page 30, Meyerhof and Randall (1948) and Burrough (1955) are quoted on the inhibition of epidermal mitosis by adrenaline and adrenochrome in dilutions of one to a million. They found that "this inhibition occurred not only with glucose as an energy source, but with fructose, lactose and pyruvate . . . Further experiments indicated that the critical influence on metabolism imposed by epinephrine or adrenochrome was not on glycolysis, the tricarboxylic acid cycle, or the cytochrome system." Thus, in line with our thesis, the energy source that is cut off is the unidentified system which we named the preferred smokeless process initiated by activated carbonyl groups, which burns all fuels and even the inhibitors that may be present, but which can be inactivated by highly potent amine groups as of adrenochrome and epinephrine. Other data on amine inactivations further support our thesis.

Thus on page 50, Biesele reviews the contributions of Gellhorn, Hirschberg and Kream (1952) demonstrating that "the differential susceptibility of vareous tumors to inhibition by 8-azaguanine was inversely related to their ability to deaminate

8-azaguanine to the non-inhibitory 8-azaxanthine. In tissue culture, inhibition by 8-azaguanine and the non-inhibitory effect of 8-azaxanthine on Brown-Pearce tumor were confirmed by Flint, Hirschberg and Murray (1953)". Here again, the inhibitory effect is due to an activated amine group while the protection against the action is a matter of oxidation that removes the amine group and substitutes a carbonyl group in its place as we claim happens to viral and other amine poisons during carcinogenesis inhibition. A further example of this inactivation of toxic amines is found in the observation of Woodside (1953) in "tissues of the mouse, in which 8-azaguanine restricted mitotic rates in carcinomas 755 and E0771 but not in tumors C954, C1300, S180 and S91, nor in ileum, jejunum or testis." It must be recalled that the ileum, jejunum and testis are rich in diamine oxidase, and here a carbonyl action is also involved in removing the toxic amine group and replacing it with a carbonyl group in line with our thesis. Here is another indication that free radicals and peroxide free radicals are involved.

On page 50, Biesele suggest that the "inhibitory effect of 8-azaguanine may be related to its incorporation into ribonucleic acid, as suggested by Kidder, Dewey, Parks, and Woodside (1949) and demonstrated by Mitchell, Skipper, and Bennett (1950). The latter authors found, however, that the amount of 8-azaguanine incorporated into visceral RNA exceeded the amount incorporated into tumor RNA. This posed a dilemma for which Parks (1955) saw no solution. However, 8-azaguanine–2–^{14}C was incorporated into RNA of the susceptible mouse leukemia L1210 at a level 100 times that of its incorporation into the derivative azaguanine-dependant leukemia (Bennett, Skipper and Law, 1953)". "The incorporation of 8-azaguanine into tumor RNA probably produces defective RNA. It is at this polynucleotide stage that Mandel (1955) envisioned the action of 8-azaguanine as an antimetabolite, rather than as an antagonist of free purines." Here we see in line with our thesis that normal tissues are armed with many more active carbonyl groups than are the susceptible tumor tissues and these carbonyl groups can condense with the toxic amine structures and hold them in combination that leads to their oxidative destruction. So our

interpretation of the induced antimitotic activities and their prevention is that the same survival factor that is dealt with in this book is concerned, and that the antimitotic data gathered so far, gives further support to our thesis with measurable proofs of the efficacy of high dilutions. Though not recognized by the investigators, their data again shows one phase of the interaction of amine and carbonyl groups dealt with in this book.

