CHAPTER II

THE SCIENTIFIC BASIS

In 1910 I made observations on the toxins produced in the tissues of dogs after complete parathyroidectomy, and reported the findings in the Journal of Biological Chemistry in 1912, vol. 12, p. 313, and in 1913, vol. 15, pp. 43-63. The work was then followed at the University of Glasgow by Paton and his staff for three years and reported in the Quarterly Journal of Physiology, in 1917, vol. 10, Nos. 3 and 4. For the excellence in which they confirmed my work they were awarded the Triennial Prize in Medicine by Harvard University. This confirmation is important since the deductions which I was impelled to make on these findings resulted in the practical values I will report here as case histories, in the cure of atrophic paralytic diseases, both motor and sensory, and in the true cure of neoplasia in many of its various forms.

The principle findings after parathyroidectomy were excessive production of several guanidin bases and their elimination in toxic quantities in the urine, together with excessive amounts of other amines, creatine, creatinine, lactic acid, phosphate and calcium. The autopsy findings were ante mortem coagulation of the blood in the large veins, hemorrhagic hepatitis, and hemorrhagic glomerulitis, ending up with anuria and death in convulsions. The extensiveness of the convulsions and their severity was proportional to the amount of guanidin and of lactic acid eliminated even when the lungs were well ventilated. The symptoms were the same as one could produce with injections of guanidin in toxic amounts, so we held that guanidin was a key instrument in producing the functional disturbances and the pathological changes.

It seemed reasonable to conclude that the excessive amounts of the normal product of metabolism, *creatine,* that were eliminated in the urine, were displaced from their position in the tissue molecular set-up by the guanidin. We still hold this view. This is important since the type of creatine union with the cell,

and its function as displaced and blocked by guanidin is a key consideration in the whole pathogenesis that we have to discuss here. We decided that creatine was held combined with a highly active carbonyl group of the energy producing mechanism by an azomethine condensation in the performance of its normal function, and that guanidin displaced it permanently destroying that function. As a result phosphoric acid and calcium were not used and were eliminated as waste materials too. The ante mortem clots were to be interpreted as colloidal gellations due to reduction of surface charges from the colloidal particles in the sense of MacDonagh of London. Such gellations occur in cancer and syphilitic infection and reduce oxygen transport between and within tissue cells and cause a local anoxia basic to pathogenic change. It is a result of the guanidin intoxication after parathyroidectomy and can be reproduced by guanidin injections. Lactic acid production, in proportion to the convulsions and guanidin output, indicated that the tissue energy was supplied by hydrolytic glycolysis to produce lactic acid even when the lungs were forcefully ventilated. Lactic acid also accounted for much of the calcium that was eliminated. As the guanidin output increased, every function took on allergic qualities. **As a result of these and further observations we arrived at the conclusion that the energy production mechanism of each aerobic cell has to include a highly activated carbonyl group conjugated with the double bonds of an ethylene linkage from which it received a quota of electrons which made it highly basophilic while its activating conjugated double bond became more electrophilic. This conjugated system of carbonyl and ethylene groups with a carbon atom carrying a highly mobile hydrogen alpha to the double bond, constitutes the fundamental vital unit, or the simplest atomic arrangement that supports life, and plays a part in the fundamental changes that constitute all disease so far as our experience has gone.**

We assume that the carbonyl group dehydrogenates fuel substrates or toxins that come into the field to form in them free radicals which combine molecular oxygen to form peroxide free radicals, and these peroxide free radicals serve as carriers of a chain oxidation which combusts the fuel ultimate-

ly to carbon dioxide and water, and converts each molecule of toxin to the same peroxide free radical antitoxic type of structure, until every molecule of toxin is oxidized out of the way. This was our idea of the Natural Immunity Process wherein toxin is changed to antitoxin as a chain process. This we suggested in Koch Investigations 1924, p. 34, and in the Cancer Journal, October, 1924. Evidences are now accumulating to support this early conclusion.

