*American Handbook of Psychiatry*

# THE BIOCHEMISTRY OF SCHIZOPHRENIA

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## Charles E. Frohman and Jacques S. Gottlieb

In discussing research in schizophrenia, D. W. Woolley once wrote that "new and revolutionary scientific discoveries do not leap into the world complete and final as Athene was said to have sprung, mature and fully armed, from the head of Zeus. Instead, they come stumbling into view not fully formed nor completely ready to defend themselves from any possible attack. They come to full stature only as the result of modifications to meet their shortcomings." Our knowledge of the biology of schizophrenia most certainly is not complete or final. Many interesting discoveries have been made but they are just beginning to form an intelligible picture. It may well be that in the next few years these ideas will come to full stature and that then we will have a complete understanding of the biology of this disease. At the present time, only some very interesting research trends and numerous unconnected bits of information can be presented.

### Plasma Proteins

Many workers have speculated on the possibility that a toxic factor is present in the blood of schizophrenic patients. One of the earliest reports was that of Macht. He showed that human serum retarded plant growth and that

the retardation was greatest when serum from schizophrenic patients was used. Rieder showed that serum from schizophrenic patients caused spiders to spin bizarre webs and again attributed this to a toxic substance in the blood. Bishop showed that, in rats, reward learning was severely retarded by the administration of serum from schizophrenic patients but that avoidance learning was hardly affected at all. Winter and Flataker, using the reward system, showed that the material affecting rat behavior was a protein. Bergen et al. carried this work further and were able to separate and characterize the protein. Two other groups (Frohman and Lozovsky) have confirmed the work of Bergen and have been studying the same protein. These three groups have produced many similar findings on this protein. All three groups used different isolation techniques. Bergen et al. used a zinc-EDTA complex to isolate their protein. This protein when injected into rats caused a reduction of the rat's ability to perform a simple learned task, i.e., climbing a rope to receive a reward. Frohman et al. isolated the protein by means of DEAE cellulose chromatography followed by electrophoresis and finally ultracentrifugation with a sucrose gradient. They tested the protein by its effect on the ratio of lactic acid to pyruvic acid (L/P ratio) in chicken erythrocytes incubated with the protein. The protein from the schizophrenic patients caused a higher L/P ratio. Later, as an indicator, they used the protein's ability to increase the uptake of tryptophan by cells. Through a series of studies in which factors were exchanged on a blind basis, it was

shown that the protein factors that the two groups were working on were identical. Samples isolated by Bergen et al., using their isolation procedures and known to affect their rat climbing-time measure, also affected the L/P ratio in chicken erythrocytes and the uptake of tryptophan by the cell (the measures used by Frohman et al.). Samples isolated by Frohman et al. and found active by their methods also affected rat climbing-time when tested by Bergen et al. The group headed by Lozovsky has isolated the same protein. They used a modification of Frohman's method for the isolation of their protein and the same technique as Frohman for detecting it. In all likelihood, these methods have yielded the same protein. Frohman and the Lafayette Clinic group found that their protein was an α-2-globulin as did Pennell on the fraction isolated by the Worcester group. The Russians, however, reported that their protein was a *p* globulin. This apparent difference in electrophoretic mobility probably arises from the use of two different electrophoretic systems (the Spinco CP electrophoretic apparatus used by the Lafayette Clinic and the Russian-made apparatus of the Academy of Science) and certainly does not suggest that the two groups are working on different proteins. Quite the contrary, the similarity between the biological effects reported by the different groups working on the factor would indicate that all are working on the same protein.

In studying the plasma protein further, the Lafayette Clinic found that it significantly increased the ratio of intracellular to extracellular tryptophan

and 5-hydroxytryptophan while that of most other amino acids is affected only slightly. Further work has shown that bovine brain incubated with the protein from patients produced more dimethyltryptamine (DMT) than bovine brain incubated with the same protein isolated from nonschizophrenic subjects. The effect of increased production of DMT will be discussed in the section on indole amines. Many other attributes of this protein have been investigated. The Russian Institute claims that complement enhanced the activity of the α-2-globulin. The Worcester Foundation group showed that the protein decreased the amplitude, increased the latency and increased the variability of photically evoked EEG responses in the rabbit. The Lafayette Clinic group has found that when the protein is injected into the lateral sinus of a rat's brain it decreased the rate at which the animal will press a bar to receive pleasurable sensations from stimulation of the medial forebrain bundle. This possibly may mean that the protein blocks the enjoyment of pleasure stimulations in the rats. Using a clinical classification system which differs from that used in the United States, Lozovsky has demonstrated that the activity of the α-2-globulin is related to the malignancy of the disorder. The more rapidly the patient deteriorates, the more active is the α-2-globulin. By measuring the activity of the protein upon admission to the hospital and at bimonthly intervals afterwards, they have been able to demonstrate that the activity of the factor is high on admission, that it increases for about two years, then levels off. The activity of the plasma diminishes only after ten or

more years. The Russians interpret this as an indication of a relationship between the active process and the protein. Thus, at two years after the start of the disease, the process is at its most active stage, and after ten years or more the process has discontinued and the patient has entered a chronic deteriorated level of the disorder.

Other groups have isolated a protein from the blood of schizophrenic patients similar to and possibly identical to the α-2-globulin. Walaas and co-workers have isolated a protein which affects the uptake of glucose by rat hemi-diaphragm and have indicated that it is a β-globulin, and Ehrensvaard has isolated a protein which affects the oxidation of an aromatic amine.

As mentioned previously, Bergen found that the α-2-globulin affected evoked potentials. A labile serum factor which decreases the amplitude of evoked potentials recorded from the cerebral cortex and limbic system structures of cats has also been described by Fayvishevsky and Nemtsov. Another serum neurotropic factor is said by Fayvishevsky to affect the spontaneous electroencephalogram and to be stable during storage. Until protein fractionation techniques are applied to purify these latter two neurotropic factors, one can only speculate about their possible relationships to the α-2-globulin.

**Biochemical and Biophysical Nature of the α-2-globulin**

All three groups (the Worcester Foundation, the Lafayette Clinic, and the Russians) agree that the protein has quite a high molecular weight, the Lafayette Clinic group placing the molecular weight around 400,000. All agree that the molecule contains a great deal of lipid (about 80 per cent lipid, according to the Lafayette Clinic group). They also agree that the activity is quite labile and the protein can be inactivated by heating, freezing, or aging, and that it can be protected with compounds which inhibit sulfhydryl oxidation such as ascorbic acid, mercaptoethanol, and sucrose. The activity is preserved best if the protein solution is adjusted to pH 6-8 and stored at about 4 C. The protein appears to bind large amounts of ethylenediaminetetra-acetic acid (EDTA). Pennell felt that this indicated that the protein might also bind a metal. His careful and thorough analysis for metal in the protein showed that the protein contained only trace amounts of any metals believed to be involved with biologically active proteins. Consequently, he discarded the idea that a metallic ion was involved with the protein. Nevertheless, Bergen demonstrated that the activity of the protein could, through double dialysis, be transferred from an active protein to an inactive one. This indicates that the activity of the protein could be contained in a small molecule attached to the protein. As a possible aid to the identification of this small molecule Pennell demonstrated that a portion of the protein was chromogenic; upon heating, it formed a red pigment with an absorption spectrum consistent with a Quinone derivative of a catecholamine

or indole.

The Lafayette Clinic group has isolated the α-2-globulin in relatively pure form; they refer to it as the S-protein. Examination by disc gel electrophoresis, analytical ultracentrifugation, and DEAE cellulose chromatography revealed only a single component. Using this homogeneous protein, further careful studies became possible. Earlier, it was believed that the level of the S-protein was higher in schizophrenic patients than in control subjects, but following the isolation of pure fractions, it could be shown that there was no difference in the level of this protein between the blood of control subjects and schizophrenic patients.

