Possible Synergistic Effects of Nonesterified Fatty Acids and Lysolecithins, a Toxic Methionine Metabolite, and Ammonia in the Production of Hepatic Encephalopathy and Schizophrenia

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Abstract

Hepatic encephalopathy is due largely to the toxic effects of three synergistic compounds: methanethiol (a metabolite of methionine), toxic detergents such as nonesterified fatty acids, and/or lysolecithins, and ammonia. Ingested methionine is very toxic to patients with hepatic coma and an abnormal response to methionine has been extensively documented in schizophrenia. The three drugs used to treat schizophrenia (phenothiazine tranquilizers, propranolol, and nicotinic acid) all share significant antili-polycyclic properties and/or inhibit the formation of lysolecithins. Similarities of schizophrenia and hepatic encephalopathy and/or Reye's syndrome include: elevated creatine kinase MM isoenzyme in the serum, elevated phospholipase activity, pathological changes in the liver and altered liver function tests, abnormal androgen and pyrimidine metabolism, sensitivity to ingestion of methionine, muscle pathology, and specific pathological changes of the astrocytes in the cerebrum, basal ganglia, and brain stem. I suggest that schizophrenia is a syndrome that is a type of hepatic encephalopathy induced by viral disease, hepatic metabolic disease, especially porphyria, hepatotoxic agents in the environment, deficiency of nutritional factors involved in fatty acid metabolism, intolerance to animal proteins which are rich in methionine, reduced ability of the adipose tissue to remove circulating nonesterified fatty acids from the bloodstream due to biochemical defects or obesity, abnormal phospholipid metabolism possibly involving lecithin cholesterol acyl transferase, and/or phospholipase, or a combination of the above factors.

Introduction

Recently, I reviewed the etiology of Reye's syndrome (a type of hepatic encephalopathy) and was struck by many similarities between this disease and schizophrenia:

1. Hallucinations or inappropriate behaviour are common in both disorders.
2. Sera from individuals with both disorders were toxic to cells or cell organelles.
3. Liver disease is present in both diseases.
4. Viral infection sometimes is associated with Reye's syndrome and may also cause encephalitis in adults, with symptoms indistinguishable from schizophrenia.
5. Virus epidemics are also associated with increased incidence of schizophrenia and Reye's syndrome.
6. Defects in ammonia detoxification and abnormal metabolism of nonesterified fatty acids occur in both disorders.

In the previous article, a great deal of evidence implicating excessive nonesterified
fatty acids and lysolecithins in the pathogenesis of Reye's syndrome was presented. However, another recent article presents very convincing evidence that ammonia intoxication plays the predominant role in this syndrome. As in many scientific controversies, I considered the possibility that both viewpoints might be correct and found a very interesting and exciting paper by Zieve that supports the synergistic effects of ammonia, nonesterified fatty acids, and a methionine metabolite in the production of hepatic encephalopathy (or coma). I also knew that the amino acid methionine had unique psychosis-inducing properties and that altered metabolism of nonesterified fatty acids and ammonia have been demonstrated in schizophrenia. Liver pathology and altered liver function tests have also been found in schizophrenia and I decided to explore the possibility that schizophrenia might be a type of hepatic encephalopathy.

The hypothesis that schizophrenia is an hepatic encephalopathy is not a new one and this hypothesis has been promoted by a large group of Italian scientists for over 60 years, most notably by the Buscaino family. The paper of Zieve provided an integrating concept that allowed me to integrate schizophrenia research in areas such as brain abnormal serum protein conformations, claims for the therapeutic use of megadoses of nicotinic acid, induction of psychosis with methionine, toxic body fluids, and the therapeutic effectiveness of the neuroleptic drugs, and propranolol for the treatment of schizophrenia, and recent evidence for elevated serum phospholipase into a new conceptual model for this disease. A number of workers prefer the term schizophrenic syndrome because of the possibility of multiple etiologies and I will use this term instead of schizophrenia for the rest of the paper.

