DRUGS—A TOOL FOR RESEARCH IN PSYCHIATRY*

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"For want of a nail . . . a kingdom was lost; for want of a hydrogen transfer . . . a mind was lost—all for the lack of functioning chelates" (1).

THE history of medicine reveals man's search for drugs to ease his diseases and possibly cure them. Advances have been made pharmacologically in the treatment and prevention of many infectious diseases. While psychiatry has benefited from these discoveries in the treatment of certain infections of the central nervous system, in general, the treatment of psychiatric diseases remains largely empirical. The psychopharmacologic treatment of psychiatric diseases continues to be based on the presenting symptom-complex of the patient; this is because the aetiology is still unknown, for in reality our explanations do not explain. The phrenotropic drugs currently used in psychiatry are important for their pharmacodynamic effect since they change the cellular environment in which mental processes are maintained. Pharmacodynamic research in psychiatry has revealed possible neuroanatomical sites and many biochemical effects of these drugs. The specific correlation of these findings with clinical effects is lacking. When this is accomplished, it is probable that better drugs will be developed.

Obviously, in the rational use of drugs for the treatment of mental diseases, it is essential to have a complete understanding of the known effects of these drugs on total behaviour; this includes both anatomical and biochemical nerve structures as well as their over-all pharmacologic effects in the total organism. Fortunately, some, but too few, of the aims of psychopharmacology have been achieved. The phenothiazines and rauwolfia alkaloids have a high degree of specificity for the symptomatic control of virtually any state of psychomotor excitement. They are useful in the control of agitation, aggression, anxiety, catatonic muscular signs, delirium, destructiveness, delusions, excitement, hallucinations, illusions and in many of the chronic patients, deterioration. These tranquillizers have only a minimal influence on effect, a primary disturbance in all neuropsychiatric diseases. There is a greater lack of unanimity as to the drugs which are to alleviate depression and improve affect. The antidepressives and psychic energizers alleviate these symptoms in many neuroses and psychoses. This clinical finding provides the rationale for combination therapy in the schizophrenics (2).

If the ultimate aim of psychopharmacology is to be reached, that is, to devise a rational therapy, the elucidation of the pathology must be made. It is my opinion that drugs have been the most important tool for investigating the biochemical and physiological mechanisms in diseases of man.

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Therefore, we must use the presently available psychopharmacologic agents to provide the changes at the cellular molecular level necessary for the elucidation of both normal and pathological mental processes. This can be accomplished only by a correlation of all the clinical changes (therapeutic and untoward) with their pharmacologic mechanisms.

Previously, I have pointed out the value of the side-effects of drugs in giving us an understanding of probable aetiological factors in neuro-psychiatric diseases (3, 4). Every action we observe, objectively and subjectively, may assist us in the acquisition and systematization of positive knowledge. This is the development of a science. In view of my present knowledge, my remarks will be concerned with changes in amine and protein metabolism and what an understanding of these changes by psychopharmacologic agents may bring.

Both tranquillizers and energizers have been shown to shift the dynamic equilibrium of several known amines and serum proteins. Amine metabolism certainly holds a paramount position in psychiatric diseases since the level of several autonomic amines is known to change the ebb and flow of these disease states. An example of a dynamic amine equilibrium is the histamine-catechol amine relationship. Nonspecific stress brings about a discharge of epinephrine from the adrenal gland and release of norepinephrine from the sympathetic nerve endings. Histidine decarboxylase activity is increased by stress and the injection of epinephrine and norepinephrine. These observations suggest that there may be a physiological balance between histamine and catechol amines. This would imply that a failure to maintain a dynamic balance would result in a pathologic state as indicated by circulatory shock (5). Previously, I pointed out the evidence for histamine stimulating the hypothalamic-pituitary-gonad axis via rhinencephalic pathways and that there was considerable data to support the concept that the limbic system was a potential anatomical site for emotional and intellectual functions (6). Reserpine releases catechol amines and they will antagonize the elevated histamine levels from hydralazine (a diamine oxidase, histaminase inhibitor) in the treatment of hypertension. There is another histamine metabolizing system that is inhibited by iproniazid. This system is composed of a methylating enzyme and an oxidative enzyme. Iproniazid inhibits only the oxidative and not the methylating mechanism. Methylhistamine is a substrate of monoamine oxidase; therefore, the metabolism of histamine can be regulated by levels of catechol amines and inhibitors of monoamine oxidase. This metabolic balance is known to be affected by both tranquillizers and energizers in the treatment of neuropsychiatric diseases (3). Tryptophan peroxidase-oxidase is an adaptive enzyme and an increase can be brought about by the stress reaction of the adrenal-pituitary system (7). Tryptophan peroxidase-oxidase opens the pyrrole ring of tryptophan with the loss of carbon to yield kynurenine. Both the phenothiazines and hydrazines block the eosinopenic response to stress probably by their action on ACTH secretion of anterior pituitary lobe (8). These studies indicate their mechanisms are still obscure and their elucidation should give valuable information on the normal mechanism of action of physiological processes. The enzyme systems for the metabolism of these amines are known to be influenced by hormones, trace metals, central nervous system monitoring mechanisms and phrenotropic drugs. Further elucidation of these regulatory factors will depend upon increasing knowledge of the co-ordination structure (chelate) of these reactants *in vivo* with their thermodynamic interrelationships.