Other properties of the S-protein were investigated in an effort to explain the difference in effect of this protein in plasma from schizophrenic patients and control subjects upon tryptophan accumulation in cells. This difference of the effect of the S-protein must be the result of some difference within the protein molecule isolated from the two types of subjects. Amino acid content of the protein isolated from control subjects and that of the protein isolated from schizophrenic patients were the same. In addition, the levels of cholesterol and of fatty acid were the same in both samples so that the difference in activity could not be attributed to a difference in the lipid content.

The tertiary structure of the S-protein was investigated by means of optical rotatory dispersion. In this procedure, the rotation of polarized light at various wavelengths is indicative of certain organized structures. The protein isolated from schizophrenic patients was found by Harmison and Frohman to be primarily in the a-helical conformation. They found that the inactive protein from control subjects had little or no a-helical conformation, and was primarily in the β and/or random chain form (Figure 26-1). In other words the shape of the protein molecule isolated from plasma from schizophrenic patients is very different from the shape of the one isolated from the control subjects.

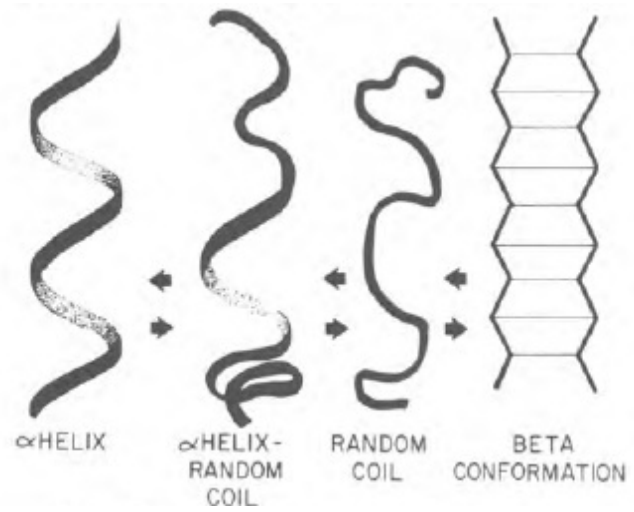


**Figure 26-1.**
Graphic representation of three conformations which the tertiary structure of a protein can assume.

It has been known for some time that the shape of some proteins is intimately related to their biological activity, although laboratory evidence from work with purified proteins has been relatively scarce. Definite proof has now been presented that this is the case with the S-protein. Figure 26-2 shows the correlation between tryptophan uptake and the percentage of a-helix in the molecule. The correlation coefficient is 0.84 ($P < 0.01$). From this correlation, it can be postulated that the a-helical form of this protein is responsible for its effect on tryptophan accumulation.

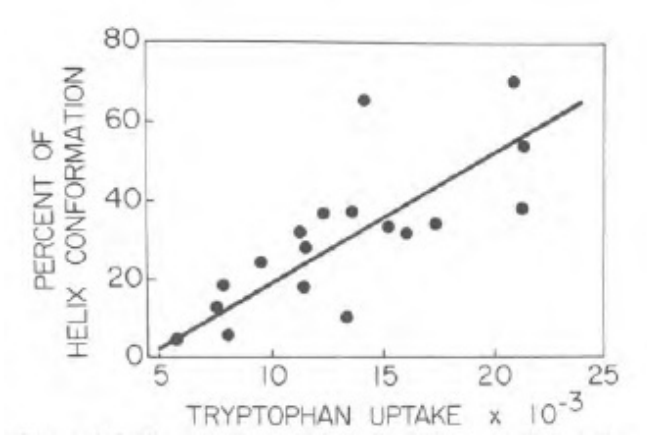


**Figure 26-2.**
Correlation between tryptophan uptake and percentage of a-helix in the molecule of S-protein.

Frohman and co-workers have isolated a second protein which counteracts the effect of the S-protein. This anti-S-protein is present in both human and animal tissue. It is purified by starch block electrophoresis

followed by DEAE cellulose chromatography. The activity is enhanced by administering norepinephrine to the animal before the tissue is removed. There is four times as much activity in brain as in erythrocytes. It has been demonstrated that the a-helical form of the S-protein is converted to the random chain conformation when incubated with the anti-S-protein. At the same time the effect of the S-protein on tryptophan levels in the cell is negated. Levels of the anti-S-protein have been measured in the human brain from both schizophrenic and nonschizophrenic patients and are almost four times as high in the nonschizophrenic patients. It is suggested that the large amount of the a-helical form of the S-protein in the schizophrenic patients could result from the lack of anti-S-protein in brains of schizophrenic patients, and that the excess of the *a*-helical form of the S-protein results in the changes observed in tryptophan metabolism.

**Biologically Active Amines**

Much work concerning the biochemistry of schizophrenia has focused upon indole amines and catecholamines. This occurred after the discovery of how the action of reserpine, the earliest tranquilizing drug used to treat schizophrenia, is related to the binding of catechol and indole amines. These two classes of compounds, both believed to be involved in nerve transmission, came under systematic study. Since reserpine releases some of the bound serotonin and bound norepinephrine present in the brain, thereby

lowering the amount of serotonin and norepinephrine available for nerve transmission in the midbrain, it is probable that the tranquilizing action of this drug involved depletion of one or both of these neurotransmitters in the midbrain.

**Indole Amines**

The observation that some naturally occurring analogs of serotonin (e.g., LSD and bufotenin) could cause symptoms which resembled some of those found in schizophrenia made work with the indoles even more intriguing. Since lowered serotonin apparently caused improvement of symptoms, administration of these structural analogs probably increases the apparent level of serotonin through some sort of agonistic action. Woolley predicted that synthetic analogs of serotonin would cause hallucinations when given to humans, and then actually proved that this was the case with the benzyl analog of serotonin. The interest in serotonin spread to other physiological indoles and to their precursor in mammalian metabolism, the aromatic amino acid, tryptophan. Figure 26-3 shows several of the pathways by which tryptophan is metabolized in the body. It can be hydroxylated to 5-hydroxytryptophan which then can be converted to serotonin. A limiting step in this conversion is the 5-hydroxylation to 5-hydroxytryptophan.124 Serotonin (a neurotransmitter) can be O-methylated and N-acetylated to form melatonin (a compound closely connected with sleep and diurnal rhythm).

Serotonin can also be N-methylated to form bufotenin. O-methylated serotonin can be N-methylated to form N,N-dimethyl-5-methoxytryptamine. Both bufotenin and N,N-dimethyl-5-methoxytryptamine are reputed to be psychotomimetic. Serotonin and melatonin are also oxidized to 5-hydroxy-indoleacetic acid, the normal excretion product. On the other side of the scheme, tryptophan can be decarboxylated to form tryptamine. If an excess of tryptophan is present, most of the excess is likely to be disposed of in this manner since the 5-hydroxylation is the rate-limiting step. Tryptamine can then be methylated to N,N-dimethyltryptamine (another psychotomimetic compound) or oxidized to indoleacetic acid (an excretion product). In addition, tryptophan can be converted to kynurenine and ultimately to niacin. All of these pathways could be involved in some way in schizophrenia.