In this article, I would like to explore the evidence that schizophrenic syndrome, like Reye's syndrome, is a hepatic encephalopathy possibly caused by a variety of dietary, hereditary, and infectious agent factors that are biochemically linked to disorders in nonesterified fatty acid and/or lysolecithin metabolism, ammonia metabolism, and methionine metabolism.

In this article, I wish to review the following topics:

I. A description of the disease and its impact.
II. The induction of psychosis in schizophrenic syndrome by methionine and the synergistic effects of methionine, nonesterified fatty acids, and ammonia in coma production in hepatic disease.
III. Evidence for altered metabolism of lipids, primarily phospholipids and nonesterified fatty acids in schizophrenic syndrome.
IV. Evidence that the predominant drug therapy (phenothiazine tranquilizers) for this disorder and two other less common drug therapies (niacin and propranolol) may mediate their effects through reductions in the concentrations of nonesterified fatty acids and lysolecithins.
V. Evidence for altered ammonia metabolism in schizophrenic syndrome.
VI. Clinical laboratory and pathological studies which support the concept that the disease is a systemic disease rather than limited to the central nervous system.
VII. Evidence for viral infection as a cause of some cases of schizophrenic syndrome.
VIII. A plan of action for the elimination of this disease.

I. A description of schizophrenic syndrome and its impact on society.

Some background material is very helpful in understanding the schizophrenic syndrome. There are no objective criteria for confirming the diagnosis, no accepted laboratory tests, no single known cause, and no definite prognosis for this disease. However, clinicians agree that this disease can be characterized as a thought disorder with a lack of logic, confused associations, detachment from reality, auditory hallucinations, and delusions, often of a persecutory nature. Diminished or blunted affect (demonstration of emotions) and deterioration of personal hygiene and interpersonal affairs are characteristics of this
Synergistic Effects of Metabolites in Schizophrenia

A book by Torrey\textsuperscript{55} is an excellent source on the impact of this disease on society, family, and individual and the following material is drawn from this source. Schizophrenic syndrome affects 1% of the population of all cultures in the world but is less frequent in developing nations. The incidence in one part of Ireland is 1 in 25. The estimated cost of this disease in treatment and lost wages is at least $20 billion per year in the United States, including the costs of hospitalization, Social Security benefits, welfare payments, and lost wages. One out of every two mental health hospital beds is occupied by a schizophrenic. There are 10 million schizophrenics in the world today. Despite the magnitude of this disease, federal funds for research on schizophrenic syndrome is about $20 million per year. Thus, funds to cure this disease are only one-millionth of the cost of this disease. The disease usually begins in adolescence or young adulthood and follows a variable course. Demographically, schizophrenic syndrome is the most expensive of any chronic disease, since the individual remains well throughout the years of rearing and education, then becomes ill and often dependent on society just at the age the person would normally become a productive wage earner.

A quotation from Torrey is useful in assessing the human element of this disease: "Not only must persons affected and their family bear the disease itself, but they must bear the stigma as well. Schizophrenics are the lepers of the twentieth century. The aunt, son, or sister may be discovered at any minute, and the word will be out. Disaster, Dishonor, Disgrace. The magnitude of schizophrenic syndrome as a national calamity is exceeded only by the magnitude of our ignorance in dealing with it."

II. Involvement of methionine in schizophrenic syndrome and interactions of nonesterified fatty acids, ammonia, and methionine in hepatic coma.

A large number of studies\textsuperscript{25} 26 27 28 29 have documented that, uniquely among amino acids, administration of methionine led to transient exacerbations of psychosis in a substantial proportion of patients with chronic schizophrenic syndrome. The occasional coincidence of "schizophreniclike" psychoses and homocystinuria, an inborn error of metabolism in which there is often an excess of methionine gave further support to the idea that methionine or one of its metabolites might be involved in the pathogenesis of schizophrenic syndrome.\textsuperscript{25} The effect of methionine in schizophrenic patients is one of the few metabolic observations in schizophrenic syndrome that have been repeatedly and consistently replicated.\textsuperscript{25} In 10 studies reviewed by Cohen et al,\textsuperscript{29} 57.9% of chronic schizophrenic patients responded to methionine with a functional psychosis.