Biesele refers to the doubtful trigger action that sets off mitosis. If he doubts its existence, we are in agreement, since after all mitosis and its resultant cell multiplication is compensatory, to supply working units–cells, where the functional requirements are not met adequately for the best survival, (See page 65). This is seen also in Biesele's review where both benzoquinone and maleic acid inhibit mitosis so long as they are not inactivated by sulphydryl. This of course means they inhibit mitosis so long as their carbonyl groups receive electrons from their conjugated double bonds and can therefore serve as dehydrogenators and start new oxidation chains. We testified to the action of benzoquinone and maleic anhydride as dependant on the active carbonyl groups in our Federal Court trials in 1942. We found the anhydride to be more active than the acid because here both sets of conjugated double bonds lay in the same plane as those of the carbonyl group and in the acid only one set does. Thus the anhydride offers steric advantage for a perpendicularly attacking radical and should be effective as an antimitotic agent in a higher dilution than the acid. The action here then is to improve the cellular oxidations. Under such circumstances mitotis is not needed so much to supply additional function. (It is this function depression in tissue cultures that probably demands constant mitosis.) Further, the improved oxidations dispose of interfering agents and antibiotic effects. So the cells live longer and do not need replacement so fast.

The data presented in Biesele's review then may in our opinion mean that carbonyl works on a physiological basis while amine is a pathogen toward the mitotic function. Since cancer cells are functional failures, good clinical support to this thesis is had in the recovery of a cancer of the liver patient who was treated with 6X dilution (10^{-6}) benzoquinone. (See page 155.)

Anoxia and its Co-factor Pathogen

Warburg is the recognized Nestor of the Biochemical Profession. He developed the methods and apparatus that made it possible to study the tissue respirations (oxidations). His work stands with the firmness of Gibraltar, and fortunately so, since there seems to be an organized effort to eliminate the facts about the tissue oxidations and their importance in the cause and cure of disease. One gets this idea when reviewing the literature of the past decade and a half, where the important work of Warburg is ignored or superceded by other data that is contrary, poorly obtained, and stupidly stated. It would appear that such data is favored and invited. However, no matter how tightly the biochemical profession is controlled by commercial interests, only truth can survive in the long run. Warburg's work confirms our own most beautifully, especially the main pillar of our thesis: "When the oxidation catalysis wanes, disease results, and when it ceases, death follows". Here we have stated not only that molecular oxygen is essential to normal metabolism and life, but that the activity of the Grana, the Mitochondria are also required. This is what Warburg has shown in his whole life's work. Recently Goldblatt presented conclusive experimental evidence that anoxia changes normal cells to neoplastic cells, and all the data presented by Maisin and Pourbaix fit in perfectly. We will give some quotations from an article by Professor Warburg which was published in German [Naturwissenschaften 42, 401 (1955)] and translated by U. S. Government biochemists Dean Burk, Jehu Hunter, and W. H. Everhardy. This article, "On the Origin of Cancer Cells", was printed in Science, February 24, 1956, Vol. 123, No. 3191, pages 309-314. These quotations cover much experimental observation and are also valuable in that they are clearly and simply stated.

If one examines them in the light of the data we have presented in the preceding pages, it will be evident that they confirm our own thesis on the pathogenesis of cancer and disease in general. They point out the essential status of anoxia, which we have claimed is necessary for the pathogen to be changed by dehydrogenation (of the tissue metabolism) to a free radical which instead of being burned and disposed of as fuel in the

presence of oxygen, is not burned but is able to add to the cell Grana and do so at the very point where the activation of the oxidations is generated, namely the double bonds that activate the carbonyl group which we credit with initiating the tissue oxidations by serving as a dehydrogenator of fuels and pathogens. Thus anoxia is essential to the pathogenesis as it disposes the pathogen, carcinogen, virus or what not, to be able to integrate with the host cell and block grana function.

