1968

Metabolic considerations in schizophrenia

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Written Under The Direction Of

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January 26, 1968

Introduction

At the turn of the 19th century, Kraeplin first described dementia praecox;[1] the name "schizophrenia" was given to this disease complex by Eugen Bleuler. It was Bleuler who described this disease so commemorably and his definition is quoted here.

> By the term ""dementia praecox"" or ""schizophrenia"" we designate a group of psychoses whose course is at times chronic, at times marked by intermittent attacks, and which can stop or retrograde at any stage, but does not permit a full restitutio ad integrum. The disease is characterized by a specific type of alteration of thinking, feeling, and relation to the external world which appears no where else in this particular fashion.[2]

> The fundamental symptoms consist of disturbances of association and affectivity, the predilection for fantasy as aginst reality, and the inclination to divorce oneself from reality (autism). Furthermore, we can add the absence of those very symptoms which play such a great role in certain other diseases such a primary disturbances of perception, orientation and memory, etc.[2]

The research into the etiology of schizophrenia is part of the new approach medical science has taken to mental illness. Psychobiology instead of psychoanalysis is the ultimate aim of psychiatry as a science.[3]

> ...schizophrenia is a genetic limitation, involving particular enzymes within the brain or elsewhere in the organism. In the force of environmental stress, such limitations become prominent and metabolic products accumulate. The psychosis itself is ushered in by the sensory distortions, altered feeling states and hallucinations so induced. Subsequently when the patient attempts to reconcile his present state with his past experiences, the disorganization of cortical function begins.(4)

The controversy over the etiology of schizophrenia began when Kraeplin first described dementia praecox and is now after almost seven decades still unresolved.(1) The author of this paper believes that the psychobilogic view point towards the etiology of schizophrenia is the most promising towards the ultimate solution. This paper is an attempt to review the literature on the research done on the metabolic aspects of schizophrenia in the years 1955 - 1967.

products of amines. The problems of attempting to differentiate between true exacerbations of schizophrenia and mere toxic psychosis, however, made it difficult to attribute the changes to one factor.(5)

On another study eight chronic schizophrenic patients first received a mixture of methionine and tryptophan throughout a 30-day period. The biologic amine serotonin is formed from tryptophan and is important as a neural transmitter. In comparison with control values, increases in urinary tryptamine, 5-hydroxyindoleacetic acid (5-HIAA) and 1-methyl-nicotinamide occurred in response to tryptophan intake but without any significant worsening of the psychotic symptoms. The excretion rate of norepinephrine, another important neurohumor, first rose and then returned to control values. Epinephrine and its break-down product, vanilmandelic acid (VMA), did not show conclusive changes but the excretion of dopamine appeared to increase. The excretion of 17-ketosteroids remained unchanged and that of 17-hydroxycorticoids showed a slight reduction.(7)

After a two-month interval the same group of patients received tranylcypromine, another monamine oxidase inhibitor, in combination with increasing doses of DL-methionine. All seven patients who tolerated 30 to 40 g of DL-methionine. per day showed a moderate to severe intensification of the individual behavior patterns. The combination of methionine and MAOI resulted in a greater urinary excretion of tryptophan metabolites than that obtained when only the MAOI is administered. These urinary increases are the result of methionine-induced exogenous releases of tryptophan from body proteins including those of muscle as is indicated by elevations of creatinine concomitantly. Peak excretions of tryptophan metabolites

Some Aspects of Protein Metabolism in Schizophrenia

The possibility of a disturbance in transmethylation in schizophrenia was first suggested in 1952. In the hope of inhibiting methylations in the body, administration of niacin and niacinamide, which are methyl acceptors, was tried. The clinical improvements seen have not been confirmed. When large doses of l-methionine and ordinary doses of iproniazid were administered to chronic schizophrenics to learn whether possible increases in the amounts of methylated amines would potentiate a schizophrenic process, only four of the twelve schizophrenics to whom these compounds were administered demonstrated a brief intensification of their illness.(5) The monamine oxidase inhibitor (MAOI), iproniazid, was expected to slow amine catabolism, and it was felt that the methionine load might favor the formation of methylated compounds by way of the high energy compound, S-adenosyl-nethionine. The CH_3-S^+ bond of S-adenosyl-methionine serves as the methylating agent in the formation of the numerous methylated compounds such as creatine, choline, and adrenaline. It also serves the function of detxification of amines by way of methylation.(6) Of seveteen schizophrenics sho ingested methionine and isoxycarboxazid, (on MAOI) two became clearly more psychotic and a third appears to have reaced less strikingly. The effectiveness of the monamine oxidase inhibitor (MAOI) was demonstrated by assaying urinary excretion of tryptamine andindoleacetic acid which are the excretory

coincided in some instances with those of urinary 17-ketosteroids (17-KS). Methionine with an MAOI may act on behavior through the release of tryptophan with a concomitant accumulation of tissue tryptamine-line psychotomimetic substances. This is because of the large number of methyl groups made available by the methionine loading. Tryptamine appears to be the common denominator for both methionine and tryptophan in causing behavioral alterations in humans in the presence of an MAOI. In the absence of an MAOI, the lack of behavioral variations in relation to amino acid intake results chiefly from the fact that urinary tryptamine then is derived from free plasma tryptophan. The contrasting behavioral results of the two aspects of this study underline the necessity of an MAOI for induction of behavioral variations by amino acids.(7)

Another group of workers who experimented with methionine administration gave their nine male schizophrenics DL-methionine at two dosage levels of 20 and 40 g/70 kg. of body weight in combination with isoxycarboxazid, an MAOI. In seven of their nine patients, on both dosage levels, marked behavioral changes were obsereved which are described in terms of two components. One component was characterized by symptoms common during intoxication as exemplified by euphoria, somnolence, disorientation and confusion, while the other component appeared to be an occurrence and exaggeration of individual psycho-pathological symptoms. In general the accentuation of individual psychopathy was more severe under the high doses of DL-methionine than under the lower dose. These authors also felt that the increased indoles derived from tryptophan and an elevated level of methyl groups donated by the methionine may facilitate the formation of

N-N-dimethylated indoleamines which are potent psychotogens. Support for this conclusion has come from Axelrod who has demonstrated in vitro studies that N-N-dimethylation of tryptamine and serotonin is indeed accomplished by mammalian tissues.(8)

Isolated abnormalities of methionine metabolism may appear as behavioral abnormalities. A 24-year-old female with a known defect in methionine metabolism and homocystinuria showed affective inappropriateness, autism, loosening of associations, concrete thinking, and at the time she was seen, paranoid delusions. This woman had been diagnosed as a chronic undifferentiated schizophrenic after having been obsereved six months in a psychiatric day care center. This was before the methionine disorder was discovered.(9) This methionine disorder leads to urinary excretion of homocystine: it is also found in plasma, suggesting that the amino aciduria is the result of overflow rather than as a result of a primary renal tubular defect. This compound, homocystine, is not metabolized along normal pathways as a result of the absence of cystathionine synthetase in the liver: it appears that the disorder is transmitted as a autosomal recessive trait. As a result of this defect, cystathionine is absent from the brain. Cystathionine has not been found as a component of any structural protein and has no known function other than that of metabolic intermediate. The behavioral significance of low levels of cystathionine in certain tissues in homocystinuria thus remains unknown. The normal pathway of methionine which leads to cystathionine is shown schematically in Fig. 1. The parents of these affected patients have one-half the normal enzyme activity in the liver.

Features of the homocystinuric syndrome include mental retardation, ectopia lentis, fair skin and hair, malar flush, genu valgum, osteoporosis, and frequently a history compatible with spontaneous vascular thromboses. The biochemical alterations in homocystinuria which might predispose to schizophrenia are possible errors in trans-methylation, the absence of cystathionine from brain tissue or a relative cystine deficiency and excessive levels of methionine metabolites such as homocystine.(9)

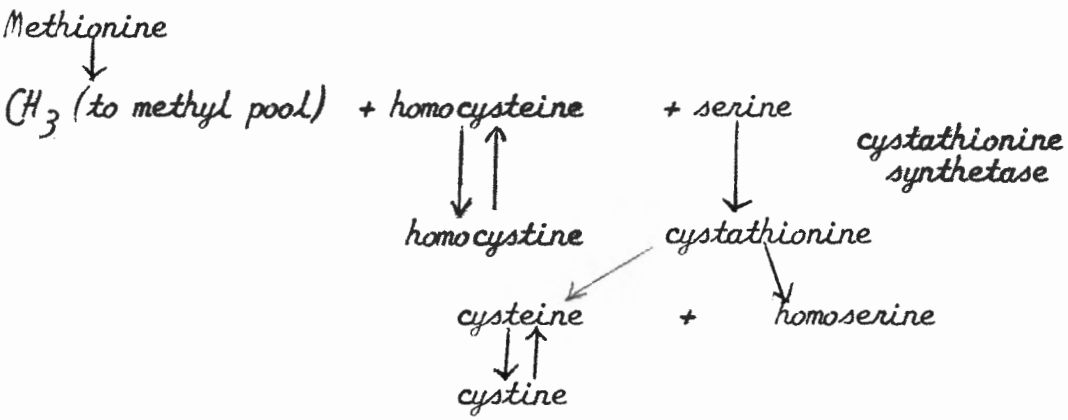


Fig. 1

The compound DL-methionine-d-l-sulfoximine (MSO) was given orally in doses ranging from 200 mg twice daily to 200 mg given four times daily to nine schizophrenics and a control group of nine non-schizophrenics. The two groups were off all other medications and were on an identical diet. The nine volunteers on MSO who served as controls exhibited psychotic manifestations, usually primary symptomatology such as autism, thought deprivation, disturbances of affect, blocking and association defects. Several of the volunteers

displayed well developed secondary symptoms, including severe catatonia in two and referential persecutory symptoms in five: three experienced auditory hallucinations as well. All ten schizophrenics manifested some diminution of overt secondary psychotic symptoms, but improvement was most pronounced and consistent in the affective sphere with enhancement of ability to relate toward personnel and clinical examiners during interviews and testing. Mental status exams, however, disclosed minor memory impairment in most patients and controls with lesser doses: pronounced memory impairment in both groups on the larger doses was noted.(10)

Electroencephalographic (EEG) records done on schizophrenics and controls were all normal before the study was begun. After MSO all control subjects had abnormal EEG's beginning with the fourth day of medication. The changes ranged from moderate slowing to prevalent focal paroxysmal slow activity, especially over the temporal lobes. The EEG's of the control subjects returned to normal after the medication had been stopped for six days. None of the EEG records of the schizophrenics were abnormal either before, after or while they were on MSO.(10)

Tryptophan, like methionine, is an essential amino acid for humans. In order to understand the importance of tryptophan in considerations of schizophrenia, its metabolism must be understood. A scheme clarifying this is shown on page 8. Tryptophan is the only amino acid with an indole nucleus.(6)

Examinations of urine samples from patients exhibiting various incompletely described diseases recently revealed an abnormality in amino acid excretion in a child affected by a severe mental condition suggesting autism. This abnormality

was also detected in the younger sibling of the patient although the sibling displayed no abnormality in mentality at this time. As shown on page eight, one normal tryptophan pathway is through formation of 5-Hydroxytryptamine which is excreted in the urine as 5-hydroxyindoleacetic acid (5-HIAA). Although the patient had normal levels of indole metabolites in her usual environment, she apparently is limited in her ability to convert large quantities of tryptophan through the pathway leading to excretion of 5-hydroxyindoleacetic acid, (5-HIAA).(11)

Since no example is known in which two enzymes are under the control of a single genetic locus, there may be parts at which their similar structures could be simulateneously influenced such as in transport across membranes, where the mechanisms are frequently less specific. This would require a block subsequent to tryptophan since the kynurenine pathway is unaffected.(11)

In this study an 18-month-old girl who was diagnosed as autistic was loaded with L-tryptophan: she showed a decreased ability to metabolize tryptophan via the 5-hydroxyindole pathway to 5-HIAA and to indolelactic acid. This is not believed to result from a primary enzymatic block but rather it is suggested that the mental aberration may be a result of an altered ability to maintain normal brain serotonin levels.(11) The loading of normal children with L-tryptphan resulted in increases of urinary 5-HIAA levels in contrast to other reports that hydroxylation of tryptophan is maximal with normal levels of tryptophan.(11)

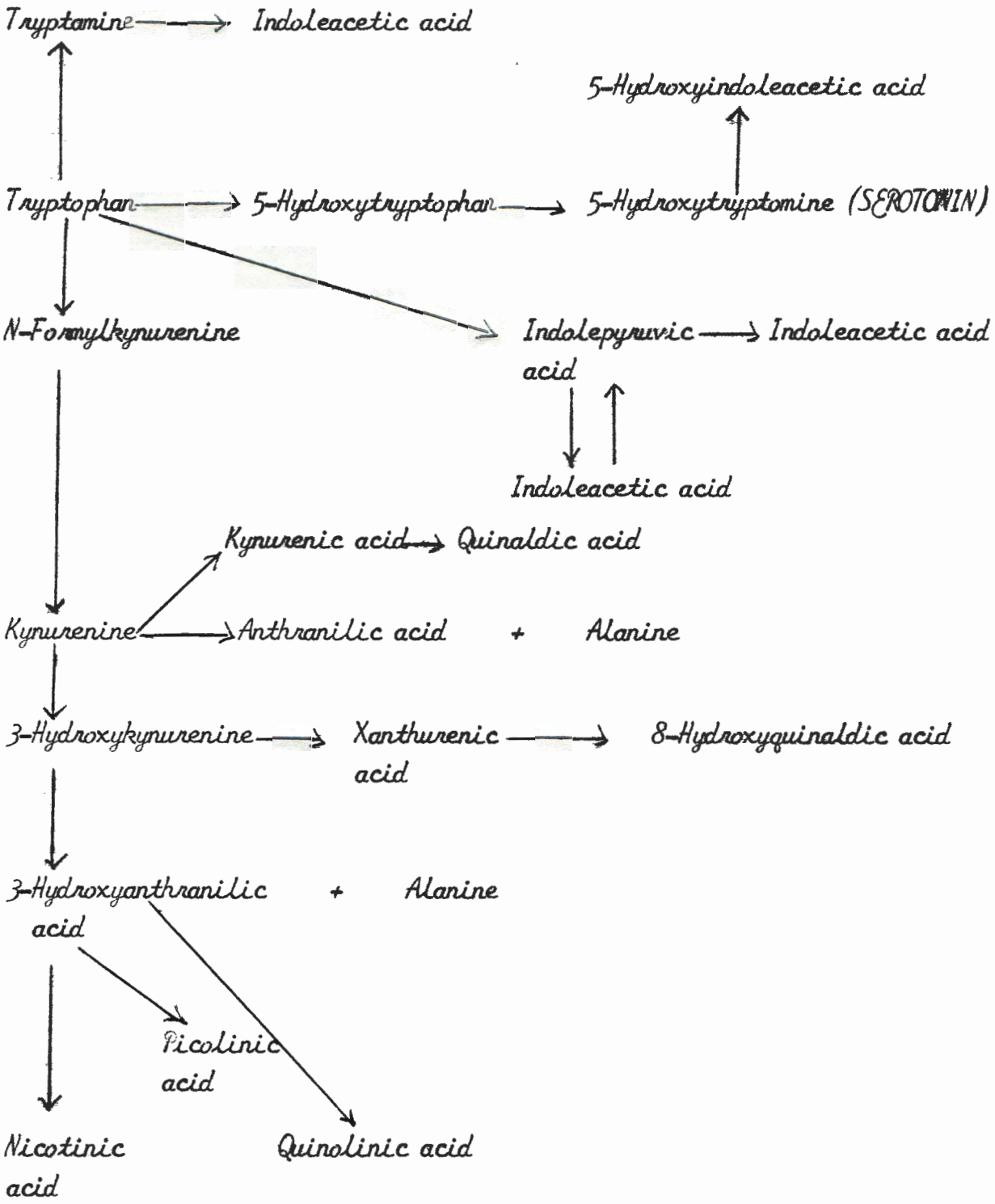


Fig. 2 Tryptophan Metabolism[6]

Disturbed indole metabolism has been well defined in at least three diseases which have mental aberrations.(12) One of these is Phenylketonuria (PKU) in which excretion of indoleacetic and indolelactic acid occurs. Another is Hartnup's (H or Hart's) disease which is characterized by increased excretion of tryptophan, indican, indoleacetic acid, and indole acetyl glutamine. The third is pellagra in which increased excretion of tryptamine and indican has been reported.(12)

Attention is called to the fact that the indole nucleus is common to three classes of compounds: (1) psychotogens, or compounds capable of producing mental disturbances, (2) those amines occurring naturally in the brain, like serotonin, and (3) those capable of alleviating mental disturbances, such as reserpine.(12)

Some of the indolic psychotogens are the following:(12)

1. D-Lysergic acid diethylamide, (D-LSD-25), has an N-methyltryptamine moiety. A psychotogenic dose is 100 u.g.
2. The adrenochromes and adrenolutin of which psychotogenic doses are 10 mgm. and 50 mgm., respectively.
3. Harmine and harmaline are products formed from tryptophan by oxidation from tryptamine through condensation with formaldehyde. These substances antagonize the action of serotonin on smooth muscle. An I.V. dose of 200 mgm is psychotogenic.