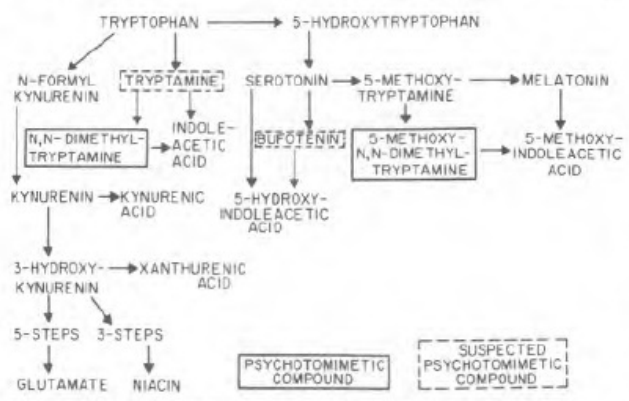


**Figure 26-3.**
Some aspects of tryptophan metabolism.

Many workers have shown that loading the diet with tryptophan results in a number of abnormal indole metabolites appearing in the urine of schizophrenic patients, suggesting the possibility that deviant indole metabolism may play a significant role in schizophrenia. However, the presence of some of these abnormal metabolites has not always been confirmed when other laboratories repeated the original studies.

Studies that are more sophisticated seem to indicate that indoles may play a role in producing the symptoms of schizophrenia. Much attention has been centered on the methylation of both indole and catecholamines. Pollin and co-workers caused exacerbation of schizophrenic symptoms by feeding methionine and a monoamine oxidase inhibitor simultaneously. Substituting tryptophan for the methionine produced some effect on symptoms but not as great an effect as with methionine. This would indicate that increased methylation of indoles may be related to exacerbation of schizophrenic symptoms. Alexander et al. were able to repeat the study of Pollin with the same results. Kakimoto also administered methionine and a MAO inhibitor and caused symptoms to worsen. After administration, an increase of methylcatecholamines and indoles was found in the urine of the patients. In a similar experiment by Jus et al., tryptamine was found to increase in urine of the patients before exacerbation occurred. Administration of a-methyldopamine by Herkert and co-workers also caused exacerbation of symptoms. He reported a decrease in the excretion of 5-hydroxyindoleacetic

acid and an increase in urinary tryptamine, possibly suggesting that the exacerbation was the result of a block in the conversion of tryptophan to 5-hydroxytryptophan. Spaide et al. substituted cysteine for methionine. Again, behavior worsened and indole excretion increased. The behavioral worsening appeared to correlate very closely with the excretion of the indole amines, many of which were not those usually found in normal urine. However, Feldstein reported that the excretion of indoles was probably more closely related to urine volume than to symptoms, but in his experiment he did not make clear whether the urine volume increased because of the extra indoles or whether the reverse was true. In another series of experiments, he administered labeled serotonin to schizophrenic patients and control subjects and found no difference in the conversion of serotonin to 5-hydroxyindoleacetic acid in the two groups. Therefore, he hypothesized that serotonin was not involved in schizophrenia. From the data of others indicating increased tryptamine excretion during exacerbation of schizophrenic symptoms, it would be logical to expect that the conversion of tryptophan to 5-hydroxytryptophan was the faulty step. Under the circumstances, one would not expect much effect on the metabolism of serotonin. A better approach would have been to study excretory products, particularly tryptamine, indoleacetic acid, 5-hydroxytryptamine, and 5-hydroxyin-doleacetic acid, following administration of labeled tryptophan. According to Naneishvili, plasma from schizophrenic patients, especially from

the acutely ill, elevated the blood levels of serotonin when administered to dogs. The elevation was reported to be accompanied by a corresponding fall in the excretion of the serotonin metabolite, 5-hydroxyindoleacetic acid. This, of course, is the opposite of the results described by Feldstein.

If tryptophan metabolism is particularly responsible for some of the symptoms of schizophrenia, one would expect that a decrease of the indole content of the diet might cause amelioration of the symptoms. Berlet et al., however, have shown that a decrease of indoles in the diet causes no improvement in schizophrenic patients. On the other hand, Dohan claims that schizophrenic patients do improve on a gluten-free diet. Gluten is unusually low in tryptophan but extremely high in glutamic acid. This result is very difficult to reconcile with other evidence.

Not only are there more indole amines excreted during the exacerbation of schizophrenic symptoms but these indole amines contain more methylated products than those found in urine of nonschizophrenic subjects. Berlet et al. have now identified two of those methylated products as N,N-dimethyltryptamine (DMT) and 5-methoxy-N,N-dimethyltryptamine (5-methoxy-DMT). Fischer has confirmed that there are methylated indoles in urine from schizophrenic patients. He identified the indole as bufotenin but it is questionable whether his method could differentiate between bufotenin and DMT. Even more to the point, Heller et al. have found DMT and 5-

methoxy-DMT in the blood of acute schizophrenic patients but not in the blood of control subjects.

The presence of methylated indoles in the body fluids of schizophrenic patients is very interesting and important indeed. Most of these compounds are known to be potent psychotomimetic agents. If these compounds are present in the schizophrenic patients, then it could be possible that they are responsible for some of the symptoms of schizophrenia. The behavioral effects of administering methylated indoles to humans have been thoroughly described. To be sure, these effects are quite different from the symptoms of schizophrenia. However, this does not necessarily mean that these indoles are not responsible for the symptoms of schizophrenia since the acute effects of a drug (as in the case of administering a single dose) can be quite different from the chronic effect (as the result of the presence of the compound over periods of years in the schizophrenic patient if produced *in vivo*).

Unless enzymes capable of converting indoles to methylated derivatives can be found in human tissue, a theory involving production of methylated indoles would not be of much value. Such an enzyme has been isolated from the human brain. As mentioned previously, Frohman and co-workers demonstrated that the a-helical form of the S-protein increased the uptake of 5-hydroxytryptophan and tryptophan by cells. This excess in the cell might then be converted to methylated derivatives. In a study of the effect of the S-

protein on bovine hypothalamus it has been shown that in the presence of the a-helical S-protein, bovine hypothalamus produces almost two and one-half times as much DMT as it does in the presence of the nonhelical protein. Further evidence that indoles enter the cell in greater amounts in schizophrenic patients was presented by Polishchuk, who found that oral administration of 10 gm. of tryptophan caused a much larger increase in urinary indicans, anthranilic acid, kynurenine and 5-hydroxyindoleacetic acid from the patients than from control subjects.

Methylated indole amines could be at higher levels in the schizophrenic patient for several reasons: (1) increased methylation due to more active N-methyl transferase, (2) increased amounts of methylating agents such as methionine, (3) increased amounts of tryptophan and other indoles in the cell. The work of Frohman would indicate the latter is true. The experiments on methionine feeding lend some credence to the increased methylation hypotheses. However, an increased level of methionine has never been found in schizophrenia and the work of Frohman has shown that the a-helical S-protein has no effect on the uptake of methionine by the cell. There still remains the possibility that the brain of the schizophrenic patient could have a highly increased N-methyl transferase activity. This hypothesis is very attractive and has been proposed by many workers.'' Recent work by Domino, however, has failed to reveal any difference in N-methyl transferase activity between brains from nonschizophrenic and schizophrenic patients.

Regardless of how the methylated indoles are formed, the evidence indicates that they may play an important role in the production of schizophrenia. There is a possibility that there is also a change in serotonin level which could be related in some way to the schizophrenic process. Both the serotonin level and the level of methylated indoles could be affected by an increase of tryptophan in the cell, but since the 5-hydroxylation of tryptophan is the limiting reaction in the scheme (Figure 26-3), the effect of excess tryptophan would have a more pronounced effect on DMT production than it would on serotonin production.

Other studies indicating that tryptophan metabolism through the kynurenine pathway is somewhat different in schizophrenia have been performed by Brown and co-workers who found a decrease in the excretion in kynurenine metabolites in schizophrenia. However, Benassi found the opposite result i.e., that the metabolites of the kynurenine pathway were increased, especially 3-hydroxykynurenine which was increased threefold. On the other hand, Faurbye reports that the excretion of kynurenine metabolites is completely normal in schizophrenia. It does not appear that any definite information has been gained from study of the kynurenine pathway to date.