Creatine phosphate was unknown when we first found the guanidin poisoning that followed parathyroidectomy. Here the phosphoric acid is condensed with the amine group instead of with a hydroxyl as in the other phosphorylated energy storing and releasing compounds. This is a high energy bond carrying some 13,000 kilocalories, and the lability is largely due to the double bond of the imide group with which it is conjugated. By the action of a transphosphorylase the phosphoric acid and energy of equal amount is transferred to adenosine diphosphate (ADP) to form the triphosphate, (ATP). The ATP combines with actomyocin, releasing energy to it and liberating a molecule of phosphoric acid. The energy taken up by the actomyocin changes its viscosity and the shape of its particles, it is assumed, to produce motion.

Every cell has its energy pool, just as it has its nutritional pool. The energy pool is carried in the esters and condensates of ADP, ATP, Creatin Phosphoric acid, and dozens of other compounds no doubt. We take it that the virus can make its combinations here as well as with the energy generating mechanism as we describe it in this text, and hence the atomic units concerned are much the same in both. Thus the Nissl substance of the nerve cell may be so considered, and when the polio virus attacks, it combines with the Nissl material first. If this holds out until all virus is inactivated, the rest of the cell is not attacked, and a non-atrophic and very transiently paralysed or weakened muscle may result. But where the Nissl substance does not hold out, as is true after too much activity with its nerve exhaustion, then the virus integrates with the energy producing mechanism and destructive disease has thereby been established. What holds for a virus holds also in general for

metabolic products and bacterial or synthetic products that are not fully combusted and invite dehydrogenation as via an alpha placed hydrogen atom with reference to a double bond, or one that is "peri" placed. Thus the combining free radicals are produced. The potentials of energy storage and release are a big chapter also.

The phosphoric acid liberated shows how much energy has been taken out of storage, and that its carrier is free to take on more. So we assume it goes to the azomethine bond and causes its separation, which is indeed very easy, and then the carbonyl group is ready for another dehydrogenation to set another oxidation chain going, so more energy is produced to make the condensate between creatine and phosphoric acid; and while this is handing over its load to ADP, the hydrogen is being taken from the carbonyl group by some oxidase and the creatine and carbonyl group can again condense with some energy storage, waiting for the next hydrolysis via phosphoric acid. In this cleavage the energy released helps fix the phosphoric acid to the creatin carboxyl group until energy evolved by the oxidation chain can form a high energy bond between it and the amino group. The phosphoric acid released by the transphosphorylase has the calcium action to keep it from breaking the N-P bond until it can react on the azomethine creatin bond. Such matters are hypothetical applications of known activities. These we must extend to picture both the antagonistic and conjugate actions of amine and carbonyl groups, and the factors that control both. Even now very little of what is needed to be known of the nature of the participants and how they react is well understood. Forty years ago practically all was blank. All we had available was the discovery of the free radical by Gomberg, my chemistry professor, and no one applied it to biochemical processes for many a decade. Today we are in a different position. In line with our hypothesis we may assert with confidence that the ketosteroids function through their carbonyl group as activated by the double bonds with which it is conjugated in ring A. This is proven by the fact that the spent products of their action (dehydrogenation), present hydroxyl instead of carbonyl attached to ring A, and the double bond is saturated. Corticosterone

would be expected to condense, not with creatin but with adrenaline*, and Testosterone with spermin, to regulate energy supply for muscle and sperm fibril contractions as a chain process. As the steroid is bound to the F. M. at C17, only very minute traces are required to co-function with more material doses of the amine in rapid turn-over (see diagram VI). We consider this type of mechanism to be used quite generally also by the lowest forms of plant and animal life for energy liberation for motion, such as the mechanism whereby crocin activates motion in algae sex gametes, and Echinochrome (A) activates motion in the sperm of the Sea Urchin. These substances were demonstrated to act in dilutions higher than one to a billion by Kuhn and Moewus, and Kuhn and Wallenfels (1938-1940), as well as by Prof. Gilbert Smith in 1947. Such is *physiology*. For further discussion see the appendix.