The amine derivatives of tryptophan will be discussed again at length later but it should be noted here that tryptamine

produces catatonia in cats and convulsions of central nervous system origin in rats, rabbits and monkeys. In humans, urinary excretion of tryptamine increases after administration of monamine oxidase inhibitors.(12)

The mode of action of indoles in brain may be summarized as follows:

1. " As a rule indoles depress synaptic transmission activities of brain as measured by EEG."

2. "They may alter the spontaneous electrical activity of the brain as seen on EEG."

3. "They may affect the rhythmic contractions of brain cells as evidenced by contractile effects of serotonin on oligodendroglial cells.

4. "Serotonin, an indole, may act as a chemical transmitter of nerve impulses to parasympathetic centers of the brain just as norepinephrine does to the sympathetic centers.

The indoles have been found to have a number of biochemical effects which are of importance in the consideration of schizophrenia. (12)

1. "Monamine oxidase inhibition has been demonstrated by harmoline and a-hydroxy-tryptamine."

2. "Pseudocholinesterase is inhibited by eserine, LSD, serotonin and bufotenin, and tryptamine."

3. "Oligodendroglial cells are rich in pseudocholinesterase and have been claimed to be abnormally swollen in scizophrenic brains."

4. "Pharmacological ""arousal"" reactions in brain are speculated to result from selective inhibition of pseudocholinesterase."

5. "Glucose oxidation depression can be caused in ""invitro"" systems by the indoles."

6. "Hexose monophosphate utiligation is retarded by LSD."

7. "Inhibition of succinic dehydrogenase and stimulation of cytochrome oxidase can also be caused by LSD."

8. "Adrenochrome, another indole, has been reported to inhibit the utilization of glucose, pyruvate and succinate by brain tissue."

The excretory products of tryptophan are dependent upon intestinal bacterial action and are varied by the nature of the dietary protein intake of tryptophan, bowel stasis, and by the efficiency of the indole detoxification enzyme present in liver. Thus the excretion changed upon bacterial infection of the bowel, dietary habits, etc. The excetory products of tryptophan are increased in such varied diseases as pellagra, Hartnup's, phenylketonuria, and alkaptonuria.(12)

One of the pathways for tryptophan excretion which is important is the pathway from tryptophan via oxidation to N-methyl-2-pyridone-5-carboxamide. Schizophrenics supposedly excrete significantly less urinary N-methyl-2-pyridone-5-caroxamide before or after tryptophon ingestion as compared with normal controls. This degradation product is formed by oxidation of N-methyl-nicotinamide, which has been reported as psychotogenic.(12)

Tryptamine, which is found in the urine, is usually formed from decarboxylation of tryptophan by tissues and also through bacterial metabolism. It is oxidized via monamine oxidase to 5-hydroxyindoleacetic acid (5-HIAA). This excretory product is found in higher concentrations in the urine when the pH is high and also when the dietary intake of tryptophan is increased. The greater the bacterial population is present in the gut which metabolize tryptophan to 5-HIAA, the higher its concentration will be in urine. Disease states which result in higher than average urinary levels of 5-HIAA are non-tropical and tropical sprue, pancreatogenous steatorrhea and maple sugar urine disease.(12)

Five-hydroxytryptophan penetrates the blood-brain barrier and is converted in the brain to 5-hydroxytryptamine by decarboxylation. This compound, known as serotonin, exerts behavioral effects. Although 5-HIAA is one of the excretory products of 5-hydroxytryptamine, the 5 HIAA found in the urine is not an indicator of brain serotonin nor of platelet serotonin. This has been shown by the administration of ordinary doses of reserpine (0.5-2 mg/day) which are sufficient to release serotonin from the brain and blood platelets but which do not result in uniform increases of urinary 5-HIAA.(12)

Nineteen schizophrenics were included in a group for the study of tryptophan metabolism. Nine of them were experiencing their first psychotic episode and the other ten were in more chronic phases of the disorder. A single 24-hour collection was made: each of the patients was then given two grams of L-tryptophan in divided doses and a second 24-hour urine specimen was collected. Urine creatinine was determined on each of the specimens.

Also determinations of urinary N-methyl-2-pyridone-5-carboxamide (pyridone), aromatic amine fraction A, anthranilic acid glucuronide, o-amino-hippuric acid, anthranilic acid, kynurenine, N-alpha-acetyl-kynurenine, and 3-hydroxykynurenine were made along with zinc, copper, delta-aminolevulinic acid and porphyrins. Six of the nineteen schizophrenic patients showed distinctly abnormal tryptophan metabolism in this test while the other thirteen metabolized the amino acid in a normal manner. Both groups of schizophrenics excreted significantly less of the pyridone before or after tryptophan ingestion as compared to control patients. The six with abnormal metabolism excreted significantly more kynurenic acid, o-amino-hippuric acid, acetyl kynurenine, kynurenine, and hydroxy-kynurenine after tryptophan ingestion, while the other thirteen excreted significantly less kynurenic acid and o-amino-hippuric acid before or after tryptophan and less kynurenine after tryptophan metabolism of these patients suggests a functional pyridoxine deficiency, neither biochemical nor clinical improvement resulted with pyridoxine supplementation. Both clinical and biochemical improvements were often observed following treatment with chelating agents.(13)

When childhood and adult schizophrenics were compared in a study of 5-HIAA urinary excretion after loading doses of L-tryptophan, no significant difference was found between the two groups with respect to either absolute amount of 5-HIAA excreted or increases following tryptophan loading. The urines were collected after 10, 15, 19, and 24 hours on the day of tryptophan ingestion. It is believed that the basic

pathology in childhood and adult schizophrenia is the same and Bender's long term follow-up studies have shown that most child schizophrenics remain so into adulthood.(14)

A longitudinal study of the urinary excretion of tryptamine and total indole-3-acetic acid was correlated with behavior in twenty male schizophrenics. They were otherwise in good health and on a constant protein diet with intake and output. The drug regimen on this study was as follows: placebo I and reserpine I before, and reserpine II and placebo II after, the endogenous amines in the brain and the simultaneous administration of isoxycaroxazid, an MAOI, prevents theimmediate detoxication of the released amines, amoung which is serotonin, so that theoretically it should affect behavior. It was found that the average urinary output of tryptamine did not differ from normal values when all the data were considered, there being only a slight elevation of total indole-3-acetic acid when compared with the results from the normal subjects. A wide variation in individual patients was the rule in excretion pattern. There was, however, a carrelation between the excretions of tryptamine and total indole-3-acetic acid and the degree of psychotic activity. Both indoles attained increasingly high abnormal levels with augmentation in the severity of the psychosis: reduction of indoles toward or to normal levels resulted in improvement of the mental state.(15)

In order to determine whether the abnormal aromatic excretion pattern reported in schizophrenics refleats an increase in the urinary output of hydroxy indoles or hydroxylated metablites of tryptophan, paper chromatographic studies were done on schizophrenics and normals. Serotonin,

5-HIAA and bufotenin were the compounds of greatest concern. Bufotenin is an indole which has been reported to produce hallucinations in humans. Using tetrazotized di-o-anisidine and Rf values to identify the compounds in the urines, it was found that seven out of forty schizophrenics and six out of forty non-xhizophrenics had a red-blue spot with an Rf corresponding to 5-HIAA. Since its appearance was infrequent in both groups, it was felt that the samples were not large enough to demonstrate a significant difference betwen groups.(16)

A spot numbered "14" which has been found on paper chromatography of urine specimens of schizophrenics but not in that of normals has been identified as indoxyl glucuronic acid, probably resulting from bacterial putrefaction in the gut. It was discovered that on cleansing the gut with achromycin, an antibiotic, and acidifying the urine to pH 2.5 this spot became insignificant and thus is thought to be a result of bacterial action.(17)

The glyoxylic acid reaction on urine is an indication of a disturbance in tryptophan metabolism if positive. It has been found that if the glyoxylic acid reaction is positive, there is also found an increased gamma globulin in the serum: toxic depression of the urine of such patients on yeast growth has been found concomitantly. The Modified Takata-Ucko Test (MTUT) and thymol reactions indicate an increase in gamma or beta and gamma globulins when positive.(18)

The glyoxylic acid reaction is as a rule positive in idiopathic schizophrenia, epileptics, and other organic psychoses of primary and secondary neuronic origin and in mentally normal

patients when physically ill. The test is negative in physically healthy normals, in neurotics and uncomplicated cyclothymics. The growth of yeast is gennerally depressed in glyoxylic positive urines. The turbidity reactions on serum, particularly the MTUT, are positive in active schizophrenics and also often in epileptics. The correlation between the outcome of the MTUT and the glyoxylic acid is not straightforward as it is with yeast toxicity. No definite conclusion can be drawn as to the significance of these tests in schizophrenia except that so far all reactions performed have been positive only in people suffering from some kind of physical disease.(18)

Four variations of the glyoxylic acid test were used on the urines of 161 subjects whose diagnoses were not known at the time of testing. The groups were found to be made up of 55 schizophrenics, 34 chronic alcoholics, 28 arteriosclerotics, 7 oligophrenics, 3 progressive paralytics, 6 paraphrenics, and 24 psychotics other than schizophrenics. All four variations of the test were more positive in the schizophrenic group.(19)

The metabolites of tryptophan which are believed to be involved in the glyoxalic reaction are hydroxyindoleacetic acid, potassium indoxyl sulphate, and perhaps also traces of kynurenic acid. The indoleacetic acids are urinary chromogens from which are formed the urinary dyes, uroresin and uroerythrin, which may be identical whith one another. The darker the urine, the more positive is the reaction. An increased excretion of urinary chromogens is variable from time to time in patients:

patients with chronic kidney disease, tuberculosis, liver disease, and pellagra as well as schizophrenia, show increases more consistently.(19)

Twenty-four schizophrenics and 75 non-schizophrenics were compared in a double blind study. Factors such as diet, age, sex, and medication were ruled out. The glyoxyic acid test of Hopkins-Cole was found to be positive on the urines of 62.5% of the schizophrenics and in 8% of the non-schizophrenics. (P less than 0.001) (20)

The effects of cysteine with and without tranylcypromine, an MAOI, were examined in four schizophrenics. During the administration of L-cysteine without the MAOI, urinary tryptamine rose significantly, but with the combined treatment of L-cysteine and tranylcypromine, the rise in tryptamine excretion was greater. No consistent trend was seen in the excretion of 1-methylnicotinamide during either period. In general the results of the combined treatment of cysteine and tranylcypromine may be compared to those of methionine and tranylcypromine in demonstrating correlations between behavioral worsening and increased excretions of tryptamine.(21)

The amino acids present in the urine, blood, and cerebrospinal fluid (CSF) were determined throughout the lucid interval and the catatonic phase of a patient with periodic catatonia. The patient was treated with adrenal corticotropic hormone (ACTH), adrenaline, and thyroxine to compensate the condition. Nitrogen retention and especially the periodically changing excretion of urea, seems to be a charcteristis finding of this

psychosis. The amino acids were traced hoping to get a clue regarding which metabolic process or chain might be deficient in periodic catatonia. In the first part of the catatonic phase a relative increase of arginine and glutamine was found in the urine, serum, and CSF. It was suggested that insufficient arginine and glutamine could probably produce a slight ammonia intoxication which could influence the central nervous system ((NS) in a psychotic direction. In the latter half of the catatonic phase, the arginase is apparently activated since urea excretion goes up at the same time as the arginine and glutamine decrease in the blood and urine. Thyroxine and thyroid substance in large doses compensates the condition and prevents any specific disturbance in urea synthesis.(22)

Urinary excretion of the following amino acids was measured in 12 non-schizophrenic and 10 schizophrenic children: Valine, leucine, tyrosine, alanine, glutamine, lysine, threonine, taurine, glycine, serine, and beta-amino-butyric acid. No significant difference was found between the two groups. patterns of amino acid excretion differ widely from individual to individual but the patterns remain fairly constant within individuals. The factors which determine these individual patterns of excretion are not fully understood but appear to be genetically determined. One factor which is known to affect urinary output of amino acids is adrenal cortical activity. Dietary intake within reasonable limits of variability does not greatly affect the excretion of most amino acids.(23)

Forty-one nonpsychotics and 40 schizophrenics were

similarly compared for orosomucoid and albumin levels in the serum. Orosomucoid, a glycoprotein extremely rich in carbohydrates, is the principal constituent of the perchloric acid-soluble seromucoid fraction of human serum. Elevation of seromucoid and total serum glycoprotein levels occur in a number of diseases such as malignancies, tuberculosis, rheumatoid arthritis, multiple sclerosis, fractures, epinephrine injection, and burns. An inverse relationship between orosomucoid and albumin has been noted.(24) In this study it was found that the mean albumin concentration was lower in schizophrenics than in controls. (P less than 0.01) The mean orosomucoid was higher for schizophrenics than for controls. (P less than 0.001.) This result suggests that the schizophrenics are in a chronically stressed state.(24)

In addition it has been found that in a chronically psychotic population there is a high incidence of positive tests which normally depend upon the presence in the serum of proteins found in various connective tissue diseases, especially systemic lupus erythematosus (SLE) and rheumatoid arthritis, (RA). Thus 1.3% of chronically psychotic patients had positive nucleoprotein latex agglutination tests and 8.2% had positive F. I. I. tests. A small group of patients with positive tests had clinical evidence of connective tissue disease. A substantial group of patients had congenital skeletal disorders and several patients had retinitis pigmentosa. The significance of the serological and clinical findings is not yet fully apparent and it would seem premature to discuss them now. The results are apparently not artifacts.(25)

Biologic Amines of Importance in Schizophrenia

Elkes has postulated that there may be three types of receptors within the brain possibly related to and dependent on the physiological turnover of three types of substrates within the CNS.(26)

(1) "Those receptors which are cholinergic in nature and which may have a diffuse distribution and which are unlikely to play a dominant part in the great centrenphalic steering mechanism governing basic states of arousal and attention." (26)

(2) "The non-cholinergic recptors susceptible to amphetamines and other catecholamines and which may involve elements high in the reticular formation as well as in the cortex and may depend upon the turnover of naturally occurring catecholamines (or group of catecholamines) which through the possession of some special properties may modulate the play of inhibitory tone in key cell assemblies governing the storage or release of old and firmly coded integrating patterns, including those making up patterns of emotional expression and experience. The peripheral autonomic system is the outer instrument of these patterns and the limbic system may be its inner counterpart."(26)

(3) "The third receptors are the target of LSD-25 and may depend on the natural turnover of an indole derivative with which LDS-25 specifically and peculiarly related to the afferent system and may play a dominant part in the maintenance of a highly patterned reciprocal inhibitory

> process which plays a key part in the organization of temporal and spatial experience as well as in the selective exclusion inherent in the processes of logic and abstraction. It is possibly this suppressive mechanism that may be defective in schizophrenia." (26)

In order to determine what areas of the brain are susceptible to certain biological substances a cannula was accurately implanted into specific brain areas and minute quantities of chemicals in amounts of 0.01 to 0.02 ml were injected into cats, monkeys, and humans. Behavioral changes and EEG records were utilized to detect the effects of the biological substances on the brain.(27)

Unquestionable behavioral changes which invariably were associated with significant alterations in recordings appeared only when chemicals were injected into the septal region and hippocampus. No significant alterations in behavior were induced by injection into other subcortical nuclear masses which included the caudate nucleus, the hypothalamus and the putamen.(27)

The regions where chemical stimulation induced changes in behavior and recordings were well circumscribed and injection into a region only two or three mm removed from a very active site often induced no changes.(27)

The three compounds in the group tested which induced the most intense changes were septal extract, atropine and histamine. Variable responses occurred with injection of epinephrine, iproniazid, d-LSD, and levoarterenol. With septal extract behavioral changes were most marked with

injections into the septal regions and somewhat less intense with stimulation to the hippocampus. The monkeys became more placid and electrical recordings showed focal seizure discharges.(27)

Septal extract contains a large number of amino acids, peptides, and variable but quite high quantities of electrolytes. Gamm-amino-butyric acid, (GABA), has no effect when injected nor do sodium or potassium chloride. Extracts lose activity over several months. Atropine causes relaxation, but in a schizophrenic given atropine there was an increase in spiking in the septal region and the hippocampus and the patient became more agitated and from retarded catatonia she changed to excitement. When injected with epinephrine, d-LSD, iproniazid, and levarterenol, the schizophrenic was relaxed, calm and more cooperative. When electrodes stimulate the human septal regions, "good feelings" are reported accompanied by objective changes in the direction of immediate alerting.(27)

There appears to be a relationship between the activity of the septal region and stress as measured by urinary 17-ketosteroids and the eosinophil response to electrical stimulation. The authors speculate that histamine and an as yet incompletely identified enzyme for metabolizing the compound might exist in high quantities in the septal region and that the interaction between them could be of considerable importance as the chemical substrate for the physiological activity of this key brain region with associated fluctuations.(27)

A theory suggested on the etiology of schizophrenia is that the oxidized derivatives of epinephrine were etiologic factors in the genesis of schizophrenia. The unified hypothesis is as follows:[28]

(1) " Biochemical constitution plus the unknown autonomic change."
(2) " Autonomic change (initial) leads to increased parasympathetic activity."
(3) " Autonomic change (secondary) leads to increased sympathetic activity."
(4) "Epinephrine is detoxified via amine oxidase, sulfoesterase, and phenolase. This phenolase mechanism predominates in schizophrenia with the production of quinone indoles (adrenochromes and adrenolutin)." [28]
(5) "Quinone indoles interfere with carebral metabolism."