From the fragmentary experimental data available in 1957, I speculated

that a possible mode of action of the phenothiazines, rauwolfia alkaloids and iproniazid was to maintain the physiological dynamic equilibrium between oxidative deamination and transamination (9). This disturbance in equilibrium results from unsatisfactory chelate formation (10) with aberrant oxidation and coupling of phosphorylation. These phrenotropic drugs have a regulatory action on the protein synthesis of the reticuloendothelial system and the liver; specifically they regulate a large number of biogenic amines essential for globulin synthesis. The primary effect of these proteins in a biologically active molecule is the regulation of the intensity and duration of chelate bonds for essential enzymatic processes. The phrenotropic drugs may also be able to substitute as amines in enzyme complexes and regulate the strength of bonds between the two donor atoms during the catalytic process. Two independent investigators have observed that indoles form chelates with riboflavin in which one electron from the tryptophan is taken up by a riboflavin molecule (11, 12). Proteins that contain tryptophan, as well as serotonin and other indoles may reduce and form chelates with a semiquinoid form of riboflavin. In addition to the high affinity of serotonin for riboflavin, so has lysergic acid and bufotenine and these substances have been implicated in physiological and pathological psychic functions. The tryptophan-riboflavin complex probably represents a molecular compound (13) through the formation of a co-ordinate covalent bond between the two components. It appears that one pair of the pi (π) electrons of a double bond in the aromatic compound (tryptophan) may be the donor pair and constitutes a charge-transfer (14) where an electron goes from the highest filled orbital of the donor to the lowest empty orbital of the acceptor. This reaction is probably important as a means to transfer energy in biological reactions. The semiquinoid form of riboflavin resulting from the acceptance of one electron is a free radical; another free radical could result from the protein or tryptophan donating an electron. It is possible that flavoprotein itself contains a semiquinoid form stabilized by tryptophan in the protein as this form can be produced and stabilized by the simple addition of serotonin, an indole derivative at neutral pH.

Michaelis (15) names the intermediary, half-reduced and half-oxidized form with the configuration of a free radical, a semiquinone. Compounds of this type, having an unshared electron, are extemely unstable owing to their great reactivity. Many oxidation-reduction systems both biologic and of synthetic origin frequently take place in two overlapping steps, each involving a single electron; the resulting semiquinone or free radical formation, at a certain pH, is believed to be essential for all biologic oxidation processes as they depend on intermediary production of such radicals (16). In the cell, mental complexes such as cytochrome with a one-electron shift have relatively high potentials, whereas the substrate lactic acid, in combination with its specific enzyme, has a two-electron shift and a relatively low potential. The flavins of intermediate potential can be oxidized by transferring one electron at a time thus bridging the gap between the one- and two-electron shift systems. Without an enzyme system of this type it is difficult to picture the mechanism for transfer of electrons from lactic acid to the cytochrome system for its oxidation to pyruvic acid.