Inspection shows Crocin to be a Carotenoid presenting two carbonyl groups conjugated with seven ethylene linkages each of which receives electrons from a methyl substituent that mesomerically migrate to the carbonyl groups, thus activating them. Echinochrome (A) is a naphthoquinone with two activated carbonyl groups and is quite similar to vitamin K in structure. In line with our hypothesis they may serve with specific amines for energy production and utilization as described above. Vitamin K combines the structures of both the quinone and the carotenoid, the animal type and the plant type, described above, and we propose, in like manner supplies energy with the aid of other carbonyl compounds and amines for motion in the leucocyte and to provide surface energy to preserve the dispersion of the blood plasma colloids, so that when this is inactivated by an amine of strong azomethine bonding, as guanidin in our parathyroid work, or when the energy is removed by a foreign surface, the plasma colloids gellate. The latter situation creates anoxia so that the free radicals formed can no longer serve the oxidative detoxication, but are free to copolymerize with the

*The structure of adrenaline offers opportunity for removal of the methyl and hydroxyl groups right in the tissue where it is destined to function and thus create a double bond that should activate its amine group and facilitate the azomethine condensation. The specificity for involuntary muscle fibers of the blood vessels should be examined from this standpoint.

collagenous units that form the fibrin, and thus enter the clot, in storage as it were. The detoxication function of vitamin K is demonstrated by various observers and we assign this property to the conjugated system of carbonyl and ethylene double bonds it contains, but as their oxidation reduction potential is weak, they are not very effective. Still they serve by inducing oxidations in the incompletely burned germ and tissue metabolites in line with our hypothesis. The cure of coronary, renal, and cerebral deficiencies due to the fibrosis of hypoxia and its resulting occlusions, can be accomplished as we showed decades ago by the timely use of highly activated carbonyl groups. Our hypothesis, clinically proven, is each day receiving new support from each new examination of a pertinent physiological phenomenon. Case histories will demonstrate the reversal of the pathogenesis in vascular occlusions of the heart, kidney and brain, as well as the quick detoxication of partly burned products of metabolism of tissue cells and germs, as well as those produced by steam and fire burns, with quick relief and healing. This will be given thorough discussion in the completed text, where it will be shown that the potential of action of the carbonyl and amine groups determine health when oxygen is present.

The Virus Situation

Well established facts in the demonstration of the infectious agent in cancer, perfectly following the four rules of Robert Koch are reported with conflicting features which appear to be readily harmonized by our working hypothesis. The splendid work of San Felice two thirds of a century ago, and of von Brehmer and of Glover a third of a century ago, and recently of Gerlach, Irene Diller and also Wuerthel-Caspe, using modern facilities of technique, confirm the pleomorphic nature of the infectious agent, reported as being coccus, bacillus, filamentous and filterable virus, in its various cycles of life. Gerona besides showed it to be a coccus that withstood boiling at 120° C. Thus with a filterable phase as a sure transmitter one may assume that an adapted virus, living in symbiosis with the bacillus, the fungus filament, the coccus or spore of any of the foregoing, is the active agent, and since it has a predilection to liv-

ing in the symbiotic state as presented in our diagram IV a, it is part and parcel to the cancer cell and not filterable from it until it dies, having also the identical progeny yield with the cancer cell when infecting epithelia. When integrated with a spore it shares its resistance to heat, irradiation, and chemicals. The type of union with the host cell will determine if a tissue atrophy or a neoplastic response will follow. This will be diagrammed farther on. When the reactive groups of the virus are free, its delicacy is understood, but when it is bound by absorption to some protein surface, or a union takes place by condensation of the virus amine group with a carbonyl via an azomethine condensation, it is inactivated and protected until the azomethine bond is split, and that is easy by hydrolysis often via weak acidity. But it may be separated and inactivated by oxidation of the carbon atom alpha to the azomethine double bond, with comparative ease because of the high mobility of the hydrogen atom there attached. Probably the first reaction observed in virus is the inactivating condensation with formaldehyde to produce a vaccine. Probably the most reactive carbonyl group in the tissues is that which initiates oxidation chains for function, and this would be the first for amine attack. This amine condensation of the virus with the host's carbonyl group must block its activity so as to not only throw the energy producing mechanism off the oxidation path and onto the hydrolytic glycolysis path, as we diagram later on in Diagram II, for guanidin or other activated amines, but also serve as hook up whereby the virus received vital energy. When the functional mechanism is crippled so as to not be able to accept the energy produced by the glycolysis, this energy has no other place to go than to the attached virus and the mitotic mechanism, as explained farther on, to support the neoplastic virus symbiosis. This type of integration to cause neoplasia could take place during the presence of oxygen, if anoxia existed only during the moment the azomethine bond was being formed, that is, during the initiation phase, only. Obviously this type of integration is easily broken by highly active carbonyl groups, and while the virus is protected and nourished during the neoplastic response. After it is oxidized away, it is no longer pathogenic as we will show. The