It has been noted that autonomic disturbances are very frequently found in schizophrenics and that increases in concentration of acetylcholine (Ach) will aggravate schizophrenia. Many indoles, too, are effective esterase inhibitors: since esterases inactivate Ach, the inhibition of esterases results in prolonged Ach action. An increased production of Ach also stimulates the sympathetic ganglia because Ach is the transmitter there: this results in an increased secretion of norepinephrine and epinephrine from sympathetic nerve endings and schizophrenia is thereby induced or aggravated. Thus the combination of an increased concentration and activity of Ach centrally and an abnormal diversion of epinephrine into some indole (quinone) will produce schizophrenia.[28]

Further positive facts towards this theory is that inhibitors or amine oxidase when given in excess will produce toxic psychoses, i.e., cocaine, desexyephedrine, (which blocks both amine oxidase and sulfoesterase), amphetamine, LSD, morphine, caffeine and atropine. Fluids of schizophrenics will contain increased concentrations of quinone indoles in the presence of normal concentrations of epinephrine. Adrenochrome and adrenolutin and blood serum to which epinephrine has been added for some hours are anti-metabolic substances. Therefore, if present in blood, the serum of schizophrenics will also be toxic to cells. Adrenochrome inhibits mitoses in mouse epidermis. The L-strain fibroblasts originally obtained from mouse epithelial tissue are destroyed by the serum of schizophrenics. Over 90% of samples of blood from schizophrenics markedly inhibited growth of these cells. The toxicity is greatest at the beginning of the growth phase. Occasionally, cells survive and may produce flourishing cell cultures after five to six days.(28)

The most ardent proponent of this theory of aberrant detoxication of epinephrine and norepinephrine and other mediators states that the compounds present in the body which can be converted into adrenochromes or similar compounds are tyrosine, tyramine, dopamine, noradrenaline and adrenaline.(29) Another proponent claims to have found an aminochrome which is present in the erythrocytes and urine of 90% of all schizophrenics tested.(29)

Adrenochrome has the following biochemical properties and activities:(29)

1. " It is readily polymerized to darkly colored pigments and this could account for the increased pigmentation of some patients."
2. " It is a strong poison of cellular mitoses and should therefore produce an alteration of all tissues where growth is rapid. This may produce reduced rates of tissue repair and so account for the increased incidence of tuberculosis in schizophrenic patients."
3. " Adrenochrome has antihistaminic properties, and this can account for the decreased incidence of allergies in schizophrenia and their increased resistance to surgical shock."
4. " Adrenochrome reduces ascrobic acid and dehydroascorbic acid to a non-vitamin substance. This can account for the increased demand for ascorbic acid seen in schizophrenic patients and for some therapeutic success achieved with asorbic acid."
5. " It is an inhibitor of choline esterase and this could account for the increase in acetylcholine in schizophrenic saliva."
6. " It interferes with carbohydrate metabolism of cells and inhibits synaptic transmission."

The theory that adrenochrome and one of its derviatives, adrenolutin, are toxic chemicals is being confirmed by many workers. The behavioral changes which adrenochrome induces have been produced in guppy fish, spiders, pigeons, mice, rats, rabbits, cats, dogs, monkeys, and humans.(29)

The human studies in which up to 30 mg. of adrenochrome sublingually were administered, resulted in perceptual changes of depersonalization, feelings of unreality, increased sensitivity to color, and pseudo-hallucinations,

both visural and auditory. Changes in thought and marked changes in the word association test occurred, as well as changes in mood.(29)

A table which lists a number of indoles, the hallucinogenic dosage, their derivation and the type of psychotogenic activity caused by them is presented below:(28)

Table 1*

Substance	Dosage	Psychomimetic Properties	Esterase Inhibition	Nature of Activity
LSD	100 mcg.	strong hallucinogen	strong	indole, leads to increase of epinephrine
Bufotenin	15 mg.	moderate hallucinogen	strong	indole
Adrenochrome	25 mg. I.V.	moderate schizomimetic	medium	indole
Adrenolutin	50 mg. P.O.	marked schizomimetic	?	indole
Eserine	?	moderate schizomimetic	strong	indole
Serotonin	Intra-ventricular	moderate hallucinogen	strong	indole
Tryptamine	Oral	moderate catatonia	mild	indole, leads to increase of epinephrine

Table 1 Continued:

Substance	Dosage	Psychomimetic Properties	Esterase Inhibition	Nature of Activity
Caffeine	large	moderate euphoriant	mild	epinephrine production up
Mescaline	400 mg.	strong hallucinogen	?	?

*(28)

In summary then the aminochrome hypothesis of the etiology of schizophrenia postulates that there is an abnormality in the autonomic nervous system which is expressed chemically in the increased production of both Ach and some oxidized derivatives of adrenaline: these oxidized derivatives are similar in structure to either adrenochrome or adrenolutin.(30) Both adrenochrome and adrenolutin have similar properties in producing psychological changes as can be seen from Table 1. Adrenochrome (3-OH-N-CH_3-5, 6-dixoindole) and adrenolutin, (3, 5, 6-tri-(CH)'-1'-CH_3 indole) have not been detected in blood nor have enzyme systems been clearly demonstrated which can produce them from adrenaline.(30)

Two other workers have however demonstrated that epinephrine added to schizophrenic serum was rapidly converted to a new substance having an absorption peak at 395 mμ. The same conversion occurred to a lesser degree in normal serum. On adding adrenolutin to schizophrenic serum it is found that after one minute the absorption peak of adrenolutin and epinephrine is much the same as at eighty minutes, suggesting

that the substances formed in blood serum from adrenalin is adrenolutin. These workers supposedly found an enzyme in schizophrenic serum which converts adrenalin to adrenolutin but they do not further elaborate on it in this work.(30)

In support of the aminochrome hypothesis is a recent study which consisted of chromatograpy of material precipitated from schizophrenic urine with lead acetate. Seven different solvent systems were used and in studies made with one solvent system, fourteen of nineteen patients diagnosed by the clinic and staff as having schizophrenia were found to have aminochromes in their urine. Of the twenty control subjects, two had amino-chromes in their urine.(31)

Such favorable results were not obtained in a study utilizing the urines of 30 male schizophrenics and non-schizophrenics who had been admitted to a research ward in groups of five after unanimous diagnostic agreement between three independent psychiatrists. All were of medications and on a constant diet for four weeks. No differences could be detected in the aminochrome content of urines from the two groups.(32)

In a study done on aromaturia, much care was taken to eliminate the variables such as diet, drugs, urine dilution, and instrumental aberrations. Therefore all urine specimens submitted for the test were first tested for the possible presence of drugs, particularly acetylsalicylic acid and the phenothiazine tranquilizers. A densitometer was used for objective recording and all values were related to the urine creatinine. The patients were selected early in the course of hospitalization before psychopharmaceutical agents or

schock therapy was istituted.(33)

The two tests run on the urines were for colorimetric determination of indican and for a broad chromatographic study of diazo-coupling compounds. There were 134 schizophrenics and 129 normal subjects studied. Both the aromatic rating and indican ratings varied with sex and age and this was related to the same variation in the creatinine. Essentially similar values were obtained when acute schizophrenics were compared with appropriate controls, subdivided according to age and sex. The authors state that this study does not provide evidence against the excretion by schizophrenics of abnormal trace metabolites which would not be detected on the chromatograms.(33)

Dietary studies done also indicate that several common foods or drugs may produce a significant increase in aromaturia. The particular items are acetylsalicylic acid, coffee, prunes, pyridoxine and to a lesser extent, bananas. These must be suitably controlled to get meaningful studies.(33)

Another hypothesis formulated on the etiology of schizophrenia is the catecholamine hypothesis of affective disorders: it expounds that some, but not all, depressions are associated with a relative deficiency of catecholamines, particularly norepinephrine, at functionally important adrenergic receptor sites in the brain. Mood elevation, inversely, may be associated with and excess of such amines. It was suggested that norepinephrine, dopamine, and serotonin may each function directly as transmitter substance; others postulate that these amines may act as moculators or regulators of synaptic transmission mediated by some other direct transmitter such as acetylcholine, for example.(34) Summation of the properties of some of the pharmacological agents which support this hypothesis are

presented in Table 2.

Table 2*

Drug	Effect on Mood in humans	Effect on Behavior	Effects on Catecholamines in the Brain
Reserpine	Sedation	Sedation	Depletion (intracellular deamination and inactivation in mitochondria by MAO, etc.)
Tetrabenzine	Sedation	Sedation	Depletion (intracellular deamination and deactivation)
Amphetamine	Stimulation	Stimulation Excitement	Releases norepinephrine (onto receptors?) Inhibits cellular uptake and inactivation of norepinephrine.
Monamine oxidase inhibitors	Antidepressant	Excitement, Prevents and reverses reserpine induced sedation	Increases catecholamines in the brain
Imipramine	Antidepressant	Prevents reserpine-induced sedation	Increases them (catecholamines)

Table 2 Continued:

Drug	Effect on Mood in humans	Effect on Behavior	Effects on Catecholamines in the Brain
Dopamine *(34)	Reverses effects of reserpine	Excitement Reverses reserpine effects	Increases catecholamines

This hypothesis may ultimately be confirmed for certain subgroups but not necessarily for all depressions. The suggestion from these studies is that the actions of both major classes of antidepressants are mediated through the catecholamins. The two inactivators of epinephrine and norepinephrine are catecholamine methyl transferase (COMT), and monamine oxidase, (MAO). The monamine oxidase inhibitors (MAOI) increase the brain concentration of norepinephrine while imipramine-like agents potentiate the physiological effects of norepinephrine.(34)

In a determination of urinary epinephrine in a 24-hour-urine sample, it was found that 14 out of 17 patients with various psychiatric disorders had increased excretion. These increased outputs varied from 200 to 500 mcg./24 hours; the largest output was 1184 mcg./24hrs. The normal range in twenty-four patients varied from 0-59.5 mcg./24 hrs, or 20 mcg/24 hrs. for an average value. These increased values are within the range of pheochromocytomas and emphasize the fact that increased epinephrine excretion is not pathogonomic for adrenal medullary and chromaffin chain tumors.(35)

The presence of strikingly larger amounts of catecholamines such as epinephrine, norepinephrine, and other related substances in the urines of schizophrenics have been reported.

On subcutaneous injection of epinephrine it has also been found that schizophrenics excrete much higher quantities of the catecholamines in their urines than normals.(36)

Aberrant para-omethylation of 3,4-di-hydroxy-phenethylamine (dopamine) in schizophrenics may contribute to the mental illness. As reviewed before, the major metabolic end products of the catecholamines are the corresponding acids resulting from deamination and oxidation. The vanilmandelic acid (VMA) content of urine is considered to represent a major portion of metabolized epinephrine and norepinephrine. When dopamine was administered to rats, they excreted the same product almost exclusively, 3,4-dimethoxyphenylacetic acid. The same metabolic pathway is followed in humans when dopamine is administered to them. (37) The concentration of 3,4-dimethoxyphenylacetic acid in the urine of humans was found to be 10-30 mcg/gm. creatinine in a large number of samples. No truly significant differences could be detected between the schizophrenics and normals. The identity of the urinary excretion product as 3,4-dimethoxyphenylacetic acid was confirmed by its chemical properties and by thin layer chromatography on a variety of columns and it was further confirmed by mass spectrometry.(37)

Aberrant o-methylation in catecholamine metabolism is significant in the etiology of schizophrenia because of the pharmacological effects of a number of para-o-methylated catecholamines and because of the detection of an abnormal o-methylated catecholamine metabolite in the urine of schizophrenics.(38) Liver and brain slices of both normal

and schizophrenic subjects were immediately upon death incubated with dopamine to determine any differences in the amounts of 2-(3,4-dimethoxyphenyl)ethylamine-1-^{14}C hydrochloride produced. The results from the incubation of liver slices from six schizophrenics and three normals failed to show conversion of dopamine to labled 3,4-dimethoxyphenethylamine. There was also no conversion by the brain slices of four schizophrenics and one normal to 3,4-dimethoxyphanethylamine of dopamine. Since very high counts of labeled 3-methoxy-4-hydroxyphenylethylamine were obtained, it was believed that the results are valid and that high catecholamine methyl transferase activity was present in the liver and brain slices.(38)

In a further study 3,4-dihydroxyphenylalanine-2-^{14}C was administered to two chronic schizophrenic patients and levels of 3,4-dimethoxyphenethylamine and 3,4-dimethoxyphenylacetic acid were determined on their urines. It was found that minute amounts of both of these were obtained where as the yield of 3-methoxy-4-hydroxyphenylacetic acid was high, suggesting that 3,4-dimethoxyphenylacetic acid and 3,4-dimethoxyphenethylamine are not metabolites of 3,4-dihydroxyphenylalanine in the chronic schizophrenic.(38) In general, there has been disagreement as to these findings.(39)

The compound 3,4-dimethoxyphenethylamine (DMPEA) has close structural kinship with mescaline, a well established psychotogen. The compound e,4-dihydroxyphenethylamine (dopamine) serves, in normal metabolism as the precursor of noradrenaline and epinephrine but it has been argued that an abnormal methylation might occur preferentially in psychotics. This specific conversion yielding 3,4-dimethoxyphenethylamine

(DMPEA) has been shown in systems "in vivo". An alteration of dopamine metabolism has been observed in schizophrenics and this has been associated with an abnormal transmethylation.(39)

In a study to determine whether DMPEA is a psychotomimetic agent in normal human subjects, graded dosages of the amine hydrochloride were administered orally at levels that ranged from 20 mcg. to approximately 6.8 mg/kg of body weight. Three subjects received 500 mg. of the amine salt, and another received a total of 900 mg distributed over seven days. No behavioral or psychotropic effects were noted, nor were there any indications of autonomic disturbances. Analysis of the urine of one subject receiving 100 mg. showed that although 3,4-dimethoxyphenylacetic acid was the primary excretory product and accounted for more than one half of the administered dose, unchanged DMPEA could still be detected from the original ingestion. This lack of psychotomimetic effect argues against the participation of this compound in the etiology of the disease.(39)

The urine specimens of ten recently admitted acute schizophrenics were analyzed for 3,4-dimethoxyphenethylamine (DMPEA). The ten schizophrenics were kept on a vegetable-free and fruit-free diet and their diets were free of any artifical flavorings. Nine received no drugs except paraldehyde and chloral hydrate; one of them had been on chlorpromazine seven days prior to collection of the urine sample. Urine volumes containing 500 mg creatinine equivalent were analyzed using cation exchange resins. No 3,4-dimethoxyphenethylamine was recovered on any specimen. No amine was detected when volumes containing 2,000 mg creatinine equivalent were analyzed.

