THE PRODUCTION OF THE KETENONES

The search for physiological evidence of the existence of the normal oxidation carrier (O=C=C=O), the internal anhydride of glyoxylic acid, was made in 1917 to 1920, and curative results obtained by the use of tissue extracts in the treatment of malignancy were reported in the New York Medical Record, October 30, 1920 (12). In 1931 (5) and 1937 (11) Maisin reported confirmatory results of organotherapy in cancer. Naturally a substance so unstable as glyoxylide or the internal anhydride of malonic acid could not exist long in aqueous solutions or be isolated as such, but formic and glyoxylic acids were found. It appears that isorrhopesis changes within the molecules of the potassium salts of glyoxylic acid, or formic acid, and of formaldehyde and its peroxide, yield the unsaturated molecule transiently either directly or by the union of two carbonyl groups set free. Clinical utilization of these intermediary substances in the allergies and neoplasia yield identical results to those obtained with the tissue extracts. However, it must be emphasized that neither tissue extracts nor the solutions prepared as mentioned are uniformly reliable sources of the active material. But where conditions are favourable and the preparation process is correctly carried out, the unsaturated molecule is produced with active life long enough to start the chain reaction desired to bring about recovery. When this happens the recovery processes in all instances are identical.

The solutions yield similar spectrographic curves,

moreover, and their identical activity demonstrates that the same active substance is generated even though we start out with different materials in several different ways. "Glyoxylide" is too unstable to be isolated even as a dry gas and can exist in solution only as an intermediary substance during some reaction as stated. Important corroboration is found in recent interpretations of the formula of formic acid by P. C. Ray (7) where, a "lone pair" of electrons is credited to the carbonyl group. He finds that the hydrogen atom attached directly to carbon ionizes to form salts, and that the failure of formic acid to form an anhydride or acid halide like other organic acids depends upon this fact. This behavior is interesting from our standpoint because it explains also that the calcium of calcium formate may form a hydroxide by uniting with the two hydroxyl groups present and thus liberate two carbonyl groups that may unite to form the Glyoxylide. Satisfactory support to the unsaturated structure of the active molecule is afforded by the internal anhydride of malonic acid "malonide" (O=C=C=C=O) which possesses the same unsaturated groups as "glyoxylide" (O=C=C=O). Both possess the unsaturated valences between carbon atoms and between carbon and oxygen atoms. Both absorb quite similarly spectographically. Both behave in the same way clinically and in the catalysis of oxidation of living tissues in vitro, except that the "malonide" owing to its extra carbon atom is less reactive and less efficient. As we have seen in the foregoing pages it becomes converted into glyoxylide as the chain reaction progresses. Aqueous solution of both unsaturated bodies reverse their structure back to the saturated glyoxylic and malonic acids. For reliable preparations

therefore it is necessary to produce the glyoxylide and malonide by special methods.

The method of extracting the substances from tissues that I used early in this work is expensive and only occasionally successful. Beef heart or brain is taken fresh from the animal and rapidly ground up into three times the weight of ice cold absolute alcohol in which a good quantity of anhydrous sodium sulphate powder was added. Thus the tissue is dehydrated and the protein precipitated. It may stand over night. The alcohol is filtered off and then the residue is extracted with dry ether, several times. The extract is concentrated and precipitated with acetone which extracts some fats and cholesterol. The precipitate is then freed from acetone by vacuum and extracted with ether again. This extract contains the lecithin and cephaline fractions with the metabolites adsorbed. It can be precipitated again with absolute alcohol to separate the lecithin solution from the cephalin precipitate, which carries the largest fraction of the important metabolites. Because of the presence of growth promoting substances in living tissues, or produced by action of the ether upon the lipoids, these extracts may not always be curative. Sometimes they stimulate cancer growth and increase the degree of malignancy.