filtration of virus from epithelial tumors is therefore not so easy, and the progeny yield probably equals that of the daughter neoplastic cells. But when the virus is liberated from a cancer cell because of its death, the pathogenic properties remain. However when the integrations are outlined according to their most likely provisions, the virus is separable by oxidation through a vigorous dehydrogenation, free radical production, peroxide free radical formation and molecular cleavage with carbonyl terminals being formed. So provided, the virus is no longer toxic or pathogenic and its amine group is deactivated.

Possible Origin of Virus

In line with our thesis we hold that no comprehensive biological response can take place without involving the phenomena of the free radical and the double bond. This should be especially true where oxidations provide the energy for the response. We must therefore see how these phenomena could possibly play a part in the origin of the virus with its deficiency that calls for parasitism to secure survival. The deficiency indeed may also involve the protein structure and amino acid content which will produce a specific serology.

We hold that bacteria and fungi, like the matured virus, are polymeres of nucleic acid protein complexes, analogous to the nucleic acid protein complexes of tissue cells which can be depolymerized to similar structures of lesser molecular weight. When during their autonomous metabolism, conditions of anoxia and nutritional difficulties prevent the carbonyl group that accepted the hydrogen from being freed of its accepted hydrogen, and the free radical formed by the dehydrogenations meet no oxygen to combine with, then these free radicals are open to addition to the most active double bond at hand, and thus set up the polymerization chains resulting in complex conglomerates which are chemically and thermally resistent to activity since their reactive groups are already occupied and further reaction is excluded, until a depolymerase of specific nature can act under favorable conditions. Then the non-reactive affair which we may call a spore is split down to its ultimate living units, each of which is a semi-solid and filterable autonomous particle of much less molecular weight. Each is provided with a

carbonyl set-up so it can produce energy for its maturation, and it develops into a body similar to its parent. This may be a bacillus, a fungus, a coccus, rickettsia, or matured virus that is not parasitic, but serves the great biological economy. Such a creature has never been identified since we know virus only by the disease it causes. Since many ultimate units are formed by the desporization, the progeny is large. Oxygen is necessary for the process, as it is for the maturation of each unit. The procedure facilitates adaptive mutation against the conditions that caused spore formation, and the situation is physiological and what one would expect.

However, when such a depolymerized unit gets into a tissue cell where anoxia prevents the peroxidation of the free radicals formed by the host cell, **in it,** or formed by its own carbonyl group acting **on it,** this free radical cannot form a peroxide free radical, and it is open to additions to the closest highly reactive double bond at hand. This position is the host's carbonyl activating double bond. Since its carbonyl group is inactivated by the anoxia, or if it is condensed with an amidine as guanidin, it becomes parasitic automatically on the host, through the union with one pole of this double bond, the other pole of which attaches to the hydrolytic glycolysis system we assume. Then it may follow one of the two courses outlined and diagrammed below, to produce either total host cell lysis with rich progeny yield, or, divide the energy equally with the host cell to produce equal progeny with it numerically, as a neoplastic process. On the other hand the virus may unite with the two poles of the activating double bond so that the hydrolytic glycolysis system is excluded and no energy goes to the virus or to the mitotic mechanism or to the functional mechanism. There is neither neoplasia nor allergy of any function then, but an inactivation that may lead to death without virus progeny, or to a pseudo-mort symbiosis with resultant paralytic and atrophic sequelae, that is curable. Pathogenesis then depends upon the coincidence of several factors, among which anoxia or hypoxia is important and determinative.