Pooled chloroform extracts of ten schizophrenics' urines analyzed on ion exchange still yielded no amine. Therefore it was concluded that 3,4-dimethoxyphenethylamine (DMPEA) excretion results from vegetables and fruits in the diet. It was also suggested that the bacterial cultures present in the gut of hospitalized patients may be responsible for DMPEA also.(40)

The "pink spot" reportedly found on paper chromatograpy of schizophrenics' urines was investigated. Only one patient was found to have a pink spot. She had had a leucotomy - and it is thought that leucotomies cause secondary changes in the basal ganglia which renders them susceptible to toxic damage by the phenothiazines. This patient had also been treated with the phenothizines. The possibility of "pink spot" being associated with brain damage induced by the phenothiazines is supported by the fact that it is found in high concentrations in the urines of patients fn the urines of patients suffering from Parkinsonism, a disease in which the brain is indisputably damaged. The "pink spot" may also have a relationship to dopamine.(41)

Chronic schizophrenics were given a potent MAOI in an effort to increase the urinary excretion of amines such as 3,4-dimethoxyphenethylamine, p-methoxyphenethylamine, and bufotenin. These amines were not detected in any of the urines. Neither were they able to detect any sifnificant differences between the pattern of urinary amines excreted by chronic schizophrenics and that of mentally ill patients without schizophrenia who shared the hospital environment with the schizophrenic patients. It is concluded that no

convincing evidence has yet been presented to implicate either ring methoxylated phenethylamines or N-methylated indole amines in the etiology of schizophrenia.(42)

An analysis of compounds present in urine pools from schizophrenics and normals was done. Only those compounds which give colors with diazotized sulphanilic acid and which can be extracted with ethyl-acetate or eluted with aqueous phenol from charcoal absorbates were determined. of the over 80 compounds detected, only three which do not contribute markedly to the overall coloring pattern have appeared uniquely in three urine preparations from schizophrenics. The three compounds are not identified. Three compounds which have never yet been chromatographically detected but which are present in the urines of both schizophrenics and normals are urocanic acid, 2-acetamideobenzoic acid, and imidazole-4-acetic acid.(43)

Another amine which has previously been discussed as an indole derivative and which has been implicated in schizophrenia is serotonin. Serotonin's major metabolite is 5-hydroxyindoleacetic acid (5-HIAA), found in the urine. Schizophrenics have variously been reported to excrete supernormal, subnormal, and normal amounts of this metabolite and to show excessive variability in its excretion. In an experiment well controlled as to diet, medication and adjustment, 123 subjects (63 schizophrenics and 60 non-schizophrenics) were admitted to the research ward in diagnostically mixed groups of five. The psychiatric and ward ratings were carried out using the Lorr MSRPP and the Graham Ward Rating scale. Urinary 5-HIAA, creatinine, and sodium were determined. It was found that

schizophrenics and non-schizophrenics do not differ in excretion of 5-HIAA. Although a pattern was observed of decreasing psychopathology with increasing 5-HIAA, this pattern may be related to alteration in physical state accompanying psychopathology rather than to psychopathology per se.[44]

Ceruloplasmin, Copper, Ascorbic Acid and N-N-dimethyl Paraphenylene Diamine Dihydrochloride (DPP)

Akerfeldt had first reported that the sera of schizophrenics was capable of oxidizing N-N-dimethyl paraphenylene diamine dihydrochloride (DPP) at a greater initial rate than the sera of normal controls. (45) This oxidation was attributed to ceruloplasmin, which is a copper globulin complex present in mammalian serum. It has been demonstrated that ceruloplasmin is a polyphenol oxidase capable of acting on a great variety of substances. It is an alpha-2-globulin with a molecular weight of 151,000 which contains eight copper atoms per molecule and accounts for over 95% of copper present in human plasma. (45)

As ascorbic acid oxidase is also a copper-protein complex and the influence of ascorbic acid as a factor then comes into play, it was deemed necessary to determine the role of ascorbic acid in the serum onoxidation of DPP. In normals with higher ascorbic acid levels the ascorbic acid is oxidized prior to DPP and therefore, schizophrenics must have a lower level of ascorbate. (45)

Base line values for ascorbic acid and DPP oxidation were followed by administration of 500 mg of ascorbic acid (Vitamin C) for three days and then the levels were agin measured as well as DPP. No significant difference between control subjects and schizophrenics in base line value nor differences in induction period in either group after ascorbic acid was found. (45)

The concentration of ceruloplasmin in the sera of schizophrenics was found to be significantly increased when compared to that

of normals but the difference is not applicable to differential diagnosis because of an overlap of 63% between groups. It was also observed that ascorbic acid was not the exclusive factor for the increased induction period of the OPP oxidation rate in normal controls. Preliminary dilution experiments indicate that the principal inhibiting factor was present at higher levels in the seral of normal controls than schizophrenics.(45)

It is important to realize that ceruloplasmin is not the only serum factor which has been found to change in schizophrenia. The disease has in common with other acute and chronic diseases decreased albumin and transferrin, increased gamma globulin, orosomucoid, and haptoglobin, increased incidence of rheumatoid factor, occasional presence of C-reactive protein and a normal concentration of lipoproteins, ceruloplasmin and bactericidins. Another feature of acute and chronic disease is an increase in serum protein-bound carbohydrates. Carbohydrates are covalently linked constituents of the serum globulins and hence can serve as an index of changes in the concentration of these glycoproteins. Two serum globulins particularly responsive to illness, inflammation and trauma are the alpha-2-glycoproteins, ceruloplasmin, and haptoglobin. Both increase in the above situations but are dfferently affected by endocrine manipulations. Ceruloplasmin increases two to three times during illness from a normal value of 32mg% in serum. This protein has been suggested to be a more sensitive indicator of inflammatory and tissue destructive processes than the C-reactive protein. It also increases with antigenic stimulation and correlates with thyroid activity. The concentration of ceruloplasmin is increased during

pregnancy also and during estrogen administration.(46)

One study revealed that in a group of 34 schizophrenics followed for six weeks to four months there was a higher remission rate in those with higher ceruloplasmin levels. Those who had spontaneous remissions had the highest copper levels while those who failed to respond had the lower levels.(36) The extraction of ceruloplasmin from normal serum and its injection into schizophrenics along with catecholamines was done and it was found that the patients responded much more like the normal groups. It is hypothesized that adrenalin oxidation is related to copper levels, the speed of oxidation being greater in direct proportion to the amount of copper present.(36)

Twenty anxious patients, ten of whom were schizophrenics and ten of whom suffered from personality trait disorders or neuroses, were compared as to levels of serum copper, plasma ascorbic acid and rates of oxidation of N,N-dimethyl-p-phenylenediamine (DPP) by plasma. The schizophrenics were also rated as to "a process" versus reactive types of schizophrenia using the Elgin State Hospital Prognosis Scale and levels of current severity of personal disorganization and social alienation by the Gottschalk scale.(47)

A trend toward more rapid rates of oxidation of DPP by the group of patients with the psychoneuroses or personality trait disturbances was found. Specifically, a significantly greater proportion of the schizophrenics than the non-schizophrenics had oxidation rates at or above 3.5. (p less than 0.05) There was no significant relationship between the rate of oxidation of DPP and level of free anxiety.(47) From this study the authors conclude that patients having slower rates

of oxidation of DPP may have a poorer prognosis than those with more rapid rates.(48)

Ascorbic acid levels correlated very highly with the lag period but very poorly with the rate curve fro oxidation of DPP, suggesting that ascorbic acid levels are not an important factor for the rate of oxidation once the "lag period" has ended. The level of current severity of the schizophrenic disorganization and social alienation, as measured by the Gottschalk scale, did not correlate significantly with either rates of oxidation of DPP or with serum copper levels.(47)

A longitudinal study of the relationship between serum copper levels and psychotic behavior was done on a patient who was compared with himself during the study. A 31-year-old white male chronic schizophrenic was studied for 246 days consecutively. He was followed with serum copper levels every other day and was on four different periods of 64 days each: the first 64 days he was on a placebo; the next 64 days he was on chlorpromazine; the nex 64 days he was on chlorpromazine and electroshock therapy (EST), and the last 64 days he was on placebo again. The results were plotted and it was found that on the placebo there was no relationship between serum sopper levels and word association but after the 121st day when he was either on chlorpromazine or chlorpromizine and EST, the day to day variation in serum copper levels was markedly reduced. (P less than 0.01) (48) This finding, together with the consistent correlations found during this period--a decrease in copper levels on chlorpromazine and EST improvement and an increase with relapses, suggests that

serum copper has some relationship to psychiatric conditions.[48]

A recently synthesized atropine-like compound, N-ethyl-3-piperidyl benzilate induced altered feeling states, visual and auditory hallucinations and increased serum ceruloplasmin in 7 out of 9 patients. In this same investigation, the infusion of four pyrocatecholamines—epinephrine, levarterenol (norepinephrine), isoproterenol, and serotonin, had no effect per se on serum ceruloplasmin. Iproniazid was also ineffective.[48]

A deficiency of ascorbic acid (Vitamin C) causes a marked lowering of many essential enzymatic reactions. Ascorbic acid is in high concentrations in the medulla of the adrenal gland for it is essential in the formation of noradrenaline and adrenaline, and these are active hormones in metabolic processes of the nervous system. Since humans cannot synthesize the vitamin and can store it only in limited amounts, it can be seen how a defect in its utilization could effect body economy. The blood levels of ascorbic acid do not correlate well with the tissue concentrations. The non-utilizeable ascorbic acid is excreted as such in the urine.[49]

A laboratory procedure in which ascorbic acid gives a color reaction with the Forrest Reagent was utilized to determine the presence of the vitamin in the urine. Ten schizophrenics and 8 normal patients were given ascorbic acid six times daily and the urine was tested after each voiding. The average daily dose which was required by the normal patients in order to give a positive urine ascorbic acid test was 4 g. The schizophrenics required 36-48 g daily in order to give a positive test. Therefore, the schizophrenics required ten times as much ascorbic acid as the normals.[49]

All patients receiving the vitamin in large doses made some clinical improvement, mainly in the area of socialization. The authors feel that the vitamin can improve the capacity to function but cannot furnish learning experience, the essential ingredient in ego maturation and integration of which the schizophrenics have been deprived.[49]

The Influence of Psychopharmacological Agents in Schizophrenia

Since 1954 the ataractic drugs have replaced electroshock therapy (EST) in the treatment of schizophrenia. Ataractics are drugs which normalize certain hyperemotional conditions such as mania, hallucinations, and extreme anxiety and tension states without producing concomitant central nervous system depression resulting in drowsiness, confusion, and motor incoordination. The most potent antipsychotic drugs are the Rauwolfia serpentina alkaloids and the phenothiazines.(50)

Rauwolfia alkaloids cause a state of imperturbability in the CNS with a tendency toward drowsiness, but without depression of the contact with the environmental stimuli and without loss of coordination in response to these stimuli. Hyperemotional responses mediated by the sympathetic centers in the hypothalamus, however, are markedly depressed. Peripherally bradycardia, a slight decrease in blood pressure, increased peristalsis resulting in increased frequency of stools, increased gastric secretion, miosis, ptosis, and in animals, relaxation of nictitating membrane, are some of the side effects.(50)

The central manifestations of the Rauwolfia alkaloids resemble that of a tumor of the posterior hypothalamus. There is also a semblance to the external manifestations of removal of the amygdaloid complex, portions of the temporal lobes and the pyriform cortex. The presence of these areas is necessary in order for the Rauwolfia alkaloids to have a depressant effect on conditioned avoidance of electroshock in monkeys.(50)

Brodie's theory that the Rauwolfia alkaloids act through release of serotonin centrally is derived from the following evidence: (1) Serotonin has a Rauwolfia alkaloid (reserpine) like sedation. (2) Reserpine causes depletion of serotonin from brain storage granules. (3) Serotonin-releasing activity is confined to those Rauwolfia alkaloids which have a central sedative action.(52)

It is postulated that the hyperactivity of serotonin, rather than its deficiency, may play a role in mediating uncontrolled emotional responses in acute psychoses. Serotonin exists in high concentrations in the limbic system, particularly the medial and pyriform areas, the hippocampus, the amygdaloid and in the septal regions of the brain. Pyridoxine (Vitamin B6) is necessary to convert 5-hydroxytryptophan to serotonin in the brain.(50)

The phenothiazine tranquilizers of which chlorpromazine is the archtype, also depress conditioned avoidance behavior and have anticholinergic, antiadrenergic, and antihistaminic actions peripherally. The tranquilizing action of chlorpromazine is most effective in the patient with some form of schizophrenic reaction in which hyperactivity, agitation, hallucinations, and marked anxiety are present. The suggested blocking action of chlorpromazine is somewhere in the diencephalon.(50-26)

In a study done by the Tulane group, specific sites of the brain have been destroyed or stimulated in animals and the physiologic effects have been correlated with behavioral phenomena. Activity in the septal region of the sub-cortex of the brain was related to expression of feelings, emotions and levels of alertness. Destruction of the septal region of

cats resulted in unresponsive animals with profoundly lowered levels of awareness: many displayed symptoms resembling catatonic stupor. Stimulation of the septal region in human subjects was followed by heightened alertness and evidence of pleasurable feelings.(51) During the past 14 years physiologic activity has been explored in nearly all demarcated subcortical nuclei above the pons and cortical sites of the human brain; correlations with behavioral data have been made.(51)

Recently the routine implantation of 100-125 leads throughout the brain has been executed. Teflon coated electrodes of 0.002 inch diameters were planted into precise regions of the brain, fixed to the bone, and carried for short distances under the scalp before emerging again. The maintenance of the electrodes in the fixed portions of the brain for at least two years has permitted serial studies of patients under varying behavioral conditions with the use of the electoencephalogram (EEG) and other recordings from widely separated regions of the brain and also to record the results of electrical and chemical stimulation of these sites.(51)

Electroencephalographic (EEG) studies on psychotic patients reveal spikes in the septal region made up of a fast, biphasic spike, sometimes superimposed on a slow wave. It appears more often during sleep and is characterized by slowing and by increased amplitude. It is occasionally accompanied by abnormal recordings from the hippocampus and amygdaloid nucleus. In non-psychotics, no such spiking occurred.(51) Patients with intermittent psychoses had

spiking in the septal area present during the psychotic behavior but absent during remission of psychotic symptoms. Hospitalization of patients with temporal lobe abnormality is usually shorter and the ultimate prognosis is more often favorable.(51)

Cannulas were inserted into predetermined areas of the brain and the following substances were injected and their effects studied: acetylcholine, atropine, d-amphetamine, diamine oxidase, epinephrine, gamma-amino-butyric acid (GABA), scopolamine, histamine, l-isoleucine, Kabi 888, l-leucine, d-lysergic acid diethylamide (SD), manganese chloride, iproniazid, isoniazid, phenobarbital, saline, sodium chloride, serotonin, septal extract, tyrode solution, hemicholinium-3, and valine. Only two, histamine and atropine, produced psychotic symptoms and then only when introduced into the septal region. A dose of 100 mcg of atropine introduced into the septal region of monkeys consistently induced psychotic symptoms and spikes in recordings from the septal region. When it was introduced into the septal region of two schizophrenics and one epileptic, spiking appeared in the septal recordings and psychotic symptoms increased. An occasional schizophrenic appeared more relaxed. Resting recordings and behavior were not affected when atropine was injected into other sites, including the caudate nucleus, pallidum and the hippocampus.(51) Histamine injection of 100 mcg into monkeys induced changes in recordings as well as psychotic-like behavior although not as consistently as atropine. Again, changes did not occur when histamine was introduced into the other cerebral sites. Studies with this compound have not been made in human subjects.(51)

These data suggest that interference with acetylcholine action in the brain might be the mechanism underlying the spiking and that, more over, a specific kind of interference at the receptor sites for acetylcholine causes the localized changes. Introduction of 100 mcg of scopolamine into some sites induced some drowsiness but the effect was generally equivocal and clearly was not a psychotic-like response. In excessive dosage the pharmacologic action of histamine is similar to that of atropine.(51)