**Catecholamines**

Besides serotonin, a second compound released by reserpine and also active in nerve transmission is norepinephrine, a dimethylated epinephrine derivative. Norepinephrine and its analogs belong to a class of compounds called catecholamines, characterized chemically by an alkyl amine group attached to a dihydroxy phenol. Hoffer first suggested that adrenochrome, an oxidation product of epinephrine, might be responsible for psychotic symptoms. He synthesized adrenochrome, administered it to volunteers, and claimed that they then showed psychotic symptoms. Attempts by others to repeat this were unsuccessful. Axelrod demonstrated that epinephrine was disposed of not only by oxidation but by methylation of the hydroxyl groups on the phenol portion of the molecule. The previously described experiments of Pollin et al., in which they administered methionine and iproniazid, were primarily designed to determine if methylated catecholamines could cause exacerbation of symptoms, and the results they obtained could equally implicate catecholamines as well as indoles.

Figure 26-4 shows the metabolism of catecholamines in the body.

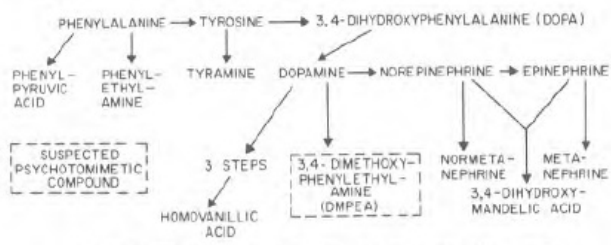


**Figure 26-4.**
Some aspects of catecholamine metabolism.

Phenylalanine is converted to tyrosine which accepts a second hydroxyl group to form dihydroxyphenylalanine (DOPA). This is then decarboxylated to form dopamine. Dopamine can be O-methylated to form 3,4-dimethoxyphenylethylamine (DMPEA). Dopamine can also be hydroxylated to form norepinephrine, which in some portions of the body, but not to any appreciable extent in the brain, is N-methylated to form epinephrine. Inside the cell, norepinephrine and epinephrine are oxidized to 3,4-dihydroxymandelic acid, while outside the cell in the synaptic cleft they are O-methylated to form normetanephrine and metanephrine respectively. The strong parallels between catechol metabolism and indole metabolism can be seen immediately. In many steps, the same or similar enzymes catalyze the reactions involved in the anabolism and catabolism of both the catecholamines and indole amines.

Just as in the case of the indole amines, there are reports of increased catecholamines being excreted in the urine during exacerbation of

schizophrenic symptoms. Himwich has proposed that the increase of catecholamines and derivatives in the urine during exacerbation of schizophrenic symptoms is the result of increased activity in the patient and is not related to the symptoms of the disease. Some of the methylated metabolites of catecholamines are psychotomimetic. As stated previously, among the methylated indoles DMT is psychotomimetic. In a parallel manner, mescaline is a prime example of a methylated catecholamine which is psychotomimetic.

Smythies has shown that all 4-methoxy catecholamines are hallucinogenic and that the most potent is the 2,4,5-methoxy compound. Hall demonstrated that administration of O-methyltransferase, the enzyme which forms O-methyl catecholamines, caused exacerbation of schizophrenic symptoms. Friedhoff demonstrated that discernible amounts of a 4-methylated catecholamine, DMPEA, were found in urine from acute schizophrenic patients but not from control subjects. This work has been confirmed by others. However, two other groups were unable to confirm it. Barbeau showed that injection of DMPEA in the rat caused increased dopamine level in tissue and proposed that it may block dopaminergic nerve endings while Hoffer claimed that dopamine is elevated in schizophrenia. Upon administering DMPEA to trained rats, Bergen found that it produced marked behavioral effects which resembled very closely the effects of the a-helical S-protein. However, Wagner has shown that tissue from schizophrenic

patients is incapable of synthesizing DMPEA. More recently, Siegel and Tefft have shown that part of the chromatographic spot that was previously believed to be DMPEA was due to metabolites of tranquilizing drugs and that when this portion was subtracted the amount of DMPEA in urine from control subjects and schizophrenic patients was the same.

If norepinephrine were involved in schizophrenia, it would seem reasonable that administering a-methyl-p-tyrosine, which blocks norepinephrine synthesis, would affect schizophrenic symptoms. Two different groups have shown that this compound has no effect at all on behavior of schizophrenic patients.

## Abnormal Antibodies

Malis, in 1959, claimed to have found a specific antigen from schizophrenic patients. He demonstrated the presence of this antibody both by complement fixation and anaphylaxis in guinea pigs. Semenov and collaborators reported that they were able to detect brain antigen in serum and cerebrospinal fluid in schizophrenic patients during the period of exacerbation of symptoms. At a later stage in the course of the illness, after the appearance of brain antigen, antibrain antibodies were discovered. For those patients who developed antibrain antibodies, a significantly greater familial incidence of psychoses was found; as a rule, the mothers of these

patients suffered from various neuropsychiatric disorders, including schizophrenia. The possibility is under consideration by Semenov that the central nervous system of the child may be subjected to immunopathological effects that will cause the child to manifest the disease later.

Heath has presented evidence that schizophrenia may be the result of an antigen-antibody disturbance. For many years, he has been working with a plasma protein factor which he named taraxein. Recently, he has discovered that this y-globulin is an antibody. Previously, Heath had been able to demonstrate that injection of this protein into normal human volunteers could give rise to the symptoms of schizophrenia. By using fluorescein-tagged anti-human y-globulin along with taraxein, Heath was also able to demonstrate *in vitro* attachment of taraxein to neural cell nuclei in the septal region of the patient's brain. This protein did not attach itself to any other area of the brain, therefore he claimed it must be considered a specific antibody to the septal region. Heath had previously shown that in schizophrenia, subjects often show abnormal EEG spiking and slow wave activity in the septal region of the brain. His conclusion therefore was that this antibody, taraxein, caused abnormal functioning of the septal area. In order to determine if such a situation could give rise to schizophrenic symptoms, Heath produced antiseptal antibody by injecting septal tissue into sheep and isolating the antibodies produced. These antibodies when administered to monkeys did give rise to focal abnormal EEG's from the

septal region and led to catatonic behavior. Sheep γ-immunoglobulin reactive to parts other than the septal region of monkey and human brains caused no discernible changes in EEG's or behavior of test monkeys. To this extent, Heath claims to have proved his point that schizophrenia is a disease involving damage to a specific area of the brain by an antibody. It should be added that full confirmation of this work has not yet been achieved. Logan and Deodhar were unable to repeat Heath and Krupp's work, reporting only negative results. Whittingham and co-workers were also unable to repeat Heath's work. In fact, the work with the technique of using fluorescein-tagged anti-human γ-globulin is certainly open to question since this type of process usually stains cytoplasm not nuclei. Bergen has partially confirmed Heath's work by showing that injection of taraxein from schizophrenic patients was more likely to cause focal abnormal EEG's than the same protein fraction from control subjects, but the results were inconsistent.