One great characteristic of pathogenic viruses is their ability to mutate in a new environment so as to survive with

the incorporation of the adapting qualities newly acquired as permanent hereditary characteristics. They thus can acquire a new specific serology just by being grown in a medium with an unusually higher added content of one or two amino acids. Or they can become fixed in their adaption to one tissue if transplanted over and over again in that tissue. In view of our simple hypothesis of origin, we may assume that when the sprouting unit finds itself through a series of generations growing in the same host and under the same conditions, it can become fixed in its nature and thus become more or less highly specific chemically, biologically and structurally. So far as knowledge of virus goes, there is nothing to exclude the existance of many more normal useful nonpathogenic types of virus than the pathogens we know about. Our idea that virus is synonomous with the acme of parasitism will have to change some day since the steps that could make an autonomous virus parasitic are rather simple, as well as subject to reversal by introducing efficient carbonyl catalysis. This simple idea of the sprouting units of a spore giving origin to a virus, which may later become fixed in its deficiency —through parasitism favoring conditions, may be "all off." However, it may explain a natural behavior too, as the pleomorphic germ of Glover and of von Brehmer and others that are well confirmed now, and at least it offers a simplification, as to the origin of the virus phase. It may explain the association of virus with a germ as in hog colera, tuberculosis, etc.

Accessory carcinogens as the polymerizing acrylic aldehydes offer free radicals that may add to a host double bond in its energy producing mechanism and lay it open to union with a carcinogenic virus or synthetic structure, and the free radicals formed from chloroform and carbon tetrachloride may do the same. But for any such pathogenic act, oxygen deficiency is essential, which is easily secured by circulatory injury, blows, rough physical examinations, etc., and by injury to the oxygen carrying power of the blood produced by coal tar medications as the salycilates, barbiturates, aspirin, etc. Cardiac insufficiency, and obliterative endarteritis are obvious accessories, but smoke laden air with the mucous generated in the lungs by way of protection, block the entrance of oxygen to the blood stream.

Hypoxia is the basic factor in the initiation phase. What follows depends upon the free radicals left uncombined with oxygen to **not form peroxide free radicals,** that carry the oxidation chain forward, but make pathogenic additions instead. Molecular oxygen is concerned, not ozone or atomic oxygen. It is only when the normal function of oxygen is prevented that the interaction of free radicals of one party and the double bonds of another follows to initiate pathogenic states. One sees that molecular oxygen by forming peroxide free radicals is the buffer against disease. Here too is an indication that the Krebs' Cycle is not the procedure of first choice in the tissue metabolism.

The Rupture Of The Symbiosis

The test for the rupture of the symbiosis of the virus with the host cell must be made on a tissue that is not able to undergo compensatory hyperplasia. This is the situation in nerve parenchyma. So we made our tests in both the sensory and the motor paralytic anaplasias or atrophies as they are called. It will be seen that what holds for virus also holds for the polymerizing free radicals of incompletely combusted germ and tissue metabolites produced under hypoxic conditions, and for their co-polymerizing free radicals, also, which can combine the carbonyl group's activating double bond in the same manner as the virus, to produce a neoplasia or an anaplasia or some disturbance of function as an allergy or an anergy. Clinical observations from several angles call for such an explanation. So the separation of the virus or of the toxin of germ or tissue cell origin from the nerve cell is demonstrated where function returns and atrophies give way to muscle reconstruction, after an established paralysis with atrophy, be it motor or sensory. Besides in the retina, the reconstruction can be directly observed. After a long standing paralysis from "Polio" with profound atrophy, the restoration of function and good muscle is demonstration enough, but we have observed the same in dogs with paralytic distemper, in one horse and in one man afflicted with paralytic rabies secured through coyote bite, and in cows with the cardiotropic form of hoof and mouth disease, where the blocked functions returned to normal. The case of optic nerve atrophy like others of the same type given below may be studied