The pathologic records from the septal region, characterized by spiking and slow wave activity and associated with psychotic behavior without demonstrable structural changes in the brain, strongly suggest aberrant neuro-humeral conductions focal at the site of pathological activity. The electrical changes associated with catatonic behavior can be duplicated by introducing chemical agents which interfere with neurohumeral transmission. This observation lends further support to the postulate that the psychotic state impairs neuro-humeral transmission.(51)

Disulfiram, an inhibitor of acetaldehyde dehydrogenase, which may also interfere at other stages of the metabolism of catecholamines, and which also forms chemical complexes with certain metals, especially iron and copper, was given to 11 schizophrenics and 12 prisoner volunteers in 0.5 g increments every five days until toxic symptoms appeared. It produced extreme mental and physical changes in schizophrenics but only minimal changes in the prisoner control group.(51)

Findings in the Cerebrospinal Fluid in Schizophrenics

It has been suggested that since substances pass from the blood to the brain with difficulty, and as the brain is involved in mental disturbances, it would be better to study brain function or aspects thereof toward the etiology of schizophrenia.(52)

The carbohydrate-containing compounds of the nervous system are the glycoproteins and the glycolipids. The chemical structure of these brain gangliosides showed them to contain water-soluble constituents of neuraminic acid--hexoseamines and hexoses--on one surface of the molecule and lipid soluble constituents such as sphingosine and stearic acid on the other surface. This suggests that the brain gaggliosides might be a membrane substance involved in receptor and transport fuctions in nerve cells. Virus studies have shown that brain ganglioside is indeed a receptor for certain neurotoxic viruses. Pharmacological studies with smooth muscle preparations made it possible to show that brain ganliosides have a marked stimulating function in a membrane activating system, the clam heart, suggesting that brain gangliosides may be involved in transmission phenomena in the nervous system.(52)

Immunological studies with specific antibodies to brain gangliosides were prepared and these were used with fluorescent antibody tecniques to demonstrate the nerve cell body localization of brain gangliosides. These studies provide evidence that brain gangliosides and substances chemically related to it may be involved in important regulating functions in terms of controlling the entry and egress of a number of important constituents in the nervous system. These functions are collectively referred to

as the "Barrier-Antibody System". (52)

Studies on cerebrospinal fluid for "total neuraminic acid" demonstrated an increasing accumulation of this substance with age. Schizophrenic adults (N equals 1024) showed lower values for this substance relative to controls and the values of the schizophrenic neuraminic acid content were comparable only with the values found in childre less than 7 years old. (52)

Longitudinal studies on schizophrenics and other psychiatric patients over weeks and months demonstrated that these low values were "group consistent" for all but 8% of the untreated schizophrenic patients and that with treatment only 7% demonstrated increased concentration of "total neuraminic acid", but these 7% brought the values of the schizophrenics into the normal range. By "dougle blind" clinical evaluation it was observed that clinical change was frequently temporally coincident with, and qualitatively, and occasionally quantitatively, related to the change in the concentration of "total neuraminic acid". (52)

Random diagnostic lumbar punctures performed in 90 general hospital patients, none of whose diagnoses was known, revealed 17 schizophrenics whose mean content of neuraminic acid was found to be lower than that of the non-schizophrenic patients and even lower than that of childred less than 7 years old whose values were much below that of the adults. It is suggested that the "Barrier-Antibody" system may be inadequately developed in the schizophrenic. (53)

Other findings support the above studies in that they show an inverse relationship between the degree of psychotic illness and the absolute amount of glycoprotein neuraminic acid and a positive relationship between clinical improvement in schizophrenic

patients and increases in absolute amount of glycoprotein neuraminic acid in the cerebrspinal fluid.(54)

From chemical values alone a diagnosis of schizophrenia was made in 122 cases: independent clinical evaluations concurred in 119 cases. Concordance of ratings of the severity of illness, family history, and changes in conditions during the period of observation was similarly high. These findings appear to be of particular significance in that the clinical population was totally removed from the chemical laboratory so that neither clinical raters nor chemical analysts had any knowledge of each other's findings and strict double blind procedure was maintained throughout.(54)

From 11-month follow-up studies of psychiatric patients in respect to neuraminic acid gangliosides and neuromolecular hexoses and hexoseamines, it appears that the changes in protein-bound hexoseamine appear to correlate with mood and other secondary symptomatology and have occurred with drug therapy as well as with electroshock therapy (EST), and also spontaneously. On the other hand, levels of protein-bound neuraminic acid do not vary with secondary symptomatology but appear to be related to the level of maturity in terms of classical psychological and psychoanalytic periods of development and other primary personality characteristics.(52)

When the levels of neuraminic acid were followed in a paranoid patient with schizophrenia for four months, and then the patient was treated with insulin, there was a 700% increase in the amount of hexoseamine synthesized in protein-bound form, but there was no change in the neuraminic acid content, and the patient did not improve during treatment. The pattern presented by this patient represented 85% of the schizophrenics' responses who were thus studied.

The second case was a patient who showed a lesser increase in hexoseamine with insulin therapy but who had marked increase in neuraminic acid, bringing it into the normal range. This patient showed marked clinical improvement, and he represented the response found in 15% of the schizophrenics thus studied.(52)

This study resulted in the following hypothesis: since hexoseamine is a synthetic precursor of neuraminic acid, this accumulation of a precursor, without the accumulation of its derivative, suggest the possibility of an enzymatic block in the conversion of hexoseamine to neuraminic acid.(52)

Spinal fluid was analyzed by use of dialyzable and non-dialyzable fractioning. One fraction of the non-dialyzable fraction, called fraction G (GNA), contained 16.7% nitrogen, neuraminic acid in a concentration of 3.0%, hexoseamine 4.0%, and hexose 9.3%. GNA was found to parallel closely the total neuraminic acid: the higher the value for total neuraminic acid in the CSF, the higher the value for GNA.(55)

Eighteen out of nineteen schizophrenics showed GNA values below 9.5 mcg with a mean of 6.7 mcg. Three children below 7 years of age also showed GNA values below 9.5mcg. Ten out of thirteen childred over age 7 and non-schizophrenic adults had GNA values greater than 9.5 mcg with a mean of 12.6 mcg. It is of note that each of the non-schizophrenics with a GNA value less than 9.5 mcg had a brain neoplasm.(55)

The findings on Fraction G provide a second independent measurement which corresponds well with measurements of total neuraminic acid in the cerebrospinal fluid and supports the finding that there is an abnormality in the neuraminic-acid-containing substances of the CSF of schizophrenics.(55)

Chloroform ethanol was used to extract centrifuged cerebrospinal fluid (CSF) of 84 patients hospitalized for more than 5 years with schizophrenic symptomatology who were given no fat-containing food or medicine 24 hours prior to removal of the cerebrspinal fluid. Chloroform extracts of the petroleum ether residue contain a lipopeptic complex composed of the lipids with sugars and amino acids bound in a peptide complex, especially with iron and copper.(56) No fundamental differences were found between schizophrenics and non-schizophrenics with this method. (59)

Findings on the Adrenal Cortex and Thyroid in Schizophrenia

The histology of the adrenal glands in schizophrenics was examined post mortem and the absence or deficiency of adrenal lipid staining was found to be significantly greater than in a mixed group of other mental diseases. Cases who had liver damage also showed a similar deficiency and this was found to be barely significant. The schizophrenic group contained more cases of liver damage than the control group but when paired for age, sex and adrenal lipoids, the findings were not significant. It was concluded that disturbances in adrenal steroid metabolism were often present in schizophrenia to a significant degree. That such a disturbance might render the liver more vulnerable to agents of disease was suggested, but in this connection numbers were insufficient to be conclusive.(57)

Factors which indicate a disturbance of adrenal steroids in liver disease are the increased secretion of aldosterone in hepatic cirrhosis and the low concentration of 17-ketosteroids in patients with portal cirrhosis it was concluded that there was inadequate adrenal function in this disease state.(57)

Ten chronic schizophrenics who were refractory to chlorpromazine treatment were divided into two groups of which one was given chlorpromazine, 200-400 mg/day and Aristocort, 8-16 mg/day for three weeks. The other group was given the chlorpromazine and Aristocort placebo. It was a double blind study and two patients, both women, showed transient improvement. The conclusion was made that adrenal steroids are only slightly beneficial in enhancing the responses of treatment-refractory chronic schizophrenics.(58)

Five schizophrenic patients were given 50 mg of cortisone four times daily for 20 days. Then the administration of cortisone was stopped and blood levels were followed for 119.5 hours after the last dose. The lowest level of 17-hydroxy corticosteroids was found at 24 hours and 48 hours after the last dose, the blood levels rose until 119.5 hours at which time they were found to be at their pre-test levels. Critical flicker frequency (CFF) did not change significantly during cortisone administration. Although there was a consistent downward trend in CFF in four cases during the period 12-48 hours after cortisone withdrawal, the change was significant at the (P less than 0.05) in only two cases. No change occurred in any patient in the EEG's. Thus, it appears that serum 17-hydroxycorticoids can fluctuate within a wide range without being associated with significant EEG changes.(59)
One subject whose mental state deteriorated during the cortisone administration was found to have an unchanging cortisone level which also did not drop after withdrawal of cortisone. The speculation is offered that in severe mental disturbances, cortisone-induced or spontaneous, the illness may constitute sufficient "stress" to preclude the depression in adrenocortical function which is normally induced by adrenal steroid administration.(59)

In a study designed to elicit stress-induced changes in adrenal cortical function twenty one subjects who were diagnosed as being anxious were used. Blood was drawn from them at 9 A.M., 10:30 A.M., and at 2:30 P.M. on four successive days with day 1 being the base day. On days 2, 3, and 4, the patients were subjected to anxiety-provoking interviews one-half hour before

the blood was drawn at the stated time periods. Twenty-four hour urines were collected from 8:30 A. M. to 2:30 P. M. and 2:30 P. M. to 8:30 A. M. There were also two control groups who were subject to the same procedures.(60) Plasma hydrocortisone levels and urinary hydroxycorticoid excretion were 60% and 70% greater, respectively, in anxious subjects on a "base" day than in normal controls. The elevated blood and urine levels were maintained in the anxious subjects over a four day testing period. When a stress inverview was given to every anxious patient on each of the last three days it failed to increase significantly the blood or urine hormone levels in the group. When the stress days were separated into high, medium and low days for each subject, the change in plasma hydrocortisone level was significantly greater on the day of greatest increase in anxiety than on the day of least change in anxiety. The increased plasma and urine levels in anxious patients are taken as evidence that the adrenal cortex is secreting at a higher rate than in normal controls in the anxious patients.(60)

For corticoid levels the acute schizophrenics are more variable than the chronic schizophrenics but not significantly so. However the impression that schizophrenia presents physiological imbalance in neuro-endocrine interrelationships persists.(61) The impaired ability to handle glucose and the insulin resistance repeatedly demonstrated in mental disease appear to indicate that the sugar-active steroids play a part although there is no complete agreement on this. Both hypoactivity and hyperactivity of the adrenal cortex appear to be present in schizophrenics who demonstrate a certain instability of function and an

impairment in the maintenance of homeostatic balance.(61)

Studies on the thyroid gland in schizophrenia have shown that the illness can be accompanied by normal, under-or-over active function of the thyroid.(62) But it has been found that normalization of both the adrenal and thyroid functions is an essential concomitant of spontaneous improvement.(62)

The hypothesis of an abnormality of thyroxine metabolism in schizophrenia has been tested in the following studies by measuring the rate of thyroxine degradation in patients with acute and chronic schizophrenia and comparing these results with values obtained in normal subjects. Patients with other psychotic illness and crippling neurologic diseases were also studied to provide comparison.(63) The majority of schizophrenics had protein-bound iodine (PBI) values within the range of the control groups (5.1 mcg.% - 9.4 mcg.%). The PBI levels within this range were highest in the paranoid patients and lowest in the chronic, undifferentiated and chronically deteriorated and catatonic groups. The differences were not statistically significant. The psychotic patients were not higher than the high normals but some were lower than the low normals.(63) Low values were found in the chronically paralyzed and in the chronically hospitalized mental defectives and in patients with general paresis. Only 4 out of 31 schizophrenics had PBI values below the lowest normal value. Thus normal PBI's are found in the majority of schizophrenics. Low PBI values in the physically abnormal patient are not specific and are comparable to those seen in the chronically ill suffering from other disorders.(63) The majority of schizophrenics with the exception of a few paranoid

and chronic dteriorated cases had normal turnover rates as well as normal PBI values.(63)

Thyroid function has been shown to have effects on the respiration of tissue in experimental animals. Kidney, liver, skeletal and cardiac muscle show an increased oxygen (O_2) consumption after thyroxine treatment and decreased O_2 utilization following thyroidectomy. Adenosine triphosphate (ATP) is essential for thyroxine to produce an effect on O_2 consumption in an "in vitro" system. Other studies suggest that thyroxine inhibits oxygen consumption of homogenates to which diphosphopyridine nucleotide (DPN) requiring substrates have been added.(64)

Studies done on O_2 consumption in schizophrenics show that the difference between them and normals becomes very small when the patients are compared with normal subjects who live under similar conditions or when only brief hospitalization has been the experience. In one study of hebephrenics no abnormality in oxygen consumption was noted.(63)

The paranoid has a significantly higher turnover rate than the normal. The PBI mean was not significantly larger than the normal (p less than 0.025). It is suggested that paranoid patients manifest a difference in some aspects of thyroid function. The possibility exists that a kind or intensity of the emotional state and not the diagnositc category influences the thyroxine turnover or plasma protein-bound iodine.(63)

Carbohydrate and Energy Metabolism in Schizophrenia

It has been noted that people suffering from diabetes mellitus are not prone to schizophrenia, and allergies such as asthma are statistically rare among schizophrenics. It has therefore been postulated that the hypothalamus may regulate the secretion of insulin as well as that of epinephrine and norepinephrine by the adrenal medulla. In diabetics who suffer from hypoglycemia it is postulated that their epinephrine production is also suppressed and that they have few allergies; conversely asthmatics do not suffer from schizophrenia because they have a relative lack of epinephrine.(65)

In the recovery frominsulin hypoglycemia schizophrenics pass through the following stages:(66)

(1) "Stage of "akinetic mutism" in which the patient sees and hears but is unable to move. This same stage occurs in going into a coma such as the "body sleep" of Von Economo."

(2) "Sensory anomalies such as increased speed of seen movements occur next. Physiologists have shown how much of the judging of speed depends on eye movements which follow the moving object."

(3) " The struggle for consciousness. Many patients speak of the enormous effort they make to drag themselves back to reality."

(4) "This struggle is followed by a feeling of relief, happiness, elation and sometimes by euphoria and over-evaluation of the patient's mental and physical faculties by himself."