Kuznetsova also reported antibrain antibody in serum from schizophrenic patients but these were antibodies to brain mitochondria rather than to nuclei. Stoimenov, using complement fixation methods, reported that 79 percent of the paranoid schizophrenic patients had antibody to white matter and subcortical nuclei. Kolyaskina also showed antibrain antibodies in the serum of more schizophrenic patients than control subjects. She found, however, that after stress, the antibrain antibodies rose in the control subjects to the point where there was a higher percentage of control

subjects than schizophrenic patients with these antibodies. In order to study the mechanism of this process, rabbits were given electroshock treatment to cause the production of the antibrain antibodies. Kolyaskina theorized that stress or electric shock or both affected the permeability of the blood-brain barrier, causing brain proteins and plasma to come in close contact and in turn producing the antibrain antibodies. The activity of the S-protein previously discussed has been shown to increase following stress. It is only a short step then to reason that since the S-protein affects membrane permeability, the presence of antibrain antibodies could be a result of this protein, and the mechanism of action of the α-helical S-protein may be through the production of antibodies which affect the functioning of the brain. There are other indications that membrane permeability is affected in schizophrenia. Meltzer has shown that two enzymes, creatine phosphokinase and aldolase, are both circulating in plasma at higher levels than would be expected unless membrane damage had taken place. Lozovsky reports that lactic dehydrogenase (LDH) is elevated in serum from schizophrenic patients. The LDH is apparently from brain cells as shown by a study of the distribution of the isoenzymes. He attributes it almost completely to the damaging action of the previously described S-protein on the cell membrane.

Many workers have reported abnormal immunoglobulin levels in schizophrenia; none of them, however, report the same immunoglobulin to be abnormal. Strahilevitz reported increased IgA but normal levels of IgG and

IgM. Bock and co-workers reported IgA and IgG normal with IgM slightly lowered.

Gosheva has investigated the morphological features of lymphocytes from schizophrenic patients. *In vitro,* lymphocytes from schizophrenic patients underwent spontaneous blast-transformation. The neuroblasts appeared to connect themselves to normal lymphocytes by means of plasmatic bridges. DNA granules have been seen in these plasmatic bridges, suggesting that the neuroblasts are able to pass information to the target cells they contact by means of nuclear substances. Many additional changes took place in the leukocytes, such as vacuolization, granular decomposition of the cytoplasm, pyknosis, and nuclear lysis. The changes described above all could be attributed to an immune reaction so that this effect may be related to antibody production in schizophrenia. Knowles and coworkers, however, demonstrated that blast formation in leukocytes in schizophrenia is the result of administering phenothiazines and not of the disease.

In addition to the change in appearance of these cells, Glazov has shown that the metabolism of the leukocytes is abnormal in schizophrenic patients. This abnormality is a diffuse effect in which the activity of practically all oxidative enzymes is decreased. Even more interesting is the increase he reported in sulfhydryl groups in the leukocytes. This was confirmed by Chalisov who also showed an increase in sulfhydryl groups in the protein-free

filtrate of blood serum from patients. He also reported a difference in the level of several metallic ions between the blood of schizophrenic patients and control subjects. This has not as yet been confirmed.

Because of the many claims of elevated antibodies, Solomon used antimetabolites to change γ-globulin levels in subjects in an attempt to influence their behavior. He was unsuccessful. To make things even more complicated, Fessel reported that psychotics, especially schizophrenics, had higher serum levels of $S_{19}$ macroglobulin as compared to control subjects. This is an α-globulin which is different from the one Frohman reported. Zahradnicka reported a decrease in albumin and an increase in α-globulin in schizophrenia, while Kopeloff reported that schizophrenic patients have higher β-and α-globulin, but there was no indication that immunoglobulins are higher.

Through all the confusion involving the various changes of levels of antibodies, there is a strong possibility that all of the results reported are nonspecific effects more closely related to hospitalization than to schizophrenia. No consistent pattern has developed concerning elevated antibodies in schizophrenia.

From all of this, it is quite clear that a definitive experiment linking immunoglobulins with schizophrenia has not been performed and it is

doubtful if it ever will be.

## Hemolytic Factors

Many groups of workers have reported the hemolytic effect of plasma from schizophrenic patients on erythrocytes of humans, chickens, and rabbits. Durell and co-workers at the National Institutes of Health have reported a hemolysin present in the blood of schizophrenic patients. They have theorized that the hemolysin and the S-protein are one and the same and that the previously described biochemical effects of the S-protein are merely the result of hemolysis. They arrived at this conclusion after observing that the rate of hemolysis of chicken erythrocytes incubated in plasma from schizophrenic patients correlated with the increase in L/P ratio of the same cells. Also, in a study of red cells from schizophrenic patients, Lideman found that the red cells from the patients were significantly more prone to hemolysis by 0.004N HCL than those of control subjects, and that cells from the patients with a more malignant form of the disease were significantly more prone to hemolysis than cells from patients with a sluggish form. His thorough study of the kinetics of the hemolysis led him to conclude that the action of the hemolysin was not an antibody reaction but probably a reaction with a lipid peroxide. As did Durell, Lideman attributed the action of the S-protein to the effects of the hemolysin.

Neither Lozovsky nor Frohman is in agreement with the above conclusion. The Russian Institute and the Lafayette Clinic group have reported that hemolysis of chicken erythrocytes correlates with the effect of the S-protein on the L/P ratio but both groups have shown that the hemolytic effect and the metabolic effect are separable. The Russian Institute demonstrated that heating the serum caused the loss of metabolic activity before hemolytic activity was lost, and the Lafayette Clinic group separated two distinct proteins responsible for the two effects. The Lafayette Clinic group have shown the hemolysin to be a β-2-globulin instead of an α-globulin. In view of this, it is impossible that the hemolysin and the S-protein are identical. It is possible that the hemolysin is the result of the long hospitalization connected with schizophrenia and is not related to the etiology of the disease. It is equally possible that damage to the red cell membrane by the S-protein permits the production of the hemolysin. The a-helical form of the S-protein probably increases the intracellular tryptophan and 5-hydroxytryptophan concentration through a change in cell membrane permeability. An alteration of this sort could possibly permit extracellular protein to come in contact with intracellular protein, thus leading to the production of an antibody to the intracellular protein. Most hemolysins are antibodies to intracellular proteins.

Uzunov and co-workers have shown that a factor affects the permeability of the erythrocyte membrane to $P^{32}0_4$. When cells are treated

with chlorpromazine, trifluoperazine, or insulin, less radioactive phosphate is taken up by the cells in the presence of this protein factor. This effect is the greatest with cells from schizophrenic patients. They therefore hypothesize that a factor present in the blood of schizophrenic subjects reduces permeability of the erythrocytes to $P0_4$. Moreover, they have isolated proteins that have this activity from the spinal fluid of schizophrenic patients. After protein electrophoresis most activity was in the pre-albumin fraction, distinguishing this factor from the S-protein and from the hemolysin which appears to be a β-*2*-globulin.

**Carbohydrate Metabolism**

Carbohydrate metabolism is one of the earliest topics studied by workers in schizophrenia. Many have tried to determine glucose tolerance in schizophrenic patients. Some have reported abnormal glucose tolerance following oral administration of glucose. Both the nutritional condition and physical condition of patients in hospitals probably have more to do with the abnormal glucose tolerance results than does schizophrenia. In fact, in many of the reports all mental patients are reported to have abnormal tolerance test results rather than just schizophrenic patients. If the patients are prepared by feeding high carbohydrate diets for three days before the test, the abnormality usually disappears, indicating that subclinical malnutrition probably is the biggest factor in producing abnormal glucose tolerance. While

oral glucose tolerances are quite often abnormal, rapid intravenous glucose tolerance tests never show this abnormality. This might, of course, indicate some abnormality in transport of glucose across membranes even though malnutrition may play a large role. It is somewhat surprising how often membrane transport appears to be involved in deficiencies in schizophrenia. To bolster somewhat the idea that membrane transport might be involved here, one can cite the work of Walaas and co-workers in which they showed that glucose uptake by rat hemi-diaphragm is impaired by serum from schizophrenic patients. Later, these workers were able to isolate a plasma protein which was responsible for this. This protein may be identical to the S-protein. The metabolism of glucose by the cell is shown in Figure 26-5.