with interest. The interactions will be diagrammed a little later. The inactivation of the functional carbonyl group by condensation with an amine group of a virus, or toxin of germ or other origin must also be considered. The Pasteur Effect is thus annuled and clinical fever produced. It will be seen that this carbonyl group controls energy production, and the oxidations of the natural immunity. We conclude it controls and is the key to the Pasteur Effect.

Hyperplasia and Energy Transfer

The mitotic mechanism exists to supply cells by reproduction that will provide functional mechanism adequate to the demands for survival. Thus when a functioning cell is worn out trying to produce the work required which is above its capacity, the functional mechanism is broken down, and energy cannot flow into its chemical processes, as it has none. So the only other direction the energy can go is to the chemical processes of the mitotic mechanism, setting them to act. The result is cell division, and compensatory hyperplasia.

We also consider the functional mechanism as a specially differentiated structure in which genes pattern the working parts. Apparently, these genes are not worn out by work, and can shed their broken down functional debris and enter the mitotic act as a pattern basis for new functional mechanism construction. Thus where excessive work has called for additional working mechanism, it is shown by functional mechanism destruction that can only be repaired by new cell production. In contrast, fatigue from severe exercise of the function provides for its cessation through oxygen want and the lactic acid production of hydrolytic glycolysis which inactivates the ferments necessary to work. In this way fatigue has an automatic block to excessive tissue destruction, and the pain caused by incompletely burned irritant products of metabolism, puts an end to the injurious overwork too. Still too much forced or repeated effort is destructive enough to call for more functional material so the adaptation is actually provided by the course the energy takes toward the mitotic mechanism after the functional mechanism is not in condition to receive it. We may diagram the procedure as in Diagram I (a), p. 65. Here, the normal relations

of Functional Mechanism, (F. M.), Mitotic Mechanism (M. M.), and the energy producing mechanism (E. M.), also includes a phosphorylation provision, (P. P.) operating with a labile amine, somewhat as we have described. Arrows show direction of energy flow. In (b) the F. M. is broken down and requires restoration with sufficient increase to serve requirements. In Grade B, the cancer cell F. M. loss includes its genes so it cannot be reconstructed during cell multiplication. This is the difference between the anaplasia of the cancer cell and the dissolution of the functional mechanism of a normal cell caused by overwork. When complete, the anaplasia of the former is not correctable through cell multiplication, while the defect caused by exhaustion of overwork under normal conditions is correctable by cell reproduction until the demands for functional material are satisfied. A different provision for survival is offered by non-reproductive nerve cells as we will show. This loss of F. M. gene activity in cancer cells is a fundamental characteristic, as we see it. This may simply be a loss through union with the carcinogen, and thus be correctable by adequate oxidations that burn the latter off. Or after many cell divisions it may be a true loss of the genes themselves, which are shed because of their uselessness when so combined. Such cells are not reparable.

The Restoration of Function

Before accepting our criterion as to the decisiveness of the test proposed to determine the curative separation of the symbiosis of nerve cell and virus, we must examine the situation in the nerve cell in detail. Tissue cells can reproduce to perpetuate their structure and preserve the adaptation and survival of the organism. Nerve cells cannot reproduce, so they possess a different type of survival mechanism. This we hold is the Nissl substance. We hold that the Nissl substance is a nucleoprotein much like the energy producing and functional material of the cell, but that it is not a reserve of food material held in position to enter the mechanism when the latter is worn down and needs replacement of parts. It is a substitute for the replacement of functional material by reproduction. Therefore it carries the conjugated system of carbonyl and ethylene double bonds, and when the virus enters the cell it can make its additions here.