In addition to the biochemical evidence that a large number of schizophrenics respond to methionine with an acute psychosis, there is a physical symptom linking schizophrenic syndrome with abnormal methionine metabolism. Capillary abnormalities in the nail folds have been described in schizophrenic syndrome with tortuosity of vessels and an increased sub-capillary plexus and increase in the length of the end row.\textsuperscript{56} Similar findings are prevalent in individuals affected with homocystinuria.\textsuperscript{56} Abnormal skin creases on the fingers have also been found in homocystinuria. Unusual fingerprint patterns have been documented in over 4000 schizophrenic patients from all parts of the world.\textsuperscript{57}

Because methionine plays a role in catecholamine and indoleamine metabolism via methylation reactions, many researchers investigating schizophrenic syndrome wished to connect this aspect of methionine with abnormal neurotransmitter metabolism, but were unable to prove such a connection.\textsuperscript{25} Thus, some other function of methionine or a metabolite of methionine appears to be responsible for its psychosis-inducing property. Methyl mercaptan (CH\textsubscript{3}SH) or methanethiol is an extremely toxic metabolite of methionine that was not mentioned in any of the reports on methionine and schizophrenic syndrome. Methionine can be hydrolyzed (Figure 1) to homoserine or reduced to...
alpha-aminobutyric acid plus methanethiol by liver mitochondria, by molds, and by intestinal bacteria. Normally, methanethiol produced in the gut is metabolized to dimethylsulfide, but in patients with extensive portal-systemic shunting, methanethiol bypasses the liver, accumulates in the blood, and is excreted in the urine and breath.

Methanethiol is 14,000 times more toxic than its metabolite, dimethyl sulfide, so that formation of dimethyl sulfide appears to be an important step in the detoxification of methanethiol.

An interesting property of methanethiol, extensively investigated by Zieve is that it greatly reduces the dose of nonesterified fatty acids or ammonium ion (NH\(_4^+\)) required to produce coma in rats. In Figure 2 are the dose response curves to NH\(_4^+\) in the presence of a sub-coma dose of methanethiol in rats. The dose of NH\(_4^+\) necessary to induce coma in 50% of treated rats, the comatose dose (or CD\(_{50}\)) decreased from 1.45 to 0.46 moles in the presence of methanethiol. The incidence of coma rose from 0% to 100% at a dose of NH\(_4^+\) that was only 1/2 of its CD\(_{50}\) when NH\(_4^+\) alone was used to induce coma.

Similar synergistic effects of methanethiol in coma induction were observed when the nonesterified fatty acid octanoate was substituted for NH\(_4^+\) (Figure 3). The CD\(_{50}\) of octanoate was reduced by 2/3 from 0.48 to 0.116 moles, and the incidence of coma rose from 0 percent to 100 percent at a dose of octanoate that was approximately 3/4 of the largest subcoma dose required for coma induction by octanoate alone. (Other nonesterified fatty acids also induce coma like octanoate.)

The striking effects of methanethiol on the dose responses of NH\(_4^+\) and octanoate raised the question of the extent of interference of each of these substances with each other's metabolism. In the same study (data not shown), at doses of administered NH\(_4^+\) below the coma-producing level, the addition of small doses of methanethiol caused almost a doubling of the blood NH\(_4^+\) concentrations. Small doses of octanoate had no effect on blood NH\(_4^+\) concentrations in the absence of methanethiol but did cause almost a doubling of the blood NH\(_4^+\) when methanethiol was administered at the same time.