The cortex is the first to be affected in insulin hypoglycemia and the first to recover on refueling.(66)

The effect of intravenous (I.V.) administration of epinephrine upon five carbohydrate moieties was studied in six normal and in six psychotic patients over a 3 hour period following the ingestion of glucose. With epinephrine, the blood concentrations of glucose, lactate, and pyruvate showed much greater rises and that of alpha-ketoglutarate a somewhat greater rise than without epinephrine. No significant effect of epinephrine was noted on plasma citrate level. Epinephrine infusion raised blood reduced glutathione levels significantly but had no effect on eosinophil levels, probably because of the small dosages employed.(67)

Abnormalities of carbohydrate metabolism similar to those caused by epinephrine are observed in many psychotic patients and also in a variety of organic disorders. At least four mechanisms which cause similar changes are anorexia, thiamine deficiency, excessive adrenal cortical activity, and excessive adrenal medullary activity.(67)

Thioctic (alpha-lipoic) acid a water soluble vitamin, was given to six chronical schizophrenic patients. Three showed slight improvement on small doses: five of the six showed considerable worsening on large doses. Impairment of keto acid utilization accompanied clinical worsening. The mechanism underlying the biochemical change is not known; it is possible that excessive intake of thioctic acid precipitated thiamine deficiency. The data of this and other studies suggest that impairment of keto acid utilization causes mental disturbances.(68)

It has been noted that patients with Cushing's syndrome exhibit defective keto acid utilization and also show mental symptoms. Sherlock et.al. and Strohmeyer et.al. found that deterioartion in the mental state such as disorientation progressing to coma occurred in patients with cirrhosis when utilization of keto acids became highly abnormal.(68) It seems, therefore, that very marked impairment of keto acid utilization, as in severe hepatic disease, may by itself cause mental deterioration, whereas in the other conditions listed above, it plays only a contributory and peripheral role.(68)

Accuracy and reproducibility of psychiatric diagnosis are the greatest barriers in any attempt to relate biochemical and genetic defects to emotional illness. This is particularly true in schizophrenia. The three major factors responsible for the reliability gap are: (1) inconsistency on the part of the patient in talking to separate interviewers, (2) inconsistency between interviews in eliciting relevant material from the patient, and (3) inadequacy of nomenclature. There is no agreement among psychiatrists whether schizophrenia is one disease, a group of diseases, or a symptom complex accompanying a variety of metabolic and/or physiological disturbances.(69)

Recent studies by Gottlieb and Frohman have shown a correlation between various parameters of glucose metabolism and the so-called basic symptoms of schizophrenia. The basic symptoms are ambivalence, disturbance of affect, disturbance of association and autism. No correlation was found with accessory symptoms such as catatonia and paranoia.(69)

Insulin is added to venous blood drawn from healthy persons

and psychotics and the mixture is incubated at 37°C for 30 minutes. The erythrocytes are then separated and hemolyzed and the filtrate is used as an enzyme solution containing hexose diphosphate as a substrate and a number of cofactors. Such systems are known to form in the presence of enzymes triphosphate from the added hexose diphosphate. If pyruvate is added to such a system, the triose-phosphate dehydrogenase step of the Embden-Meyerhof scheme of glycolysis is expected to operate. Accumulation of an easily hydrolyzable phosphorous compound as a result of the additon of pyruvate was taken as an index of the rate of the glycolytic reaction. In incubation systems containing hemolyzate from insulin-treated blood, there is a comparative deficit in the accumulation of this easily hydrolyzable phospherylated compound. Some experimental observations seem to suggest that the deficit is due to an increased rate of consumption of the high-energy phosphorous compound rather than to a dreased rate of its formation. The effect of insulin on the enxymatic properties of the red cell is thus at the cellular level, since this is the highest level of biological organization present in the blood in vitro. Under the conditions of the experiment, however, the actual detection of enzymatic effect of insulin was found after the cells had been hemolyzed.(70)

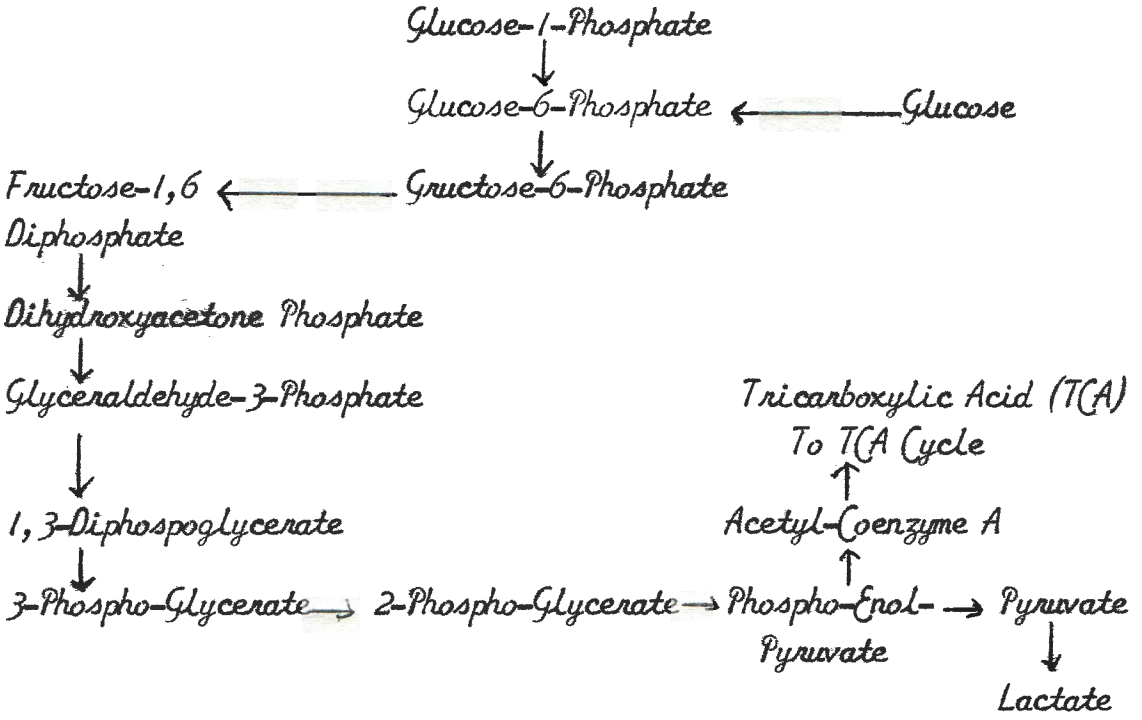
The "cellular" effect of insulin has been found to be absent in the blood cells of a very substantial number of patients suffering from the schizophrenic reaction. The test gives quite uniform results in a fairly large healthy control group of persons and a normal response also in the cases of most of the patients diagnosed clinically as suffering from psychiatric

conditions other than schizophrenia as well as in diabetes and hyperthyroidism. Pathological test results are obtained chiefly within the schizophrenic range of diagnoses but some of the most clinically characteristic schizophrenics give normal results with this test.(70)

The specific activity of adenosine triphosphate (ATP) was studied in erythrocytes, in which glucose is metabolized via two different pathways: (1) by way of the Embden-Meyerhof scheme, and (2) by way of the hexosemonophosphate shunt (HMS). Both of these pathways are schematically represented in Fig. 3 on page 65. It can be seen that the 6-phosphogluconate of the HMS can either re-enter the Embden-Meyerhof scheme or be converted to ribose-1-phosphate, a compound used for the formation of nucleoproteins and components of enzyme systems. The proportions of glucose utilized for the production of ribose-1-phosphate and for the production of energy (ATP) can be approximately estimated by incubating glucose labeled radioactively in the 1 and 6 positions with tissue and then measuring the labeled carbon dioxide resulting from the catabolism of the glucose molecule. When glucose is converted to ribose-1-phosphate, only the carbon labeled in the 1 position is found in carbon dioxide. This is illustrated in Fig. 4, on page 66. When the glucose is catabolized via the Embden-Meyerhof pathway, it can be seen from figure 4 that both the carbons labeled in the 1 and 6 position appear in the 3 position of glyceradehyde-3-phosphate. Thus in any further breakdown both the 1 and 6 labeled carbons will appear as carbon dioxide. Therefore the amount of carbon dioxide from the 6-labeled carbon must equal the amount of carbon dioxide formed from the 1-labeled

carbon. To estimate the amount of glucose converted to ribose-1-phosphate by means of the HMS, the amount of carbon dioxide formed from the 6-labeled carbon is subtracted from the total amount of carbon dioxide (CO_2) formed from carbon labeled in the 1 position.(71)

The Embden-Meyerhof Scheme of Glycolysis



The Hexose-Monophosphate Shunt

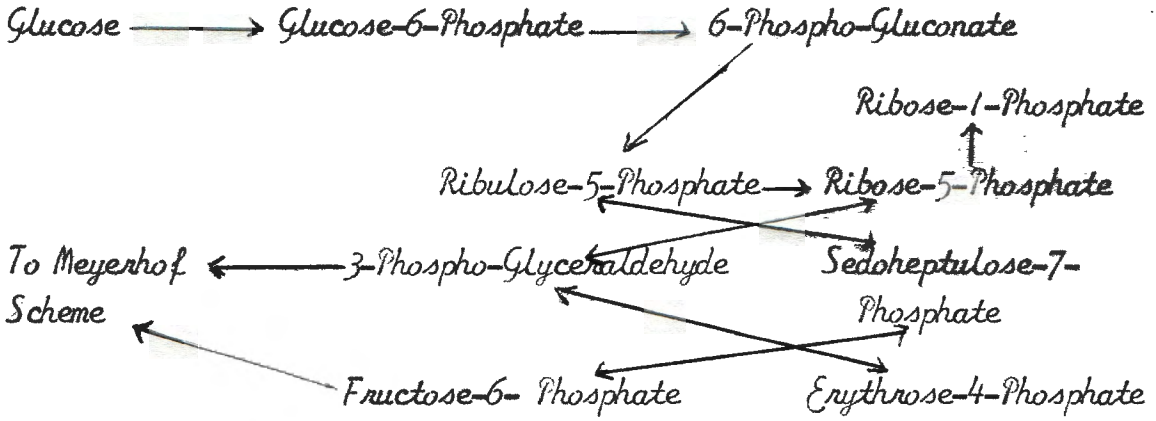
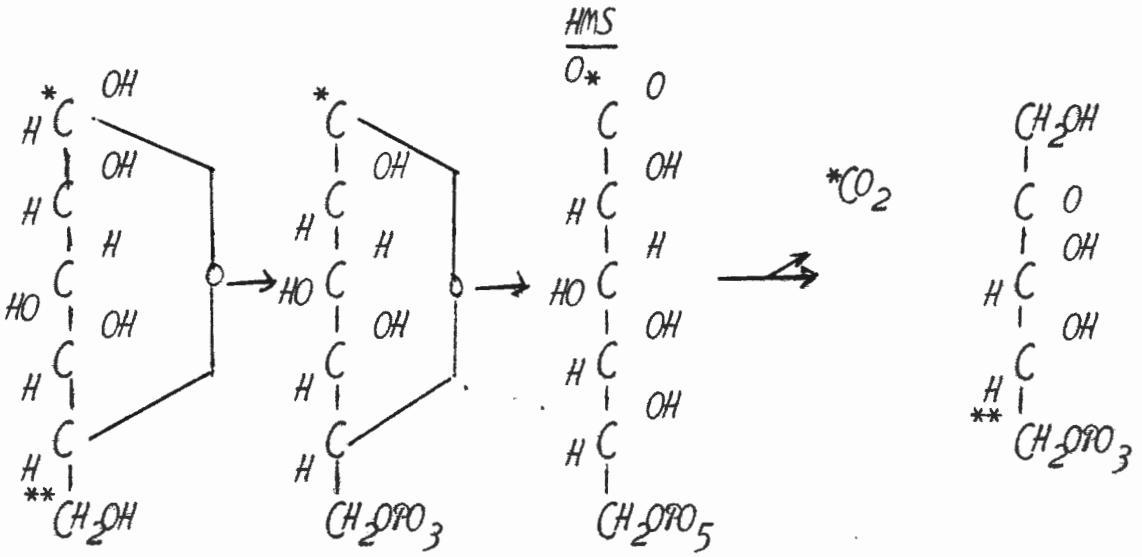


Figure 3

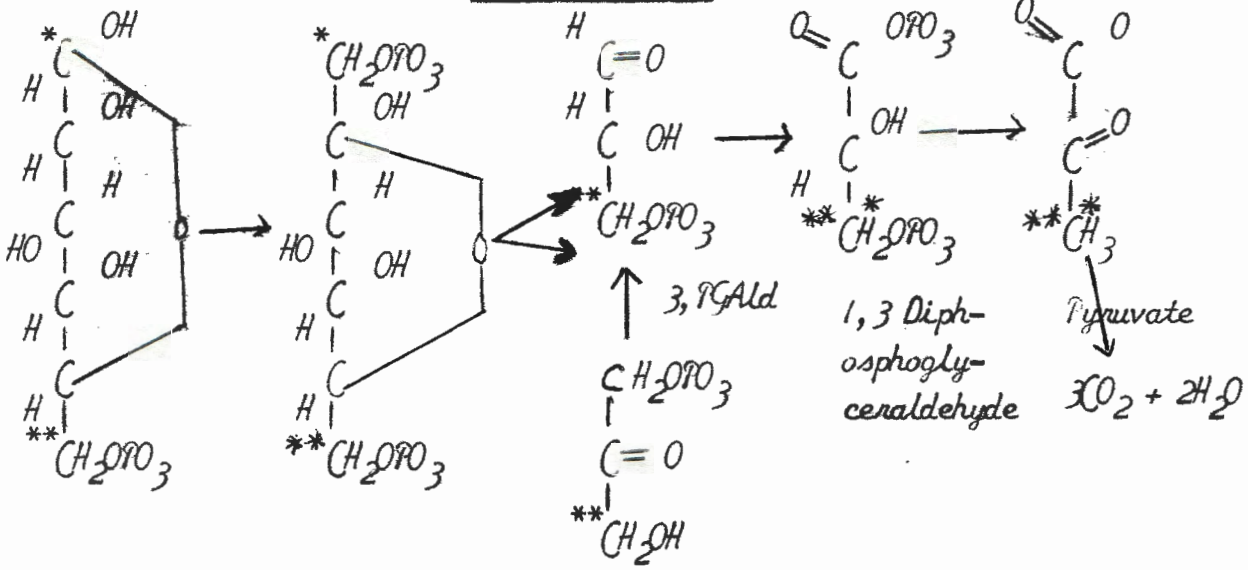
Formation of CO_2 from Carbon-Labeled Glucose



Glucose | Glucose-6-PO_4 | 6-Phospho-gluconate | Ribulose-5-PO_4

* = 1 carbon
** = 6 carbon

Embden-Meyerhof



Glucose-6-PO_4 | Fructose 1,6 Phosphate | Dihydroxy acetone Phosphate DHAP

Two equations which further simplifie the relationship of the carbon dioxide derived from the Embden-Meyerhof pathway and the HMS is the following:(71)

$$\underset{\text{Emb.-Mey. pathway}}{\text{Glucose}} = \underset{\text{6-labeled}}{6C} \qquad \text{and} \qquad \underset{\text{R-1-PO}_4}{G} = \underset{\text{1-labeled}}{\overset{\text{(Glucose)}}{C}} - \underset{\text{6-labeled}}{\overset{\text{(Carbon)}}{C}}$$

$$\overset{\text{(Carbon)}}{}$$

Studies made on the blood of 18 schizophrenics and 21 control subjects revealed that before insulin addition more ribose is being produced from glucose by the resting control subject than by the resting schizophrenic patient. Insulin stress caused a significant drop in the rate of incorporation of 1-labeled carbon of glucose into CO_2 by blood from the control subjects, but such a drop did not occur with blood from schizophrenic patients. Thus for the control group insulin stress reduced the amount of glucose going through the hexose monophosphate shunt (HMPS) but not in the schizophrenics. The insulin-stress effect disappeared when blood cells from the schizophrenic subjects affected the metabolism of chicken erythrocytes differently than did the plasma from control subjects.(71)

Chicken erythrocytes incubated in the plasma from schizophrenic subjects had lower pyruvate production and higher lactate/pyruvate ratios than those incubated with the plasma of normal subjects. This suggests the presence of some inhibition of aerobic metabolism in the plasma of schizophrenics. Results utilizing rat diaphragm confirmed the above. The data suggest that a factor in plasma from schizophrenic subjects interferes with some phase of hydrogen transport. One ml of cells incubated with

the plasma of control groups produced a mean of 51.4 mcg of pyruvate per hour while one ml of cells incubated in schizophrenic serum yielded a mean of 36.0 mcg of pyruvate per hour. This is significant at the 1 per cent level. The mean for individual lactate/pyruvate ratios was 4.88 for controls and 8.65 for schizophrenics. This also is significant at the 1 per cent level. The elevated lactate/pyruvate ratios indicate that anaerobic metabolism was more predominant in the schizophrenic group.(72)

Three different methods were used to isolate the factor present in schizophrenic serum which caused an elevated lactate/pyruvate ratio: (1) separation by ultrafiltration of serum into protein and non-protein fractions, (2) electrophoretic separation of serum proteins, and (3) further separation of the active fraction by column chromatography using DEAE cellulose. When step 1 is used abnormal values were obtained for the protein fraction only. When step 2 is used, with the Karler Misco Curtain Electrophoresis, the abnormal fraction appears with the beta globulins. With refinement, the fraction appears to be in the alpha globulin fraction. By separation with column chromatography using DEAE cellulose, activity was found in fraction III which has not yet been identified. The factor has a significant effect on metabolism as measured by lactate/pyruvate ratios in chicken erythrocytes and the stimulation of energy production by forcing glucose through the Embden-Meyerhof scheme rather than through the HMS. It is relatively stable between pH 6-9 and at 4°C. It may be an alpha globulin or a prosthetic group attached to an alpha globulin. The significance of this factor in schizophrenia has not been clarified; whether it is increased because of excessive production or failure to be

metabolized or detoxified is unknown.[73] The higher lactate/pyruvate ratio and the failure in the shift from the use of the 1-labeled carbon of glucose to the 6-labeled carbon of glucose with insulin stress in the schizophrenic subjects may represent an inhibition of a hydrogen transport enzyme system. This might involve the enzyme diphosphopyridine nucleotide (DPN) which is intimately involved in the conversion of lactate to pyruvate in the Embden-Meyerhof scheme of metabolism.[74]