The virus is thus neutralized so long as Nissl material is at hand, but when this material is exhausted, the excess of virus can join up and integrate with the functional material which is actually the living substance of the cell. Here we have the explanation of the influence of fatigue in producing the serious degenerative and symbiotic types of Poliomyelitis, and other virus infections of the central nervous system. The exhaustion opens the functional structure to attack. The non-paralytic cases of "Polio" are those in which Nissl substance neutralized the virus completely or practically all, so that if any functional structure was attacked it was in a minor degree. Reconstruction in such cases does not involve the replacement of nerve cells, but of restoring the Nissl content, and of a minor part of the functional mechanism by using Nissl material. This is accomplished in less than a month as a rule. Therefore any reconstruction and restoration of function coming after a month, must be had by an active curative process which must first separate the integrated virus from the living cell's functional material. This may take place in the symbiotic type of case months or even as long as three or twenty years after the paralysis and atrophy were established. For the symbiotic state may destroy function and result in atrophy of nerve and muscle without actually killing the motor nerve cell, and this condition may be drawn out for many years before the host cell finally dies. Scheme (b) of diagram V, represents the situation as we see it. But the lytic type of integration as represented in (a) of diagram V, generally shunts out all vital energy from the host cell vital processes so it dies quite early and of course is not replaceable. The atrophy and paralysis consequent thereto is incurable.

The rates of restoration of the Nissl involvement and the early phase of the lytic involvement requires only hours, as the virus is subject to quick oxidation by the therapy employed as it is hooked up with the host cell. Thus the paralysis that started twenty-four hours previously leaves in twenty-four hours or even less, as the case histories demonstrate. But the symbiotic type of integration may take twelve weeks to be completely corrected with restoration of muscle and of function in

a case of three years of paralytic atrophy; and it may take from six months to a year for correction to 90% of normal after 20 years of extensive paralysis and atrophy of both legs from hips to toes. This is illustrated here also. Where anterior horn cells were killed before treatment was given, no amount of treatment will restore them. However, the fact that paralysis of longer than a month's duration with the atrophy that was consequent to it is corrected as we show here, demonstrates that the virus is actually removed from the host cell and the latter is free again to reconstruct and function again. This is an accomplishment of which we are humbly proud, as it is done along physiological lines and no other system has ever been able to accomplish this feat. What has become of the virus? It gives us no information. Perhaps it too receives a carbonyl group conjugated with a double bond as a result of the peroxide free radical production at the position alpha to this double bond, and thus it may be restored so it can initiate its own oxidation chains. At any rate it is no longer pathogenic like the staphylococci and streptococci that produced the mastitis in the cows, reported later, and which either decreased in number during the healing, or even increased in number, if much tissue debris was to be removed while the healing and general detoxication of the animal was progressing rapidly.

Where the virus becomes part and parcel to the host cell with its units distributed throughout, and maybe even displacing host cell molecules, the integration is such that it must share the reactivities and properties of the host cell, be the latter tissue cell or bacterial in type. It will thus gain resistance to heat and chemicals when integrated with a spore of a fungus or germ. It will be divided during the mitosis or fission of its host cancer cell as part of that cell, and be liberatable only on the death of the host cancer cell. This type of integration will contribute the protein serological properties to the host cell which the particular breed of virus possesses. On the other hand a carcinogen of chemical origin as the phenanthrene series, or the free radicals of trichlormethane, dichlormethane, acrylic aldehyde polymeres, and incompletely combusted tissue cell and germ metabolites that polymerize in hypoxic foci, have no

protein content to serve serological identification. So two divisions at least can be made which will fit our diagram. The state of union shown here also explains the difficulty in obtaining infective filtrates from epithelial neoplasms, as well as some other puzzling features.