Administration of NH\(_4^+\) or octanoate also apparently interfere with the liver's metabolism of methanethiol. When an extremely small dose of methanethiol was administered to rats, coma did not occur and methanethiol in blood was barely detectable in blood. The addition of small amounts of fatty acid or NH\(_4^+\) (1/2 the CD\(_{50}\)'s) to rats administered the same small dose of methanethiol resulted in coma in all animals and twenty-fold increases in blood methanethiol. These experiments suggest that methanethiol and fatty acids interfere with the liver's metabolism of ammonia and that NH\(_4^+\) and fatty acids interfere with the detoxification of methanethiol to dimethyl sulfide.

These experiments may explain the toxicity of methionine. Methanethiol derived from methionine is not entirely metabolized by the liver, either because the load is excessive or because of liver disease. The brain is thus exposed to increased quantities of methanethiol which can cause confusion, disorientation, lethargy, and eventually coma.

The association of methanethiol and hepatic coma in humans was established in 1955 by the isolation of methanethiol and dimethyl sulfide from the urine of a patient in coma with massive hepatic necrosis and a prominent-fetor hepaticus, a foul smelling odour of the breath in patients with hepatic encephalopathy. Blood methanethiol in moderate or severe liver disease without overt encephalopathy is approximately 1-1/2 times normal. In the presence of encephalopathy, it is approximately 2-1/2 times normal. The average value observed in patients with hepatic coma and in animals with experimentally induced hepatic coma are similar, approximately 1000 nanomoles/liter. As with blood ammonia, serial determinations of blood methanethiol are more valuable than a single measurement. The changing stages of encephalopathy in a given patient are correlated with the changing concentrations of blood methanethiol.

Mercaptans, derived from methionine, come largely from intestinal bacteria in the gut. The most suggestive evidence that mercaptans actually have an etiologic
role in hepatic encephalopathy stems from observations in cirrhotics fed methionine. These patients become encephalopathic and develop a breath odour reminiscent of fetor hepaticus. The encephalopathy disappears when methionine is discontinued and can be prevented if a broad spectrum antibiotic is given before methionine.

To summarize, ammonia, methanethiol derived from methionine, and nonesterified fatty acids act synergistically to produce hepatic coma. Any one of these substances may produce coma by itself but relatively low amounts of these substances may produce coma if facilitated by one or both of the other two. If the schizophrenic syndrome is a type of hepatic coma due to the toxic effects of these three substances, then there are several explanations for the psychotic response of about half of schizophrenic patients to methionine:

1. Some nonreacting patients may have had lower quantities of nonesterified fatty acids or ammonia. Reacting patients may have higher quantities of these synergistic substances and so reacted to methionine.

2. The flora in the intestine or the liver of the nonreactors did not convert as much methionine to methanethiol and/or converted methanethiol to its less toxic metabolite dimethyl sulfide more efficiently.

3. Some nonreacting patients may have a disease due to other biochemical abnormalities.

III. Evidence for altered lipid metabolism in schizophrenia

Abnormal fatty acid metabolism in schizophrenic syndrome was first investigated by Mueller. These same patients have a normal response to blood glucose after insulin administration.

Obi and Nwanze found an increase in the total fatty acid content of blood of schizophrenics, due predominantly to increased linolenic acid. Linolenic acid content was also significantly increased in phosphatidyl choline, phosphatidyl ethanolamine, and sphingomyelin. Linolenic acid is one of the polyunsaturated fatty acids which are the most effective protein denaturants. Furthermore, the administration of evening primrose oil, a mixture of gamma-linolenic acid and linoleic acids, both polyunsaturated fatty acids, caused a marked deterioration of the clinical state of some schizophrenics.

Henn and Henn found an increase in phosphatidyl serine and a decrease in phosphatidyl choline and phosphatidyl ethanolamine in the red blood cell membranes of schizophrenic patients compared to normal controls.