Glucose may be converted by means of the Embden-Meyerhof scheme to the hexosephosphates and triosephosphates, then to lactic and pyruvic acids. It may be oxidized to glucuronic acid and passed through the hexosemonophosphate shunt forming pentose phosphate, and then pyruvate. Pyruvate is oxidized to carbon dioxide and water by means of the tricarboxylic acid cycle. It is first converted to acetyl coenzyme A which is then combined with oxalacetic acid to form citric acid. Citrate is converted in turn to cis-aconitate, isocitrate, α-ketoglutarate, succinate, fumarate, malate, and finally back to oxalacetate. During one turn of the cycle one molecule of pyruvate is oxidized to carbon dioxide and water and the energy is stored in ATP.

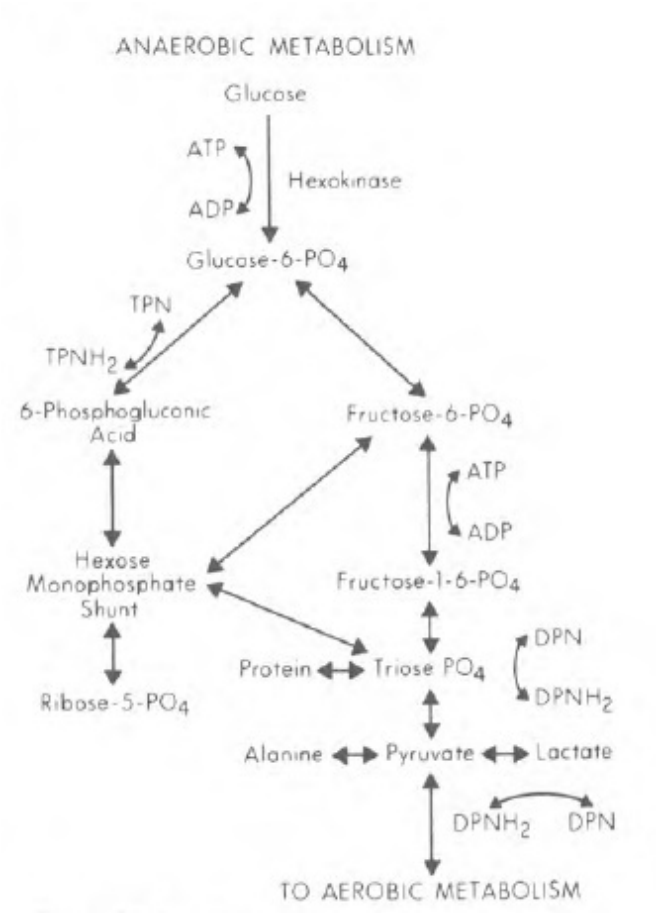


**Figure 26-5.**
An abbreviated representation of the scheme of anaerobic metabolism of glucose.

Upon administering glucose to schizophrenic patients, blood lactate and pyruvate increase abnormally. This is the opposite response to that obtained

in diabetes. In addition, α-ketoglutarate levels are increased. Experiments indicating that blood lactate and pyruvate concentration increase after exercise in schizophrenia probably demonstrate the poor physical conditioning of a patient rather than some metabolic deficiency in schizophrenia. The pile-up of α-ketoglutarate has been interpreted as inability of the patients to oxidize α-ketoglutaric acid. However, it has been demonstrated that serum from schizophrenic patients has no effect on the oxidation of α-ketoglutarate. On the other hand, when chicken erythrocytes were incubated with serum from schizophrenic patients and labeled acetate, the levels of α-ketoglutarate were significantly higher than when serum from control subjects was used. However, the specific activity of α-ketoglutarate was lower in the samples incubated with the serum from schizophrenic patients than in the samples incubated with serum from control subjects. This would indicate that the α-ketoglutarate was being formed from some substance other than acetate. Since it has been shown that in addition to tryptophan the α-2-globulin causes glutamic acid to enter the cell, it can be proposed that the excess of *α*-ketoglutarate arises from transamination or deamination of glutamic acid.

Frohman has shown that when chicken erythrocytes are incubated with the α-helical S-protein or with serum from schizophrenic patients, the L/P ratio is higher than when incubated with the nonhelical S-protein or serum from normal subjects. This could indicate a deficiency in the hydrogen

transport system, but all attempts to find such a defect resulted in failure. The real problem may result from flooding the hydrogen transport system with amino acids, namely tryptophan and glutamic acid, because of the effect of the α-helical form of the S-protein.

Most attempts to find abnormality in enzymes affecting carbohydrate metabolism have failed. Lactic dehydrogenase activity is normal, as is activity of malic dehydrogenase and the transaminases. Dern reported that glucose-6-phosphate dehydrogenase activity was related to the type of symptoms manifested in schizophrenia, but not to the disease itself. Some studies have been performed on the operation of the hexosemonophosphate shunt. The results from such experiments are conflicting. One group reported that more glucose was metabolized by the shunt in schizophrenia, while the other reported that less glucose was oxidized.

There are indications that some abnormalities in carbohydrate chemistry exist in schizophrenia, but most data suggest that these irregularities merely reflect abnormality in other phases of metabolism.

Both the oxidation of glucose and the operation of the tricarboxylic acid cycle lead to the production of energy in the form of ATP. The conversion of ADP to ATP to produce stored energy is shown in Figure 26-6.

Because the clinical appearance of the typical schizophrenic patient

would lead one to believe that the manifestations of energy may be disturbed, the metabolism of phosphate has been of interest to many workers. Upon the ingestion of glucose, serum inorganic phosphate drops much more in patients with schizophrenia than in control subjects.

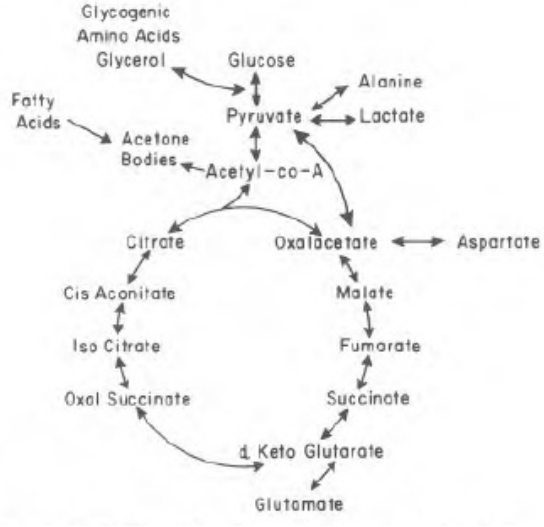


**Figure 26-6.**
The tricarboxylic acid cycle.

The phosphate on ATP is hydrolyzed by IN HCL in seven minutes at ioo° C and therefore is called A7 phosphate. It was reported that the formation of A7 phosphate in the erythrocytes of schizophrenic patients is quite different from that of normal individuals.'' In these experiments, insulin pre-treatment of red blood cells from normal subjects inhibited formation of ATP when the

cells were incubated with pyruvate and hexose diphosphate. This insulin depression did not occur with erythrocytes from schizophrenic subjects. Skaug also reported that ATP turnover was lower in schizophrenic subjects, and also reported an accumulation of phosphoglycolic acid. The concentration of riboflavin phosphate, but not that of riboflavin, was found to be lower in schizophrenic patients. This would indicate again an interference in the utilization of ATP. Many studies have been performed on the formation of ATP by blood from schizophrenic patients. Burnsohn reported an increase in ATP formation while others could not find any. Studies by Frohman and co-workers demonstrated that insulin increased the rate of ATP turnover in the blood of normal subjects, but had no such effect in the blood of chronic schizophrenic patients. These results could be caused either by a defect in an energy production system or by a lack of response to insulin. (The lack of the effect of insulin will be discussed in another section.) In addition to ATP formation there was a differential in the effect of insulin in the formation of fructose-l,6-diphosphate. Other abnormalities in ATP formation by erythrocytes, following stress with a large dose of succinate, are reported by Hofmann and Arnold. Both the ATP/ADP ratio and the fructose-1,6-diphosphate level were quite different in erythrocytes from schizophrenic patients than in erythrocytes from control subjects. The authors present evidence that the defects are genetically linked. In general, evidence seems to indicate that some defect does exist in energy metabolism in schizophrenia.