Energy Transfer

The carotenoids, Crocin, Vitamin A, Rhodopsin, and some others with multiple serially arranged conjugated systems of ethylenic double bonds, each enriched in electrons contributed by methyl substitution, offer splendid structure for energy absorption and transfer via fluorescence. This was our idea of the action of the visual purple where radiant energy was absorbed by the mobile electrons of the double bonds and passed on to the chemical processes of nerve cell excitation in the retina. We attributed the energy transfer for carcinogenesis to similar fluorescent processes of the carcinogen where the energy was absorbed from exergonic reactions going on in the field, hydrolytic glycolysis for example, and passed on into the chemical reactions of mitosis and cell division. The intimate hook-up of the carcinogen with the hydrolytic glycolysis system affords the opportunity for the energy transfer. (Koch, Natural Immunity 1936). Crocin and Echinocrome (A) offer the same facilities for energy transfer to the algae motion mechanism and to the Sea Urchin sperm taken from the oxidation process described above, where phosphorylation may also serve as intermediary. This provision seems to be a general affair since virus appears to take up a position between the energy pool and the functional mechanism which it excludes. The rate at which it can take up energy as compared with the rate the host mitotic mechanism can absorb it will determine the survival and progeny rates of both. Some of the enigmas of carcinogenesis can be answered by our fluorescence theory as they can also be explained on the basis of the diagrams given here. Thus when two differently constructed carcinogens of different polarities and different dilutions are given at the same time, instead of boosting their activities mutually, they may interfere with them by combining, each with a pole of the carbonyl group's activating ethylenic linkage, and thus exclude the hydrolytic gly-

colysis system from supplying the energy required for mitosis. It will be recalled too that saturation of this double bond also inactivates the carbonyl group so as to reduce its powers of dehydrogenation and oxidation chain initiation. Of two types of chemical carcinogen exhibiting different polarities, each will select the double bond pole to which it has most attraction, and hence even small amounts of one carcinogen can inactivate a part of a large amount of the other in this way. Likewise, too large a dose of a carcinogen of one type may hinder its own carcinogenic activity. Since fluorescent substances diminish in efficiency as they are concentrated, and increase in efficiency as they are diluted beyond the point where inactivating collisions can occur, too large a dose may postpone activity a bit.

While the schemes we offer here can never represent the situation in all its complexity, they serve as guides in the therapy, and answer many questions besides for the biochemist which otherwise are pure enigmas. They explain the Pasteur Effect as a function of the carbonyl group of a definite position. They show how the (K) region of the carcinogen may operate to make the union that provides for continuous energy transfer into the mitotic mechanism, and they show the position of anoxia in the pathogenesis and what atomic activity is required to liberate the host cell from the carcinogen, be it chemical, virus or both. They show the relation between neoplasia and atrophy and how both are a symbiotic affair that can be broken by the same atomic activity.

CHAPTER III

THE PATHOGENIC MECHANISM

When one compares the tireless activity of the child with the aches and restriction on motion as age advances, it is evident that the exchanges between the tissue parenchyma and blood stream of the child have no impediment so that waste products get out as fast as formed, and oxygen fuel and food enter as freely as is required for full combustion and tissue construction. There is no separating fibrosis between the parenchyma and the blood supply. In old age the separation reaches the limit where the exchanges are practically abolished, and finally, where life is no longer supported. One organ or other as habits and heredity have determined has suffered most at the hands of the fibrogenic agent, and cerebral paralysis or heart or kidney failure may be the immediate cause of death.

We have identified the initiating factor as an activated amine which causes a gellation of the plasma and cellular colloids and this gellation blocks the transport of oxygen causing a local hypoxia or anoxia. In addition to producing the gellation as we have observed results from the guanidin poisoning in our parathyroidectomy work, the amine condenses firmly with the tissue function carbonyl groups so as to block its initiation of energy producing oxidation chains. Incompletely burned metabolites of tissue cell origin or of germs caught in the anoxic area, then may be dehydrogenated so as to become free radicals but under the anoxic state cannot be burned. Since the amount of dehydrogenation accomplished under such circumstances is small at any time, a slow polymerization of the metabolite can proceed. This is especially true where scarring has reduced the oxygen transportation. The free radicals, be they of tissue cell or germ origin, may copolymerize with each other too, or with the collagenous material that is produced by fibroblasts in response to the irritant effects of the incompletely combusted state. Thus they are incorporated into the fibroblastic tissue intended to dis-