The cytochrome system enzymes act as the middlemen in the delivery of the oxidizing power of molecular oxygen to the eventual substrate. They are a group of metal (Fe and Cu) porphyrin-protein chelates that differ from each other in the nature of the protein, and possibly in the linkage of the

latter to the metal porphyrin. The need for the cytochrome system is to provide a series of oxidation-reduction reactions of low potential for a high oxidation potential would damage or destroy the cells. The cytochromes transfer electrons only. They do not transfer hydrogen, therefore coenzymes I and II or flavoproteins are essential for hydrogen transfer. Cytochrome oxidase is essential to the oxidation of the cytochromes, a, b, c and possibly accessory cytochromes. The oxidase is very insoluble but in combination with cytochrome c it is possible to obtain a rough idea of its potential because this combination oxidizes paraphenylene diamine (PPD) rapidly and the rate falls off when a certain amount of the diamine is formed (17).

Polyphenol oxidase (ceruloplasmin) in man is inhibited by the phrenotropic drugs, chlorpromazine, iproniazid, reserpine and procaine (18). The metabolic rôle, if any, of this enzyme system in schizophrenia remains to be determined but there are many acute psychotic patients with elevated levels of ceruloplasmin. There are publications (19) stating that ceruloplasmin was probably the responsible enzyme system for this oxidation of PPD in schizophrenics at a faster rate than observed in normals. We obtained data that would indicate a cysteine-cystine system was one of the biologic oxidation-reduction systems associated with this phenomenon (20). Cysteine is almost as active as ascorbic acid in an oxidation-reduction system. Others thought ascorbic acid to be the factor in the different rates of oxidation found between schizophrenic and normals (21). Ascorbic acid is able to relieve the decoupling effect of pentobarbital on oxidative phosphorylation. Nielsen and Lehninger (22) recently stated that the phosphorylation observed is actually coupled to electron transport between cytochrome c and oxygen, since ascorbic acid apparently acted as a nonenzymatic reductant of cytochrome c. Their experiment, however, was not completely conclusive because of the possible oxidative or phosphorylative reactions uniquely associated with the presence of ascorbic acid. Cohen and Cohen (23) indicate that ascorbic acid was significantly related to phosphorylation and their relation may be one of self-phosphorylation linked to the cytochrome system through the oxidation of ascorbic acid. They also found that ACTH had a stimulatory effect on this system for the generation of the high energy bonds of phospho-ascorbic acid and this could be a means in which ACTH controls corticosteroid synthesis.

All this raises the essential question: Do the psychopharmacologic drugs' therapeutic results depend on the previously discussed reactions? Does reserpine break this riboflavin semiquinoid-serotonin complex or does it free serotonin in order that it might complex with riboflavin and maintain a shift of electrons to the respiratory oxidative system? Reserpine containing an indole moiety may be in competition with indoles other than serotonin to form molecular compounds and enter into charge-transfer reactions. The charge-transfer from amines and proteins to riboflavin is very interesting if this electron donation is passed on by the flavins to the oxidation system. Are the electrons transferred from the amine or protein replaced by electrons produced by the dehydrogenated diphosphopyridine nucleotide (DPN) linked enzymes? If this electron transference in the DPN enzyme system were modified by the replacement of vitamin B6 (niacinamide) with iproniazid (24), this could explain a possible mechanism for its inhibition of monoamine oxidase. It was shown that oxidation of iproniazid was necessary for irreversible inhibition of monoamine oxidase. If this were so, it is possible that iproniazid acted initially as a substrate for the enzyme. The coenzymes I and II which are adenine-nicotinic acid amide complexes are reoxidized by

the flavoprotein catalysts. Iproniazid, in addition to its being a component of DPN, may act through its ability to chelate with copper. The breakdown of dilute solutions of the hydrazines has been shown to require oxygen and either cupric or ferric ions. This auto-oxidation is of biological importance because it helps characterize other biologically active substances. The formation of free radicals during the cupric-catalyzed auto-oxidation of iproniazid is supported by the fact that this system stimulated polymerization of styrene and produced coloured reaction products from phenols. It is probable that cupric ion accepts single electrons from hydrogen peroxide to form free OH radicals and reaction intermediates formed from the iproniazid oxidation may be free radicals and may be responsible for its toxicity (25). The iron may be in the form of haemin and clinically this correlates with observations noted in the haemoglobin hydrazine complexes in patients receiving these drugs. Heavy metals inhibit the oxidase electron-transporting mechanisms but not the amine dehydrogenase (26). It is probable that, like other oxidase systems, monoamine oxidase consists of a dehydrogenase, linked to a respiratory chain which may include cytochrome and flavins. Lagnado and Sourkes (27) have succeeded in linking amine dehydrogenase directly with tetrazolium salts so that the electron-transporting system of the oxidase is bypassed. Further advances on the relationship of heavy metals, sulphydryl groups, cytochromes and flavins in the monoamine oxidase system await the characterization of this system and the possible separation of the amine dehydrogenase.