Our very earliest clinical observations plus some other data made it necessary to recognize a system of tissue oxidation not included in the accepted literature. This we called the "High Efficiency Smokeless System". A review of Warburg's data convinces one that it is by this system that the grana function. One sees in a following quotation that the "intermediaries of oxidation" that are supposed to be shared by the fermentation process are not used by the grana and therefore do not fit into their mechanism. So the grana use a different mechanism. Likewise though Warburg does not offer any mechanism whereby anoxia does its damage to the grana, a mechanism is necessary, and the pathogenic process of our thesis provides the answer. It gives the grana the means of working with oxygen and of being wiped out functionally and structurally by its absence. It also provides the cofactor that is necessary for making an irreversible injury. In addition it shows how this injury may in its early phases, be reversible. The former we have shown by treatment and subsequent biopsies in the Medical Record of New York, October 30, 1920, and the latter in Cancer and its Allied Diseases, 1929. Moreover our thesis shows how the anoxia disposes the co-factor or pathogen to become a free radical that can not be changed to a peroxide free radical and thus be disposed of, but instead adds to a double bond that activates the oxidation initiator, and thus puts it out of business. The grana function is thus stopped, and after being stopped long enough is shed as useless and lost to the host cell economy. But, in addition, our thesis shows how the very atomic bondings of the co-factor or pathogen that constitutes its integration with the grana actually dispose to the oxidative rupture of this union, setting the host cell grana free in good functional status, while the pathogen is no longer to be found. Anoxia is essential to the

pathogenesis and so is the co-factor. Oxidation of the co-factor provides the energy for grana reconstruction when it happens to be a virus.

"One method for the destruction of the respiration of the body cells is removal of oxygen. If, for example, embryonal tissue is exposed to an oxygen deficiency for some hours and then is placed in oxygen again, 50 percent or more of the respiration is usually destroyed. The cause of this destruction of respiration is lack of energy. As a matter of fact, *the cells need their respiration energy to preserve their structure,* and if respiration is inhibited, both structure and respiration disappear." If one estimates the amount of normal structure in the grana, by the amount of normal function, one sees how the pathogenesis we have described will accomplish what Warburg reports here. Again,—"If an injury to respiration is to produce cancer, this injury must, as already mentioned, be irreversible. We understand by this that not only the inhibition of respiration remains after removal of the respiration poison but, even more, that the inhibition of respiration also continues through all the following cell divisions, for measurements of metabolism in transplanted tumors have shown that cancer cells can not regain normal respiration, even in the course of many decades, once they have lost it."

"But why are the body cells dedifferentiated when their respiration energy is replaced by fermentation energy? At first, one would think that it is immaterial to the cells whether they obtain their energy from respiration or from fermentation, since the energy of both reactions is transformed into the energy of adenosine triphosphate, and yet adenosine triphosphate=adenosine triphosphate. This equation is certainly correct chemically and energetically, but it is incorrect morphologically, because, although respiration takes place for the most part in the structure of the grana, the fermentation enzymes are found for a greater part in the fluid of the protoplasm. The adenosine triphosphate synthesized by respiration therefore involves more structure than the adenosine triphosphate synthesized by fermentation." Since the enzymes and intermediaries of fermentation which biochemists accept as playing a big part also in the cell respiration, bathe the grana and the grana do not use them, as the quotation shows, then the conventionally accepted process is not

Footnote: The italics are ours.

correct, and a different process and different set of enzymes and intermediaries are involved. This process must be one which inactivates the grana when oxygen is missing, hence the logical deduction is that the free radical is an essential part of an early intermediary as we have hypothesized for so long.

Further,—"The first notable experimental induction of cancer by oxygen deficiency was described by Goldblatt and Cameron, who exposed heart fibroblasts in tissue culture to intermittent oxygen deficiency for long periods and finally obtained transplantable cancer cells, whereas in control cultures that were maintained without oxygen deficiency, no cancer cells resulted. Clinical experiences along these lines are innumerable." Warburg emphasizes,—" . . . but there is only one common cause into which all other causes of cancer merge, the irreversible injuring of respiration." He states, "In recent years it has been recognized that subnarcotic doses of urethane cause lung cancer in mice in 100 percent of treatments. Urethane is particularly suitable as a carcinogen, because, in contrast to alcohol, it is not itself burned on the respiring surfaces and, unlike ether and chloroform, it does not cytolyze the cells. Any narcotic that has these properties may cause cancer upon chronic administration in small doses." So Warburg recognizes that a carcinogen must be *not* destructable by the cell's oxidative mechanism or otherwise. It can then become integrated with the cell and become a part of it, and can become accumulative as the disposing anoxia provides occasion. Warburg states in this connection,—"Any respiratory injury due to lack of energy, however, whether it is produced by oxygen deficiency or by respiratory poisons, must be cumulative since it is irreversible."