Several practical means may be used for the production of the catalysts here mentioned. They are being taught to selected groups of physicians. We believe it preferable to give exact training in the technique than to leave so important a matter open to errors that my own experience shows are bound to creep in. The methods in general have been stated in "Natural Immunity," Fourth Edition, issued by the Koch Founda-

tion in 1936. One of the metabolites that is easy to prepare, and which has a wide range of activity in malignancy, the infections, and a few allergic conditions, is the peroxide of formaldehyde. It is prepared by contact of dry formaldehyde gas with dry hydrogen peroxide, dissolved in dry ethyl ether. Since the synthesis is exothermic it must be controlled as to rate and temperature to avoid violent explosion. Dry formaldehyde can be prepared from dry para-formaldehyde by warming it. The ether solution of hydrogen peroxide into which it is lead should be kept ice cold. It is well for the operator to be protected since the reaction sometimes "runs away." The crystaline product should be recrystalized till pure as shown by the melting point. It is then diluted to one to a billion or higher by a technique that is perfect, in every detail in avoiding contamination, as to pure water, air, clean apparatus, clean hands, breath, absence of perfumes, etc. This aqueous solution deteriorates very rapidly.

A dilute solution of formic acid or calcium formate might theoretically at least yield or behave as Glyoxylide; so too an alkaline solution of formic aldehyde and the peroxide of formaldhyde; for in solution both can produce free carbonyl groups momentarily which are free to unite with double bonds. But since their free valences are so unstable they either activate oxygen and become peroxides or immediately polymerize unless some nascent ammonia, iodine, or other radicle is present to saturate the ethylene union. Glyoxylic acid may be assumed to undergo double dehydration and produce the Glyoxylide under colloidal conditions present in living cells. When the peroxide of formaldehyde undergoes internal oxidation of its hydrogen atoms to form a free carbonyl group leading to Gly-

oxylide production, an important catalytic event takes place through the migrations of the oxygen and hydrogen electrons.

In the production of the peroxides of formaldehyde and especially when the "chimney" method with platinum as hydrogen acceptor is used, both the single and double formaldehyde peroxides are formed with some Glyoxylide which soon polymerizes to a yellow and pink liquid and decomposes. The amount of Glyoxylide formed depends upon the amount of air admitted to the reaction system. Of course, other substances are formed too. Of these, glycolaldehyde is most important because it dehydrates to ketene, and because of its intermediary catalytic position in aerobic oxidation, as I interpret it, (page 56).

A very serviceable method of producing the oxyketenes and ketenes is through the phosphoric and sulphuric acid derivatives of fructose, glucose, ether and acetaldehyde, by which the active bodies are trapped as polymers and then resolved to monomers by destructive distillation and by dilution as described in my patented process. I have used this method since 1920. It proves serviceable to my students.

It is rather interesting to compare the production of curative agents in this way with the production of the most vicious pathogenic agents, and also a possible means of the production of the viruses. They form best during dry weather under influence of the August and September sun when dehydration and peroxidation of unsaturated groups by ultra-violet light is favored, and this in turn favors a polymerization of the unsaturated residues. Quinone production, and fluorescence gives such bodies the power to carry chain reactions that we have described to perpetuate any neces-

sary reaction for their existence when present in a cell that liberates exothermic energy. Thus they practically propagate and interfere with normal function. The rapid recoveries we have produced in infantile paralysis, shingles, and other virus infections by employing the diluted polymers and monomers of our Ketenones seems very corroborative to this conception. (34).

The objective in the synthesis of these bodies therefore is to secure free valency of the highest activity in molecules that are as like as possible to those engaged in aerobic glycolysis, as I have interpreted the process to be. They are the fully unsaturated ketenes and oxyketenes, and the hydroxy-ketones from which these are derivable, and also other possessors of the carbonyl group in highly active state, such as formaldehyde, formic acid, glycolaldehyde, glyoxal, glyoxylic acid, glyceric aldehyde, glyceric acid, glyoxyl-carboxylic aldohydroxy-carboxylic and hydroxyketo-carboxylic acids.

The carbonyl group when flanked by an acetylene radical, as in propargylic aldehyde exerts tremendous but not always controllable catalytic powers. It has however eradicated the worst Vincent's infection, Noma and spirochetal infection for me. On the other hand, carbonyl flanked by amino groups are quite inactive, as in the amino acids,—a provision which protects proteins from catastrophy. Therefore in the production of acquired immunity general proteolysis and desamidation may go on extensively to satisfy a local carbonyl deficiency, caused and perpetuated by a local polymerization or other inactivating catalysis. Acquired immunity is therefore a clumsy application of natural immunity principles.