There are additional data that complex formation may be essential to obtain pharmocologically active substances. A molecular compound of chlorpromazine-riboflavin has been observed (28) and this product of complex formation may infiltrate into a specific cell. Access to both the outside and inside of the cell would provide a function not common with most pharmacological preparations and could account for chlorpromazine's modification of the electron transport processes, degree of phosphorylation and group transfer reactions in protein synthesis. Chlorpromazine is a very good electron donor and there is evidence to believe that such charge-transfer reactions may be a factor in biologic energy transfers. This indicates the need to study the charge-transfer mechanisms associated from chelation of drugs with neurohumoral agents.

Riboflavin as well as the pyridine coenzymes are essential for metabolism of tryptophan. There is evidence to indicate the hydroxylation state in tryptophan metabolism is an oxidative phosphorylation rather than a simple oxidation. Riboflavin was suggested to be a factor in hydroxykynurenine formation and this has been supported by nutritional studies (29); serotonin metabolism probably involves a system similar to that involved in the formation of hydroxykynurenine. Riboflavin might be concerned only with a phosphorylative rather than a purely oxidative function and the increased xanthurenic acid excretion in riboflavin deficiency can be explained in this concept (30). Future interest in hydroxykynurenine are in the pigments formed from its copper and iron complexes and that two molecules may condense to give a phenoxazine derivative.* Phenoxazine can participate in reversible oxidation-reduction reactions and may be able to compete with the isoalloxazine derivative, riboflavin. This is another important area of amine metabolism that warrants investigation in psychic activity.

* Ommochromes.

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It has been suggested that sulphydryl linkages may play a vital rôle in the metabolism of schizophrenia (18), and in the metabolic action of chlorpromazine (31). It is suggested that chlorpromazine may act on sulphydryl linkage of the respiratory enzymes. This linkage is involved in many steps of the citric acid cycle with a resultant production of energy. Succinic dehydrogenase activity is inhibited by chlorpromazine but can be protected and reactivated by several sulphydryl compounds. ATP alone does not restore activity but when sulphydryl compounds co-exist with ATP, the restoration is significant. Cytochrome c has two cysteine molecules across the double bonds of the vinyl groups and they act as points of attachment to the protein. Chlorpromazine, *in vitro*, exerts a biphasic effect on cytochrome c, inhibition in high and stimulation in low concentration (below 10–4M). The significance, *in vivo*, of this biphasic response is not known, but could prove informative.

These findings are highly suggestive that different levels of oxidation-reduction (electron transfer) are involved with phrenotropic drugs and this approach can be used to determine the mechanisms of the respiratory chain involved in oxidative phosphorylation. There are uncoupling agents, such as the barbiturates, so this alone cannot explain the action of these psychopharmacological agents. The other reactions may be related to oxidative phosphorylation and specifically to diphosphopyridinenucleotidase (DPNase) and high energy phosphate bonds. Lehninger (32) has shown that the oxidation of DPNH (reduced) generates through three high energy phosphate groups. One is formed on the oxidation of reduced cytochromes by oxygen; the other two may be formed on the oxidation of DPNH by cytochromes through the flavins. This indicates that chlorpromazine, reserpine and deserpidine modify permeability as DPNH is generated metabolically outside of the mitochondria. The phrenotropic drugs maintain elevated levels of DPN following injections of nicotinamide into mice (33) and the hydrazine monoamine oxidase inhibitors have been shown to produce a decrease in DPN levels in both liver and brain tissues.