That the narcotic action promotes neoplastic behavior is only too well known to the clinician. Especially is this true of the oxides of nitrogen that present permanent free radicals that can block respiration and promote cancer growth most disastrously. Their essential action is to hinder respirations. Other confirmatory quotations could be given, but this is enough.

The term "lack of energy" which Warburg claims is the cause of grana destruction requires interpretation. The presence of the grana as normal structures can only be measured by

their function, and when that fails energy is not produced,—the oxidation process stops. Oxygen is required for it and if it fails to have oxygen for some hours its function is permanently stopped. That is what is observable. We have shown, of course, how the anoxia disposes to the integration of the pathogen with the grana to stop their function. So long as an efficient dehydrogenator does not come along to relieve the grana of their integrated incumbrance, they are irreversibly out of action, or so far as experiment can show, they are dead, and besides, energy is lacking. But let the correct dehydrogenator come along and remove the co-factor, the pathogen, be it virus, germ toxin or tissue metabolite that is incompletely combusted, then the grana can again function, energy is produced and they are NOT DEAD from lack of energy. The reversibility is shown by energy they produce and their function. Molecular oxygen is always required. This is our experience clinically and otherwise.

We see then that Warburg's work supports our thesis as does also the antimitotic work reported by Biesele.

The Unity Principle of Pathogenesis and its Correction

Since our purpose is to establish a least common denominator in pathogenesis as far as possible in the whole field of natural and artificially produced disease, some recently obtained observations are added to this Appendix. Hog Cholera is a 100% fatal disease that wipes out every herd it attacks in three to five days after the first symptoms show. The nervous type is quite rare, and as such a case was prominent in the present epidemic this report is made to show that the state of integration of the virus with nerve cells in paralytic disease is of the same order as its integration with the somatic cells. We showed that paralytic disease caused by different types of viruses offered an atomic bonding that could be severed by one type of chemical attack, and hence was of the one order in all of the paralytic diseases reported. This holds also for Hog Cholera as this report shows. One sees then that the integration of the viral pathogen with the host cell is of the same order in somatic and nerve cell infection. We also showed that natural and synthetic carcinogens showed the same order of integration with the host cell as does the viral pathogen. We

cited one case of Retino-Choroiditis with nerve atrophy and blindness, where freeing the host cell of the pathogen by the same chemical attack was also secured, and we concluded (as this case was one among a significant group) that toxins of suppressed infection produced integrations with host cells of the same order also. Toxins of active infections as tuberculosis, staphylococci, syphilis, leprosy, malaria and many other organisms[1] were also separated from the host cell with restoration of normal to the latter, by the same chemical attack. So we feel we have reached our goal, in blazing the trail to the least common denominator in pathogenesis in general and to its correction by scientific logical synthetic means that are easily comprehensible to the profession as a whole.

(1) A Report on Hog Cholera[2]

A. Introduction: On May 15, 1959, Dr. Rodrigues, Director of the Veterinarian Center of the Estado Major of the Army in the City Liberty, facilitated and arranged for the treatment of the animals envolved in an epidemic of Hog Cholera at Quartel 10 of San Antonio that had already caused the death of 15 vaccinated small pigs. The remaining pigs of the colony comprised a total of 72 infected pigs. 35 small and 37 large pigs.