However, whether this is a primary defect or the result of some other defect still remains to be determined.

Seeman and O'Brien reported that sodium- and potassium-activated adenosine triphosphatase activity was increased in erythrocytes of schizophrenic patients, finding that these erythrocytes split 79.1 m/x mole of ATP per hour per mg. of dry weight while erythrocytes from control subjects only split 35.2 m/x mole. Parker and Hoffman were unable to confirm this finding.

**Hormones**

A huge number of studies have been concerned with the levels and the effects of hormones in schizophrenia. Because of the wide variation of levels of most hormones from hour to hour and even minute to minute, only the most careful control can produce meaningful results. The time of day of specimen withdrawal, the environmental conditions surrounding the patient, and the mental and physical state of the patient at the time of drawing the specimen must all be controlled. In many studies, the need for these controls has not been stringently observed. In addition, many reports of lack of response to hormone administration may be merely manifestations of general lack of responsivity of the schizophrenic patient to any stress.

Funkenstein devised a test which predicted fairly well the clinical effect

of electroshock treatment in schizophrenia. If, after the patient was injected with methacholine, his blood pressure increased 50 mm. of mercury or more, or if the patient experienced a chill, the prognosis for electroshock therapy was good. If neither of these conditions existed, the prognosis was poor. This test, however, does not appear to be related to long-term prognosis since only 42 percent of the patients who had positive Funkenstein tests and who recovered following electroshock stayed out of the hospital for the next fourteen years. In any case, administration of epinephrine-like compounds does appear to have a different effect in schizophrenia. Cardon reported that injection of norepinephrine caused a smaller increase in blood pressure and glucose, but a larger increase in free fatty acids in schizophrenic patients as compared with control subjects.

It has long been known that many schizophrenic patients have an abnormal response to the administration of insulin. They are usually considered to be insulin resistant. Meduna first described a diminished response in the decrease of blood glucose level after the administration of insulin. Lingjaerde also described a diminished response of blood glucose following administration of insulin in schizophrenia. In addition this decreased response of glucose was followed by a prolonged hypoglycemic period. The deviation from the expected response was corrected if the carbohydrate intake of the patient was increased for several days prior to insulin administration. However, in the opinion of Lingjaerde, this increase in

carbohydrate intake needed to be huge and above and beyond any physiological level. Insulin is also reported to cause a greater increase of cortisone after the hypoglycemic period in schizophrenic subjects.

Gjessing has shown some relationship between the thyroid hormone and schizophrenic symptomatology. The level of thyroid hormone increased during the catatonic phase of periodic catatonia and then returned to normal following the phase. During exacerbation of symptoms of this disease, excretion of hydroxymandelic acids also increased. However, as explained earlier, this probably is more closely related to the patient's emotional state than to the disease. There are also large changes in urine volume reported in periodic catatonia. Simpson reports that 28 percent of schizophrenic patients are hypothyroid and that there is decreased I uptake in 93 percent. The protein carriers of thyroxine are increased in schizophrenia without any symptoms of hyperthyroidism being present. It has been suggested that the thyroid defect in schizophrenia might be the result of abnormally high thyroid antibody; however, Goodman reported that thyroid antibodies are not abnormal in schizophrenic patients.

Stabenau and Pollin have also suggested a link between schizophrenia and thyroid hormone in their study of monozygotic twins discordant for schizophrenia. They demonstrated that the schizophrenic twin almost invariably had a lower birth weight and a lower PBI than the normal twin.

The difference was significant at the 1 percent level of significance.

Hollister has demonstrated that the plasma levels and urinary excretion of steroids in schizophrenia are normal. Other workers have shown increased corticosteroid excretion, but usually only during acute psychotic turmoil. When organized psychotic symptoms are re-established, the excretion of corticosteroids returns to normal. Probably such a change in steroid excretion is the result of the acute agitation of the patient rather than of schizophrenia. Chulkov reported an increase in excretion of sodium and potassium in schizophrenic patients and interpreted this as a mineral corticosteroid insufficiency. In general, however, no definitive studies have shown a difference in corticosteroids in schizophrenic patients, with the exception of Cookson's work with periodic catatonic patients. In one female with periodic catatonia having a 36-day rhythm, the stuporous phase coincided with cyclic excretion of 17-ketosteroids and 17-hydroxysteroids. The 17-hydroxysteroid cycle occurred four days later than that of the 17-ketosteroids. This periodicity was not related to the menstrual cycle because it continued after the menstrual cycle had been interrupted by administration of Enovid.

Orlovskaya and co-workers apparently have discovered a factor in the blood of schizophrenic patients which has an effect on the response to stress. When serum from a normal individual is injected into a rabbit, the rabbit produces a stress response characterized by an increase in the level of

circulating corticosteroids, a decrease in eosinophils, and an increase in blood glucose level. This is a typical response to a stress situation. In experiments performed by Orlovskaya, serum was used from three groups of subjects—control, periodic schizophrenic, and nuclear schizophrenic. When serum from the control subjects or periodic schizophrenic patients was injected, a normal stress reaction followed. However, when serum from nuclear schizophrenic patients was injected, the stress reaction was either diminished or absent completely. These workers have been able to show that a protein component in the serum blocks the response to stress; however, this factor intensified the cellular damage resulting from such an injection. Whenever serum from one species is injected into another species, massive damage to cellular components can be expected. In this study, hyperemia, stasis, and petechial hemorrhages were noted. When serum from nuclear schizophrenic patients was used, the cellular damage became much more severe. This might indicate that the protein factor of Orlovskaya was acting upon adrenocortical hormones. In a later experiment, rabbits were stressed by applying electroshock, causing a change in the electrical activity of both the hypothalamus and cerebral cortex. This, in turn, affected the level of corticosteroids, lymphocytes, and blood glucose, in the same manner as in the previous experiment. When serum from schizophrenic patients was administered beforehand, the cerebrocortical electrical activity was affected by the shock, but there was no effect on the hypothalamus. Without the

change in the electrical activity in the hypothalamus, there was no change in corticosteroids, lymphocytes, or blood glucose. From this, Gerber proposed that in schizophrenia there were pathological alterations in the hypothalamohypophyseal-adrenal system, causing a long-term decrease in activity. If such is the case, many of the hormonal changes reported could be a result of change in the hypothalamus. Since many of the nerve pathways in the hypothalamus are serotonergic, disturbed tryptophan metabolism could be the basis of all the above described defects.

Schizophrenia is characterized by a number of psychosexual disturbances. This has led many workers to believe that something is abnormal in the production of sex hormones. Very early, Hoskins reported a reduced androgen-estrogen ratio for male schizophrenic subjects, but this work did not have the benefit of modern methods. The excretion of 17-ketosteroids by male schizophrenic patients is apparently normal. However, as previously mentioned, there was a change in 17-ketosteroid excretion in one female patient with periodic catatonia. Despite a great deal of work on sex hormones in schizophrenia, very little has been accomplished. Brambilla reported a decrease in pituitary gonadotropins in schizophrenia, while Brooksbank found lower excretion of 16-androsten-3ol. Finally, Tourney has reported that dehydroepiandrosterone is significantly lower in chronic schizophrenic subjects. Since this is a cortical androgen, it may be the result of a selectively reduced adrenocortical function in chronic schizophrenia.