After the administration of chlorpromazine there is an increase in the content of ATP in the microsome fraction and no significant change in the mitochondria. Almost all of the transamination reaction occurs in the microsome fraction and it is inhibited by the phenothiazines. There is a deaminating mechanism in the brain that depends on oxidative phosphorylation; this system deaminates the hexosamines which must be phosphorylated by ATP. Oxidation by transamination which requires a pyridine nucleotide and by deamination which requires a flavin would be expected to generate three ATP molecules per oxygen atom (exception α-oxoglutarate yields succinate, with 4 ATP and dehydrogenation of succinic, propionic and isovaleric acids, generates 2 ATP). The ATP generated from the degradation of tyrosine and phenylalanine includes oxidation steps which probably cannot be coupled with phosphorylation. The ammonia binding mechanism depends upon the citric acid cycle to provide the keto acids functioning as amino acceptors in transamination reactions in the brain. This suggests that the primary function of these transamination systems is to provide additional routes for the accommodation of ammonia. If the brain microsomes are like those of the liver, then there would be reason to believe that an ATP increase could indicate the drug effect on protein synthesis. Lindan *et al.* (34) observed that chlorpromazine inhibits the rate of glycine–1–C^{14} incorporation into rat brain cortex proteins. The ribonucleic acid (RNA) content of rat brain cortex is significantly reduced by chlorpromazine. These modifications by

phenothiazines in the brain of the amine and protein metabolic system indicate further investigations are essential.

Early in the clinical investigations of the tranquillizers we observed a greater difficulty in management in patients suffering from acute infections (35). We noted that it was desirable to discontinue the tranquillizer in order for the antibiotic therapy to be as effective as expected. Electrophoretic studies of serum indicated many chronic schizophrenic patients have a reduced initial albumin and increased globulin fractions. With tranquillizer therapy there was a drop in globulins up to the 7th to 10th week and then a slow rise to normal values. The α-globulins showed the greatest drop also reaching their lowest level between the 7th to 10th week. Are the previously discussed biochemical phenomena associated with this serum protein shift? Is the reticuloendothelial system (RES) and/or the liver a site of action for these drugs on protein synthesis? Does the shift in available amines for globulin synthesis account for hapten (part of the antigen) formation, with a phenothiazine, which possibly produces sensitization reactions in patients? Remember it is frequently in this 7th to 10th week period that agranulocytosis is observed. We have also observed in experimental animals a marked change in the LD_{50} following a standardized dose of bacteria if the animals had been previously treated with a tranquillizer (36). This not only indicates that the globulin formation mechanism is an essential factor in infectious diseases but also for investigation in psychoses. Can we surmise that these drugs might make tissue transplants in man possible by suppressing the antibody formation? These are a few of the many fragments of data that indicate biogenic amines and their mechanism to form chelates and transfer electrons must be understood if we are to explain psychic activity in man.

It is better to investigate and know the road leads blindly rather than have it remain unknown. Fortunately, explorations of questionable leads and side-effects of drugs continue to provide informative data in the search for explanations of mechanisms and aetiology of neuropsychiatric diseases. Unfortunately, bureaucracy does not provide competent leadership therefore it is essential for individuals with intellectual imagination, intellectual honesty and intellectual courage to provide this leadership.

Conclusions

I have proposed the concept that psychoses are a disorder of the regulation of metabolic processes rather than an insufficiency of certain enzymes or of essential neurohumoral metabolites. As a rule, only oxidations which involve pyridine nucleotides, flavoproteins and cytochromes can be coupled to phosphorylation. The tranquillizers which inhibit transamination and the hydrazines which inhibit deamination probably act through chelate formation of the pyridine, flavin or porphyrin catalysts. Experimental data allows us to accept the previously stated theories that electron transfer mechanisms have probably an essential function in the action of the psychopharmacologic agents discussed. The regulation of the coupling in oxidative phosphorylation helps to choose the substrate and explain in general terms why the available metabolites are not simultaneously oxidized as a dynamic equilibrium is essential. The regulation of choice of substrates is also a result of enzymic architecture within the cells at a given pH and salt concentration (37) (including the various trace metals). The rôle of riboflavin and potential antimetabolites from indole precursors provides a highly speculative but interesting working concept. The function of stress in providing adaptive activity to the enzymes

in indole metabolism brings it into the realm of psychiatry. The presently available phrenotropic drugs are continuing to serve as research tools in the elucidation of some of the mechanisms of physiologic and pathologic psychic activity.

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