B. Prominent Symptoms: Among the prominent symptoms that established the diagnosis were;

1) The deaths of the 15 small pigs before our arrival.
2) All of the pigs that were still alive showed,
   a) Prostration,
   b) Respiration difficult stretorous of the type characteristic of bronchiogenic pulmonary lesions,
   c) Hemorrhagic plagues, small and large, in the skin of the abdomen of the animals, extending in all cases under the neck and jaw,

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[1]*Federal Court cases 1943-1946 and other reports.*

[2]*The information given here was abstracted from a report on the treatment of Hog Cholera. This work was done through the cooperation of the Cuban Government and under the supervision of Dr. J. Peres Almeida, Chief Medical Veterinarian of the Quartel 10, de San Antonio, de Las Banos La Cayuga, Cuba, with Dr. Julian Baldor and Dr. William F. Koch.*

d) Excretion of solid and liquid material with rectal conjestion in some cases,
e) Teats inflamed and hemorrhagic, very severe in one case,
f) Nervous manifestations with torticolis very severe in one case,
g) Fevers running between 39.5° to 41°C in various animals, the small animals with 40°. The sickest animals showed a drop in temperature to 39.5°C which occurs in the advance stage.

C. Pathology: The conditions of the material was the poorest as a result of the observed facts and changes. The animals had already carried an incubation period of 10 days with a prognosis of 100% fatality according to virological standards, for after the virus is integrated with the host cell, no serological measure can set the host cell free and rescue it.

D. Treatment and Material used: The 72 animals were treated in two sessions, the first on May 16, 1959, and the second on May 19, 1959. The first group treated comprised 10 small pigs and 12 large pigs. The second group treated comprised 25 small pigs and 27 large pigs.

A solution of Dipheno-quinone, one microgram per cubic centimeter, was used. Small pigs were given from one to two cubic centimeters of the solution and the larger pigs received a dose of from five to ten cubic centimeters by injection.

E. Results:

First Group: This group was observed on May 23, 1959.
a) No deaths,
b) Temperatures normal in the checked pigs with the exception of pigs No. 3 and No. 4 on which the injection was repeated,
c) The red hemorrhagic spots on the abdomenal zone had disappeared in all animals. The congestion of the Cornea also disappeared,
d) The rectal areas appeared normal,
e) Respiration normal in all animals,
f) The female's teats that were formerly inflamed (hemorrhagic also) were normal in all animals,

g) One male of the group segregated as the most debilitated attempted one week after treatment to accomplish reproductive relations with the females, successively.

Second Group: This group was observed on May 23, 1959 (five days after treatment). The following results were observed.

a) No deaths,
b) Normal temperatures in all that were checked,
c) The red hemorrhagic areas had disappeared,
d) The rectal areas were normal,
e) The respirations were normal in all animals,
f) The teats of the females appeared normal.

This group was re-examined on May 26, 1959, one week after treatment, and they were found to be normal.

(2) Conclusion

The proof that the integration of host cell and pathogen is broken so that the host cell is returned to normal function is the disappearance of the paralysis and consequent atrophy, while the pathogen is no longer to be found. Indeed, where the host cells still retain the faintest spark of life, they appear to reconstruct at the expense of the energy produced by the stepwise oxidation of the integrated virus as previously described. The late generations of neoplastic cells are excess tissue that must be removed physiologically as it has no place in an efficient economy.

Since the reagents used to accomplish the corrective oxidations offer oxidation/reduction potentials somewhat higher than the intermediaries concerned in the Krebs and other cycles claimed to constitute the normal oxidation process, the maintenance of normal health must be attributed to a different system and of the order of carbonyl and free radical structures described in our text as the "smokeless" system of oxidations.

It is not difficult to see that if such atomic groups dominate the metabolic processes in animal life, diseases would be impossible, especially if these intermediaries were of the high order of activity as those we have found to be corrective reagents. More-

over, since they correct the error that constitutes parasitism, as some of our data indicates, then there would be no pathogenic agents to interfere with the tissue chemistry, and the parasites could lead a happy useful life in the great biological economy.

It is not difficult also to visualize a metabolism of the high smokeless protective order as the dominant type at a previous epoch of animal life, and so what we observe now must be considered a degenerated type, which can never rise out of the gutter so long as man and animals are carnivorous.

The author is gratefully indebted to the Cuban Government of Fidel Castro for the opportunities and cooperation in the treating of viral diseases, including Rabies, and for the respectful attention given by the faculty and officers to the explanations of our philosophy and system of therapy.