Glucose metabolism of rat brain tissue in medium containing serum from normal or from schizophrenic patients showed that the 10 schizophrenic sera studied had a significant inhibition of glucose metabolism and and particularly of conversion to pyruvic acid, as compared with the sera of six normal samples. No difference was noted between the sera from males and females within the same group.[75]

When labeled glucose was injected intravenously into normal subjects and psychotic mental patients it was found that about 54% of brain CO_2 was derived from glucose in the normal person and 35% in the mental patient. This represents a decrease of glucose utilization of over one-third in the mental patient. When pyruvate-1-^{14}C is injected intravenously (I.V.), the normals again have a greater venous-arterial (Δ) difference of CO_2 derived from the labeled pyruvate than the mental patients. Normals show a higher specific activity of venous blood lactate by abount 80% when DL-lactate-1-^{14}C is injected but at the end of 80 minutes there is very little difference between lactate specific activity in the normals and mental patients. This suggests that the oxidation of lactate was carried on at a reduced rate in the body of the chronic mental patient. When D-lactic-1-^{14}C

and L-lactic-1-^{14}C were injected at different intervals, the mental patients showed a somewhat higher brain catabolism of the D-isomer than did the normals. In both groups glucose synthesized by the body from the L-isomer of lactic acid had greater specific activity than those of glucose from the D-isomer. Blood lactate and pyruvate determinations confirm that in a fasting state both are added to blood as it leaves the brain. Lactic acid arterio-venous (A_V) difference is 0.47 mg% in mental patients and 0.55mg% in normals. Pyruvate is 0.07 mg% in psychotics and 0.04 mg% in normals. Compartmentalization in the brain includes metabolism as well as function and the total production of these substances through glycolysis exceeds the amounts that are oxidized by way of the tricarboxylic acid cycle (TCA). (76)

The rate of phosphorous -32 (^{32}P) incorporation by erythrocytes of schizophrenics and normals into various high energy phosphate compounds has also been studied. Venous blood samples were heparinized and placed in a Dubnoff metabolic incubator at 37°C for 20, 40, 60, and 120 minutes. This was followed by centrifugation, extraction, and the blood nucleotides were separated. Recovery of the adenine nucleotide ranged from 95-105%. The recovery of ATP was in range of plus or minus 2%. With respect to inorganic phosphorous, hexose diphosphate, and adenosine diphosphate (ADP), no statistically significant differences were apparent between controls and schizophrenics. In general the inorganic phosphorous increased in all groups during the incubation period, the hexose diphosphate remained constant, and ADP levels fell. At 120 minutes the difference in adenosine triphosphate (ATP) between the schizophrenic and non-schizophrenics was significant. (P less than 0.001). There was an increase in schizophrenic erythrocytes of 7-20 mmols

of ATP per 100 ml. of red cells.(71) It has been shown that lactate/pyruvate ratios in erythrocytes incubated with schizophrenic serum increase. However, since the steps in the glycolytic pathways are reversible it can be argued that the production of excess lactate reduces the pyruvate which is available for possible phosphorylation to phosphopyruvate and this in turn would decrease the requirements for ATP.(77)

There was no striking difference between the glucose metabolism of chicken erythrocytes incubated in the plasma of normals and schizophrenics, respectively, when glucose-1-^{14}C, glucose-6-^{14}C or glucose-U-^{14}C were utilized. There were also no differences in the glucose-1/glucose-6 ratios. In addition the administration of insulin to normal or schizophrenic subjects produced no significant difference in response between plasma taken before insulin injection and that removed after such injection. Schizophrenic plasma did however have the effect of decreasing $^{14}CO_2$ production from glucose-U-^{14}C and glucose-6-^{14}C and therefore schizophrenic plasma may produce a general inhibition of the TCA cycle. Such inhibition of glucose oxidation could arise via a decreased rate of transport of glucose across the cell membrane, from a stimulation of competing pathways for glucose utilization, such as glycogen synthesis or lactic acid production, from an increased rate of endogenous TCA cycle substrate production or a direct effect on glucose catabolism.(77)

No evidence of increased lactate/pyruvate ratios was found when chicken erythrocytes were incubated in schizophrenic plasma when compared to controls. Also no evidence was found to indicate that schizophrenic serum affects the metabolism of glucose by chicken erythrocytes any differently than serum from normal individuals.

The data indicates that the effects of human serum on chicken red cells vary from day to day and from individual to individual and from chicken to chicken.(78)

It has been observed that intact chicken erythrocytes demonstrate no aerobic glycolysis. An antibody has been found in the blood of all subjects tested, which, in the presence of complement, stimulates aerobic glycolysis of chicken erythrocytes accompanied by progressive lysis of the cells. It has also been found that: (1) low concentrations of heparin partially inhibit the plasma effects, and heparin concentrations of 12-15 units per ml. completely block the action of human plasma on chicken erythrocytes, (2) intact chicken erythrocytes in Krebs-Ringer solution did not use glucose or accumulate lactic or pyruvic acid. However, when human plasma or serum was added to the incubation mixture, aerobic glycolysis occurred whether or not the donor was schizophrenic. The rate of aerobic glycolysis was closely correlated with the amount of hemoglobin released during the incubation. (p less than 0.001) After incubation the ratio of lactate (P less than 0.001), and with the hemolysis occurring during the incubation, (P less than 0.001) (79)

The relationship between structural integrity of chicken erythrocytes and the rate of aerobic glycolysis was illustrated by the following procedures: (1) Simple mechanical disruption of cells in the absence of serum or plasma induced active glycolysis. (2) Disruption of the red cells by high frequency sound resulted in more active glycolysis than did disruption by rapid freezing in the absence of added nucleotides. (3) Addition of ATP, DPN, and nicotinamide with freezing and thawing exerted as great a stimulatory effect as the sound treatment did. The cellular loss

of potassium (K^+) beginning immediately upon mixing human serum with chicken erythrocytes at 37° suggests that the initial lesion is at the plasma membrane. Saponin causes the formation of discrete plasma membrane lesions and leads to the loss of potassium ions, hemolysis and glycolysis quantitatively similar to that induced by active human serum. When chicken erythrocytes are added to complement-inactivated serum, no potassium loss, hemolysis or glycolysis occurred but agglutination did occur. When these agglutinated cells are washed free of serum and ethylene-diamine-tetraacetic acid (EDTA) and when guinea pig complement is added, hemolysis and glycolysis in the presence of glucose occur. Complement had no effect on cells which had not previously been sensitized. This effect is apparently due to a release from the Pasteur effect and is thus a "permissive" release of glycolysis. Thus human plasma or serum damages the cell membrane of chicken erythrocytes and subsequently causes increased permeability to glucose. It appears likely that these effects are due to the reaction of a heterogenetic antigen of chicken red blood cell plasma membrane with an antibody of human serum and complement. The distribution of the antibody in the population of mental patients and control normal subjects is still undetermined.(80)

Blood studies done on a group of chronically ill male schizophrenics maintained on a regular diet with daily physical activity and without medication resulted in an average lactate/pyruvate of 11.5. This ratio was selected as an appropriate value to separtae patients into a low factor and a high factor group since all of the control subjects had mean lactate/pyruvate ratios below 11.5. A total of 117 parents and siblings of 20 high

factor and 15 low factor patients who had lactate/pyruvate ratios performed were also seen for a psychiatric evaluation and were given the Minnesota Multiphasic Personality Inventory (MMPI). Elevated lactate/pyruvate (L/P) ratios were previously found to a significantly greater extent in the parents and siblings of the high factor patients than in the relatives of low-factor patients. The per cent of expectancy of schizophrenia for the total group of parents and siblings is consistent with population studies done elsewhere. However, there was no relationship demonstrated between schizophrenia in the siblings and high L/P ratios. There was a tendency for the siblings of the low-factor patients to show more schizophrenic and schizoid symptomatology than the sibling of the high-factor patients. The data indicate that elevation of the L/P ratio is only indirectly related to the clinical manifestation of schizophreniz.(81)

Intracellular energy-producing metabolic systems were investigated in 10 control, 10 acute schizophrenics and 10 chronic schizophrenic patients. Ratings based on extensive interviews were made of 37 aspects of premorbid life and early interpersonal relationships. It was found that premorbid social isolation and diminished heterosexual drive were related to biochemical abnormalities. Several attributes of the mother were related to biochemical abnormality. These attributes were consistent in picturing the mother of the schizophrenic patient as a shielding, protective person who did not allow her son to experience the ordinary stimulation and challenges of childhood.(82)

Animal studies of the influence of the very early environment on subsequent development also suggest that a certain amount of stimulation in early life is necessary for the proper maturation

of the energy producing metabolic systems. The energy metabolism in this study was assessd by erythrocyte levels of pre-stress AMP (adenosine monophosphate), and fructose-1,6-phosphate specific activities, and failure to change with stress of the ATP specific activities with and without insulin.(82)

Intracellular energy producing metabolic systems were investigated in the red cell before and after insulin stress in 10 control, 10 acute schizophrenics and 10 chronic schizophrenics. Following the complete clinical study 28 ratings of symptoms and course of illness were made for each subject. Correlation coefficients were computed between the biochemical and clinical variables with the following results: (1) It was found that the primary symptoms were directly related to the failure of mobilization after stress of the compound fructose-1,6-di-phosphate. (2) In contrast, secondary symptoms were not significantly related to biochemical variables. (3) Scores indicating a chronic illness and a poor outcome at follow-up were found to be directly related to another very important substance in this metabolic scheme, AMP.(83)

The effect of sleep deprivation on behavior, thinking, motor performance, and biological energy transfer systems was studied in a single subject who remained awake without drugs for 220 hours. Behavioral changes included irritability, paranoid thinking, expansiveness, grandiosity, hypnagogic states, visual hallucinations, and episodic rage. Deficits in thinking and visual-motor performance occurred cyclically across days of wakefulness with gradual deteriaration, finally resulting in virtual untestability on the ninth day. Energy transfer systems responded to sleep deprivation as a stress situation with a marked increase in the specific

activities of ATP, AMP, and fructose-1,6-di-phosphate which became evident on the fourth day. Radioactive incorporation of ^{32}p revealed an increased synthesis of AMP. This emergency energy mobilization began to fail by the seventh day when the specific activities of all the adenylic phosphates fell appreciably.(84)

In a group of American Negro males studied there was no significant difference in the prevalence of glucose-6-phosphate dehydrogenase (G-6-PD) deficiency between schizophrenics as a group and a control population. No significant differences in the frequency of G-6-PD deficiency were found in various subtypes of schizophrenia and the control group. No significant differences were noted in the basic symptoms of schizophrenia between the schizophrenics with G-6-PD deficiency and those whithout it among the schizophrenics.(69)

Glucose-6-phosphate dehydrogenase is an enzyme found in erythrocytes. This enzyme catalyzes the oxidation of glucose-6-phosphate to 6-phosphogluconolactone, thereby reducing triphosphopyridine nucleotide (TPN). The reduced TPN (TPNH) is then utilized extensively in the metabolism of the erythrocyte as a hydrogen donor. When a deficiency of this enzyme is present, there is a deficiency of TPNH and therfore a deficiency of reduction potential. The excessive oxidation of cell metabolism without concomitant reduction leads to erythrocyte hemolysis. The deficiency of G-6-PD is transmitted by a sex-linked gene of partial eominance.(64)

Toxicity of Schizophrenic Fluids

Serum of schizophrenics and healthy subjects was used as a culture media for a strain of L cells derived from the subcutaneous tissue of a normal C3H mouse. The strain had been made malignant by treatment with 20-methyl-cholanthrene. A strain of Hela cells from epidermoid carcinoma of the cervix uteri was also used as a culture media. The blood sera of 80 schizophrenics showed all degrees of toxicity on the strain of L cells. Seventy-four per cent of these samples were toxic to a degree 3+ - 4+ and 26% were not toxic or were toxic to a degree of 1+ - 2+. Cells were rated as 1+ when there were only a few degenerating cells in the culture, as 2+ when there were predominantly healthy cells, as 3+ when there were more degenerating than healthy cells, and as 4+ when all but a few scattered cells were dead. Of the 29 healthy control sera, only 10% were toxic to a degree of 3+ to 4+ and 90% were not toxic at all or only to degree 1+ to 2+. Hela cells were discontinued because no effect of the sera could be found on them. Heating of the toxic blood sera to 56° for 35 minutes resulted in complete detoxification.(85)

Intraperitoneal injection of blood plasma from a majority os schizophrenic and other severely psychotic patients into rats produced a syndrome resembling, but not identical, with that produced by injection of LSD. The climbing time (CT) of trained rats was measured before and after the injection of heparinized plasma; the controls received saline and heparin. The overall average effects of psychotic plasma was 677 seconds as compared with 100 and 133 seconds for the physically ill and normal groups, respectively. The medians were 374, 88, and

96 seconds respectively. Of the 80 psychotic samples, 68 or 85% had values above the median for normals while 94% of the specimens from the physically ill patients and 91% of the normals were below the median for psychotics. Also 85% of psychotic samples and 94% of the specimens from the physically ill gave a lower value than the psychotic mean. (P less than 0.001) (86)

Blood plasma and plasma protein factors from nonpsychotic subjects and from acute and chronic psychotic increase the climbing time (CT) of trained rats, but significantly greater effects were produced by samples from the psychotic population. No differential effects were noted when serum samples were used. Plasma globulin fractions produced the greatest effects per unit of protein and less activity was noted in other fractions. The active principle may not be a protein, but rather, a small molecule attached to proteins. Since CT changes minutes after injection of the fractions it is reasoned that in this short a time a protein would not be transported across the blood-brain barrier. (87)

Two urine extracts derived from a group of acute schizophrenics and from a group of normal subjects were injected into either the cisterna magna or the lateral ventricles of monkeys and cats and their effects on the animals' behavior and EEG were noted. The schizophrenic extract caused a more pronounced reduction in spontaneous activity and no affectionate response was obtained even when the animal was caressed. In monkeys both extracts caused a marked docility, with significant reduction in emotional coloring of their behavior. The degree of this change was more pronounced following the schizophrenic extract. The schizophrenic extract brought about a variety of unusual behavioral patterns,

ranging from rage states in five out of ten cats, automatism-like states in three out of ten cats, to recurrent stuporous and catalepsy-like episodes in one out of ten cats and five out of ten monkeys. No animal, after injection of the normal extract, showed this unusual behavior, except for a brief stuporous episode in one monkey.(88)

Electroencephalographs (EEG) recorded in some animals through implanted cortical electrodes and also from scalp electrodes revealed no significant abnormality after injection of normal extract. After the schizophrenic extract injection there was a predominance of 2-5 cycles-per-second (CPS) slow-waves in background activity. Paroxysmal high-voltage sharp-wave-and spike discharges occurring at temporo-occipital regions were associated with the automatism-like behavior in two cats. While the animal's eyes were kept widely open during the stuporous episodes, the EEG frequently showed high voltage-slow wave spindle-burst activity bilaterally. In some episodes the EEG showed a low-voltage-fast. "arousal pattern" despite the fact that the animals remained unresponsive. The mechanisms which the present behavioral and EEG findings may reflect are that the rhinencephalon is a pool into which afferent impulses of all kinds of modalities enter; the amygdala and perhaps also other parts of the rhinencephalon act as a modulator of complex mechanisms integrated in the central core of subcortical structures extending from the septum through the hypothalamus into the brain stem tegmentum.(88)

Fifteen non-psychotic volunteers, three schizophrenics in remission, and two other non-psychotic volunteers were given I. V. the amount of taraxein which had been extracted from