With the emergence of methods for determination of individual sex hormones, much more work should be done in this area.

Taylor has observed that if a pregnant woman has a schizophrenic episode within one month of conception, any live offspring was likely to be female, and that if a mother has a schizophrenic episode within one month after delivery, the offspring was likely to have been male. He interpreted his data as indicating that the male sex hormone offered the mother some protection against some other factor involved in the production of schizophrenia. Thus, the drop in androgens following the birth of a male precipitated the exacerbation of schizophrenic symptoms. Other investigators could not confirm his findings.

From the above it can be seen that very little sound evidence is available at the present time that hormones are involved in schizophrenia in other than a secondary manner. However, as methodology continues to develop in the study of individual hormones, clearer relationships may be found.

## Vitamins

To study vitamins in schizophrenia, the investigator must start with the assumption that hospitalized schizophrenic patients will probably be deficient in one or more vitamins as a result of the disease or the confinement. Nutritionally, many schizophrenic patients are in notoriously

poor condition, and any study comparing schizophrenic patients and outside controls without first investigating the nutritional state of the patients is invalid. Much research suffers from this defect.

Attempts have been made from time to time to implicate vitamin C in schizophrenia. The work of Akerfeldt indicated that the oxidation of ethylenediamine by plasma from schizophrenic patients was slower because of the lack of vitamin C. Slowik reported lower vitamin C levels in patients with schizophrenia. He found that it took 6.2 days to saturate patients with vitamin C while it only took 3.2 days to saturate controls. Vanderkamp claims that tissue from schizophrenic patients destroys ten times as much vitamin C as that from control subjects and suggested that excess dietary vitamin C caused patients to improve. Binette did not find low vitamin C levels in schizophrenic patients. He did, however, report a decrease in the permeability of the blood-CSF barrier to vitamin C. More recently, Pitt, using nonschizophrenic hospitalized controls found that the level of ascorbic acid was actually higher in schizophrenic patients than in other patients. He measured the vitamin C level in the buffy coat layer of the patient's blood. He also found that there was no difference in the length of time required to saturate the schizophrenic patients and the other patients with vitamin C.

Hoffer has claimed that niacin causes dramatic improvement in schizophrenic patients and his work has led to the contemporary

megavitamin therapy for schizophrenic patients. In this treatment, huge unphysiological amounts of a number of vitamins are administered daily for long periods of time. The megavitamin therapy for schizophrenic patients has become quite popular with some physicians. Others believe that this type of therapy is completely useless. Other workers have not been able to confirm Hoffer's findings. In fact, there have been reports of niacin actually exacerbating symptoms in some schizophrenic patients. Hawkins claims that the relapse rate is better with megavitamin therapy than without it. It would appear, however, that the fact that there is still a substantial relapse rate would indicate that niacin is not a cure-all for schizophrenia. Pauling, after studying the claims for vitamin C and niacin in schizophrenia, proposed a broad, all-inclusive theory of molecular psychiatry in which he states that each individual has a different requirement for various vitamins and that by properly satisfying this requirement many psychiatric illnesses could be avoided. Oken has taken Pauling severely to task for this viewpoint, stating that such a theory would only impede progress in biological psychiatry.

Other vitamins have been mentioned in connection with schizophrenia. Several workers, have claimed that pyridoxine, a vitamin involved in the metabolism of indole and catecholamines, causes improvement of schizophrenic symptoms. It is claimed that pyridoxine particularly improved the thought-degenerative symptoms, the affective symptoms, and the difficulty in concentrating. Because folic acid may be intimately involved in

some forms of temporal lobe epilepsy, it has been proposed that it may also be involved in schizophrenia.

Much controversy, it is true, exists concerning the relationship of vitamins and schizophrenia. It would appear, however, that much more positive data must be presented before vitamins can be shown to play anything but a secondary role in the schizophrenic process.

## Inorganic Ions

Considerable controversy existed for a time concerning the copper-containing protein, ceruloplasmin, and schizophrenia. Akerfeldt found that serum from schizophrenic patients oxidized N,N-dimethyl-p-phenylenediamine more rapidly than serum from controls, and claimed that this was due to increased ceruloplasmin "activity." (Ceruloplasmin is known to act on this amine as its principal "substrate.") Abood also claimed that ceruloplasmin "activity" was increased. This was confirmed by a number of other workers.' At the time much of this work was done, it was not taken into consideration that ceruloplasmin activity was inhibited by vitamin C, and that vitamin C was often quite low in schizophrenic patients. This alone explained much of the difference in ceruloplasmin "activity" found in schizophrenia.

However, the whole concept that an enzyme called ceruloplasmin is abnormal in schizophrenia should be examined from another direction. The

protein, ceruloplasmin, itself is probably not an enzyme, and the term ceruloplasmin "activity" probably describes an artifact related to ceruloplasmin's role as a transport protein carrying a prosthetic group for cytochrome oxidase. Since ceruloplasmin is not an enzyme, the term "activity" is completely inappropriate in referring to its physiological function. It does not seem logical to base a theory of schizophrenia on ceruloplasmin activity if that activity is an artifact. When ceruloplasmin level is directly measured, no increase is found. In addition, Frohman could not find an elevated level of copper in schizophrenic subjects. When all other conditions are controlled, no significant elevation of ceruloplasmin "activity" is found in schizophrenic patients, either. The conclusion must be that neither copper nor ceruloplasmin are abnormal in schizophrenia.

It has been demonstrated that Ca++ , Na+, and K+ are normal in schizophrenic patients, as are also Fe+ + and $P0_4$.

Burdeinyi found that Zn++ was elevated in uninterrupted schizophrenia but was normal in the remitted and interrupted types. Cade found that schizophrenia was associated with raised plasma Mg++ levels. In his patients, Mg++ was almost 20 percent higher than in controls. This was also reported by Brackenridge. However, Seal reports that serum Mg++ is normal in schizophrenia.

Many investigations have been performed involving inorganic ions and schizophrenia, and as yet there is no clear indication that abnormal levels of inorganic ions are involved in any way in the disease.

## Conclusion

Over the many years that biological phenomena have been investigated in schizophrenia, almost every phase of biochemistry has been studied. Many defects have been discovered. Some of these are undoubtedly artifacts resulting from abnormal diet and the underactivity that most schizophrenic patients exhibit. However, there remain many atypical findings that indicate real biochemical deficiencies. Most notable of these are an abnormal plasma protein, abnormal amines (particularly catechol and indole amines), abnormal carbohydrate metabolism, abnormal energy metabolism, and increased antibodies in the blood. One is, of course, tempted to search for a common underlying cause to which all of these defects could be related. It may be too soon in the course of events to find such a common factor, or no such factor may exist. Yet, with all the information now available, one could offer a guess as to what the defect might be. Most of the positive findings in schizophrenia could be related in one way or another to a functional defect in the cell membrane system. Thus, the finding of decreased glucose uptake by rat hemi-diaphragm in the presence of plasma from schizophrenic patients could be attributed to a membranal phenomenon. The lack of response of the

ATP-producing system to insulin stress could be attributed to the lack of response of the cell membrane to insulin. The numerous abnormalities in catechol and indole amines could be the result of altered membrane transport of tryptophan and other amino acids. The effects on cell membranes, and the numer-S-protein has been reported to have profound ous autoantibodies and hemolysins could all result from altered membrane permeability, which would allow intracellular proteins to mingle freely with plasma globulins. While it is much too soon to attribute biochemical defects in schizophrenia to a single factor, it would appear to be very rewarding in the future for workers in the field to expend their effort studying the biochemistry and biophysics of cell membrane function in schizophrenic patients.

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