400 ml of schizophrenic serum. Taraxein is an unidentified protein which has been found only in the serum of schizophrenics. All experiments were done as a double blind study with several different control substances being used. The subjects injected with taraxein all developed symptoms of schizophrenia. Primary symptoms appeared consistently: blocking and thought deprivation developed. All were autistic and compained of depersonalization. They appeared dazed and demonstrated diminished contact with their environment. These symptoms were the most consistent and developed even with the administration of taraxein which had shown only minimal activity by animal assay. Each of the classical secondary symptoms appeared in one or more of the test subjects: catatonic stupor and excitement, hebephrenia, referential ideas, delusions of grandeur and persecution, and auditory hallucinations. None of the test group displayed the visual hallucinations or showed changes in the autonomic nervous system that are characteristic of the LSD reaction. The schizophrenics in remission had more secondary symptoms suggesting that they were more sensitive. This substance, taraxein, is present in serum and is not a product activated through the processing procedure. Thorazine (chlorpromazine) does not act on taraxein in the serum. (89) Neither the isolation of taraxein nor the effects resulting from its intravenous injection have been confirmed. (90

Plasma factor titers were investigated in physically ill persons diagnosed as having one of the following illnesses: (1) tuberculosis, (2) carcinoma, (3) chronic hospitalization, and (4) post-operative patients. Psychotic recently diagnosed and chronic schizophrenics hospitalized for several years or more were also included. The Winter-Flotaker rat rope climbing tests were used for bioassay. With is modified procedure the final

figure represents only the increase in climbing time delay due to injected substances. The hospitalized patients without psychotic complications had an increase in climbing time of 13% which agrees with the 17% increase reported in another study. Schizophrenic plasma extract produced 81% greater climbing time than the control. (P equals 0.02) Thus significantly elevated plasma factor titers appear to be associated only with the schizophrenic population.(91)

Recent data failed to support previous findings of elevated S19 macroglobulins or other serum protein abnormalities in schizophrenic patients. The schizophrenic females as compared to schizophrenic males had markedly high S19 macroglobulin levels and slightly lower S4 levels, however. Using the PPRP and BRSS as measurements of the severity of illness, no evidence of a genuine relationship between the severity of eillness and serum macroglobulin levels was found. Changes in S19 levels in schizophrenics bear no relationship to changes in psychiatric conditions.(92)

Tissues from specific brain regions of 14 Schizophrenic patients and 19 non-schizoprenic patients were studied by fluorescent antibody techniques. In vivo antibody was demonstrated in neural cell nuclei of principally of the septal region and basal caudate nucleus and, less prominently, in other tissues of the brains of 12 of the 14 schizophrenics. No antibody was detected in tissues of non-schizophrenic control patients. The reaction of schizophrenic tissues with normal sera before indirect testing with the use of fluorescent-tagged antihuman gamma globulin (FTAHgg) showed similar or slightly less fluorescence when sompared with tissues that were not reacted with the sera before addition of FTAHgg. Brain tissues from non-schizophrenic subjects

that were reacted with normal sera and then stained did not fluoresce at all, indicating that normal sera did not contain antibody against brain. Reaction of tissues with the sera of schizophrenic patients before staining with FTAHgg caused notably brighter fluorescence in tissues of schizophrenic patients and minimal fluorescence of neural cell nuclei of some non-schizophrenic patients. These observations indicate that schizophrenic serum contains antibody against brain. Total or pronounced inhibition of fluorescence after additon of schizophrenic serum and untagged antihuman gamma globulin before staining with FTAHgg indicated a specific antigen-antibody reaction. Reaction of tissues with the sera of patients with certain other diseases, principally systemic lupus erythematosys, before staining with FTA-Hgg intensified fluorescence of neural cell nuclei from all brain regions as well as from other organs, especially in tissues of schizophrenic and non-schizophrenic subjects. The anitbody in lupus sera and in sera of patients with certain other diseases differed notably from that in schizophrenic sera.(93)

Various serum fractionation methods were used to process the sera of four groups of subjects: (1) patients with chronic schizophrenia, (2) patients with acute schizophrenia, and (3) patients with other diseases as well as healthy control subjects. Serum globulins of all acute schizophrenic patients and some chronic schizophrenics studied induced physiological and behavioral aberrations in monkeys. Observation suggests that the active principle in schizophrenic serum migrates with the gamma G globulin (immunoglobulin), and it is capable of combining with neural cell nuclei of the septal region and basal caudate nucleus as demonstrated by fluorescent antibody techniques. The data support

the hypothesis that schizophrenia is an immunologic disorder and that the sera of schizophrenic patients contain a unique antibody capable of combining with specific but unidentified antigenic sites in neural cell nuclei of the basal rostral sturctures.(93)

Antibodies against specific parts of monkey brain, human brain, and column fractions of human septal-caudate tissue were produced by injecting potentiated homogenates of the tissues into sheep. Serum fractions obtained by several methods were tested by injections into the cerebral ventricles of intact rhesus monkeys which were prepared with depth and surface electrodes for prolonged study. Fractions of antisera against monkey septal region and caudate nucleus induced spiking and slow waves in the EEG's from homologous brain sites at the same time as acatatonic behavior was seen in the monkeys. Recordings resembled those for monkeys that received the psychoactive serum fraction taraxein of schizophrenic patients obtained by indectical fractionation methods as well as those for schizophrenic patients obtained during psychotic episodes. Other charcteristics of the anti-brain serum fractions resembled those of taraxein. Fluorescent antibody studies showed that sheep anti-brain serum fractions had attached to neural cell nuclei of the septal region and the basal caudate nucleus of recipient monkeys whose EEG's and behavior had been altered by the injections. Psychosis-inducing activity was identified in the presence of gamma G immunoglobulin (IgG). This was demonstrated regardless of the fractionation method used to obtain the active fraction from sheep sera containint the antibody against the septal region and basal caudate nucleus. Although the active serum fraction

migrated with IgG, the two fractions were not the same, since the inert fractions similarly obtained from sheep sera containing antibody against other brain parts also contained IgG.(93)

It is concluded that the septal-basal caudate region of the brain contains a unique antigen against which antibody can be created and which is capable of combining with neural cell nuclei of the septal caude region, to induce, possibly through impairment of neurohumeral conduction, aberrations in EEG associated with schizophrenic behavior. Since sera of schizophrenic patients contains globulin (taraxein), with essentially the same characteristics, it is postulated that taraxein may be the antibody and that schizophrenias may represent an auto-immune disorder.(93)

Summary and Conclusion

The review of the metabolic aspects of schizophrenia has revealed many fascinating findings. Although none of these findings have been confirmed by enough workers to make the hypotheses upon which the research was based valid, much information which serves as groundwork has been compiled.

Protein metabolism in schizophrenia has been found to play an important role in the synthesis of the biologic amines which determine behavior. Tryptophan, methionine and tyrosine are the amino acids which have been most studied. Since serotonin is derived from tryptophan and epinephrine and norepine/phrine from tyrosine, and, since methionine is an important methylating agent, these proteins and their metabolic fate has been presented.

The postulation of Elkes that there are three different receptor types responsive to three different substrates, the cholinergic, the adrenergic and the indolic, has also helped to open up avenues for futher research studies. It has been found, for instance, that certain areas of the brain are selectively responsive to biological substances such as septal extract, atropine, and histamine as well as adrenergic compounds. In these studies the caudate nucleus, the hypothalamus and the putamen were the areas from which behavioral changes were most often elicited upon injection of substances.

The aberrant detoxication of epinephrine and norepinephrine and dopamine has been postulated to result in end products such as

adrenochromes and adrenolutin which have numerous biologic effects such as inhibiting choline esterase and there by potentiating psychotic behavior; they also interfere with carbohydrate metabolism and synaptic transmission. Again, this hypothesis has been confirmed by some and disproved by others.

The catecholamine hypothesis of affective disorders expounds that some but not all depressions are associated with a relative deficiency of catecholamines, particularly norepinephrine, at functionally important adrenergic receptor sites in the brain. Mood elevation may be associated with an excess of such amines. The monamine oxidase inhibitors which increase the brain concentrations of norephinephrine, and the imipramine like agents, which potentiate the physiological effects of norepinephrine have been the main pharmacological tools used in the work to confirm this postulation.

Urinary analysis for breakdown products of serotonin, norepinephrine, and epinephrine, has been another approach to determine abnormalities of transmitter substances in schizophrenia. But due to the difficulties inherent in such analysis most workers have been able to contribute only more factors which influence urine analysis. They have found of what importance such factors as diet, activity, physical illness, and medications are in the results, and also the contingency of the accuracy of instruments used and methods used to determine the excretion of biologic amines in the urine.

The effect of oxidases such as ceruloplasmin, a polyphenol oxidase, and ascorbic acid oxidase, which are both copper-protein complexes present in serum on the metabolic aspects of schizophrenia have yielded conflicting results. Since schizophrenia is an acute or chronic disease and schizophrenics are most often hospitalized

for long periods of time the illness has much in common with other acute and chronic disease processes as reflected in changes in serum albumin, transferrin, gamma globulins, orosomucoid, haptoglobulins, ceruloplasmin and ascorbic acid.

Psychopharmacological agents have also been used in order to study schizophrenia. The phenothiazines and Rauwolfia alkaloids have been the most useful drugs in the treatment of schizophrenia. Both of these ataracticis have a calming effect on an agitated nervous system and produce their actions directly in the central nervous system (CNS). It has been postulated by Brodie that reserpine acts through release of serotonin from storage granules. Serotonin has a sedative action, and it exists in high concentrations in the limbic system. The suggested blocking action of the phenothiazines is someuhere in the diencephalon.

In the electroencephalographic (EEG) studies obtained by placing microelectrodes into specific brain areas it was found that psychotics have spikes in the septal region, made up of fast, biphasic spikes sometimes superimposed on a slow wave. During remission of psychotic symptoms no such abnormality was recoreded. When numerous drugs, both cholinergic and adrenergic, were inserted through cannulas into specific brain areas, it was again found that atropine and histamine had the most profound effect and thus it was postulated that interference with acetylcholine action in the brain was responsible for the spiking. The electrical changes associated with catatonic behavior can be duplicated by agents which interfere with neurohumeral transmission.

Cerebrospinal fluid findings in schizophrenics have resulted in some important findings which need to be confirmed. The brain gangliosides have been shown to have a marked stimulating function in a membrane activating system such as the clam heart,

suggesting that they may be involved in transmission phenomena in the CNS. Immunological studies have revealed that brain gangliosides may be involved in important regulating functions in terms of controlling entry and egress of a number of important constituents in the CNS; these functions have been referred to as the "Barrier-Antibody System." The brain gangliosides consist of water soluble constituents of neuraminic acid--hexoseamine and hexose on one surface of the molecule and lipid soluble constituents such as sphingosine and stearic acid on the other surface. In numerous studies it has been found that schizophrenic adults showed lower values for total neuraminic acid relative to controls and that the schizophrenic neuraminic acid content was comparable only with the values found in children less than 7 years old. Other studies reveal an inverse relationship between the degree of psychotic illness and the absolute amount of glycoprotein neuraminic acid and a positive relationship between clinical improvement in schizophrenic patients and increases in the absolute amount of glycoprotein neuraminic acid in cerebrospinal fluid. A hypothesis has been formulated that since hexoseamine is a synthetic precursor of neuraminic acid and the accumulation of a precursor, as has been found, without the accumulation of its derivatives, suggests an enzymatic block in the conversion of hexoseamine to neuraminic acid.

On studies concerning thyroid and adrenal function in schizophrenia, no direct relationship between the illness and endocrinology has been found. The possibility exists that a kind or intensity of the emotional state and not the diagnostic category influence thyroid and adrenal function, such as anxiety, agitation, etc.

Studies on carbohydrate and energy metabolism in schizophrenia have resulted in much information but also much disappointment in the non-reproducibility of results. The studies have employed mainly red cells of normals and schizophrenics. The cells are hemolyzed and the filtrate is used as an enzyme solution containing hexose diphosphate as a substrate along with necessary enzymes. The easily hydolyzable phosphorylated compound formed when pyruvate is added is an index of the rate of glycolytic reaction. When hemolyzates from insulin treated blood are used there is a comparative deficit in the accumulation of this easily hydrolyzable phosphorylated compound. This suggests that the deficit is due to increased rate of consumption rather than a decreased rate of formation. This effect of insulin has been shown to be absent from a very substantial number of schizophrenic subjects' blood. But again, not all schizophrenics' blood samples give abnormal results.

The specific action of adenosine triphosphate (ATP) was studied in erythrocytes in which glucose is metabolized wither via the Embden-Meyerhof scheme to ATP or by way of the hexose monophosphate shunt (HMPS). When glucose is utlized wia HMPS, ribose-1-phosphate is the usual end product. The proportion of glucose utilized via HMPS to ribose-1-phosphate and to ATP via the Embden-Meyerhof scheme can be estimated by labeling glucose in the 1 and 6 position and incubating it with red cells and then measuring the labeled carbon dioxide resulting from the catabolism of the glucose molecule. When glucose is converted to ribose-1-phosphate only the carbon labeled in the 1 position is found in the carbon dioxide. When glucose is catabolized via the Embden-Meyerhof scheme both carbons labeled in the 1 and 6 position appear as

carbon dioxide. Schematically this is represented as follows:

A. Glucose equals 6C — Emb.-Mey.

B. Glucose equals C1 minus C6 — Rib.-1-PO_4

Insulin stress caused a significant drop in the rate of incorporation of the 1 labeled carbon of glucose into carbon dioxide by blood from control subjects but such a drop did not occur with blood from schizophrenic patients. Thus for the control group insulin stress reduced the amount of glucose going through the HMPS but not in schizophrenic subjects. The insulin stress effect disappeared when blood cells from normal control subjects were placed in schizophrenic plasma; also plasma from schizophrenic subjects affected the matabolism of chicken erythrocytes differently than did plasma from control subjects.

Chicken erythrocytes incubated in the plasma from schizophrenic subjects had lower pyruvate production and higher lactate/pyruvate ratios than those incubated with the plasma of control subjects. This suggests the presene of some inhibition of aerobic metabolism in the plasma of schizophrenics. An interference with some phase of hydrogen transport is suggested. The factor in schizophrenic plasma which has this effect was isolated by three different methods but was not definitely identified except to say that it may be an alpha globulin or a prosthetic group attached to an alpha globulin.

When labeled glucose was injected intravenously into normal subjects and psychotic mental patients, it was found that about 54% of brain carbon dioxide was derived from glucose in the normal person but only 35% by the mental patients.

The main difficultes in these studies are that they are not

reproducible by different workers using the same procedures. The effect of human plasma on chicken erythrocytes, for instance, is probably due to the reaction of a heterogenetic antigen of chicken red blood cell plasma membrane with an antibody of human serum and complement. The distribution of the antibody in the population of mental patients and control subjects is still undetermined.

The toxicity of schizophrenic body fluids has been documented by numerous workers. Schizophrenic serum has been found to be toxic to strain L cells of subcutaneous tissue of normal C3H mice. Intraperitoneal injection of blood plasma from schizophrenic patients increased the climbing time of trained rats. The active principle is suspected to be not a protein but a small molecule attached to proteins. Urine extracts from schizophrenics produced behavioral changes in monkeys and cats when injected into the cisterna magna or lateral ventricle. Normal control subjects showed no unusual effects from the injections. These changes could be seen on the EEG as 2-5 cycle per second slow waves and paroxysmal high voltage sharp wave and spike discharges occuring at the temporo-occipital regions.

Taraxein is the name given to an unidentified protein extracted from pooled schizophrenic serum which causes behavioral changes similar to that of schizophrenics when injected intravenously into normal subjects. Autism and depersonalization as well as blocking were constant manifestations resulting from injection. Neither the isolation of taraxein nor the effects resulting from its intravenous use have been confirmed.

The most exciting finding so far has been by the Tulane group also and it is the demonstration of an in vivo antibody

in neural cell nuclei, principally of the septal region and basal caudate nucleus of schizophrenic brains when fluorescent antibody studies were done on both normal and schizophrenic brains. Various serum fractionation methods were used to process the sera of schizophrenics and controls. The serum globulins of all acute schizophrenics induced physiological and behavioral alterations in monkeys. The active principle appears to be an immunoglobulin. Other characteristics of the anti-brain serum fraction resemble those of taraxein and these researchers of the Tulane group postulate that taraxein may be an antibody and schizophrenia may represent an autoimmune disorder.

Although it may appear from reading a paper such as this that there is no direction to the research the author now thinks that the most fruitful studies have been the ones done with schizophrenic serum and cerebro spinal fluid.

In conclusion, the author of this compilation has gained much insight into the metabolic aspects of schizophrenia and believes, as at the beginning of the study that the ultimate solution will come as a result of continuing intensive research of many workers into the etiology of schizophrenia.

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