Paradoxically, deficiency of unsaturated fatty acids may also be associated with schizophrenic syndrome and administration of unsaturated fatty acids and penicillin has also been effectively used to treat some schizophrenics. An explanation for this paradox may be related to the fact that in essential fatty acid deficiencies, there is increased conversion of lecithins to lyso-lecithins due to increased phospholipase activity. Thus, either an increase in lysolecithins with their strong detergent effects or an increase in unsaturated nonesterified fatty acids which have strong detergent effects are associated with a schizophrenic syndrome.

In a previous paper, the denaturing effect on proteins of nonesterified fatty acids and lysolecithins due to their detergent properties was emphasized. If such detergents are elevated in schizophrenic syndrome, evidence for proteins with altered conformation should exist. The work of Frohman and Harmison provides elegant, indirect proof for the existence of abnormal protein denaturants in serum from schizophrenics and will now be examined in detail.

A specific and homogeneous alpha-2 globulin has been isolated by Harmison and Frohman. This protein has identical amino acid composition, electrophoretic mobility and chromatographic elution properties in both schizophrenic patients and controls; however, the conformations of this protein measured by optical rotatory dispersion and circular dichroism were significantly different in patient and

1. After this paper was accepted, Gattaz et al (Biol. Psychiatry 22:421-426, 1987) reported that 70% of schizophrenic patients had phospholipase A2 activities in serum that were higher than those in controls but returned to normal after neuroleptic treatment.
control groups. The helical content of proteins can be estimated by optical rotatory dispersion and the results expressed by the term $F_{H}$. An $F_{H}$ value of 1.0 would indicate that all of a protein is in the alpha-helix conformation while a value of 0 would indicate the absence of alpha-helix conformation. For the controls, the mean $F_{H}$ was 0.018 while for the schizophrenic patients the mean $F_{H}$ was 0.17, nearly a tenfold difference in values for alpha-helix content. All patients in the study were drug-free for at least six months and were on a diet isocaloric with the controls and both groups were maintained on similar exercise routines. To avoid circadian or other biological rhythms, blood samples were taken only at 8 a.m. on Thursdays.

Since the amino acid compositions of the proteins in patients and controls were identical, the conformational differences in the proteins were apparently due to a difference in the environment to which the proteins were exposed in vivo. When a patient's alpha-2 globulin was dialyzed against the control's alpha-2 globulin, the patient's alpha-2 globulin lost some activity while the control's alpha-2 globulin gained considerable activity. From these dialysis experiments, it was concluded that a small molecule was lost from the patient's alpha-2 globulin.

What is the chemical nature of these small molecules? The alpha-2 globulin is a lipoprotein with about 80% lipid content with a large content of nonesterified fatty acids. The detergents sodium dodecyl sulfate and other alkyl sulfates have been shown to convert other proteins from nonhelical to partial alpha-helical conformations. Fatty acids have been implicated in the alteration of the function of multiple proteins. Therefore, it seems likely that, because of their detergent properties, and because the nonesterified fatty acids and/or lysolecithins are present in high concentrations in serum, lysolecithins and/or nonesterified fatty acids may be the small molecules responsible for the differences in conformation of alpha-2 globulin in patients and controls. Since lysolecithins are produced by phospholipase $A_2$, the paper of Gattaz et al (footnote 1) offers additional evidence for the presence of high concentrations of lysolecithins in schizophrenic syndrome.

This work was not the first to indicate a physiochemical alteration in serum proteins in schizophrenics. Changes in the colloid stabilization of serum proteins from schizophrenics were reported as early as 1924. The serum proteins return to their normal physiochemical state if there is a remission in the disease.

Other work consistent with the presence of abnormal detergents is the finding of an increase in erythrocyte fragility in schizophrenics' blood. Lysolecithins have the ability to lyse erythrocytes. The finding of demyelinated nerve fibers in the brains of schizophrenics is also consistent with the known demyelinating action of lysolecithins.

Clinical studies consistent with a role for both abnormal fat and abnormal methionine metabolism in schizophrenic syndrome have been performed in the Soviet Union. Schizophrenic patients are put on a 28 day fast in which they lose 15 - 16% of their total body weight. They are hospitalized during the fast. All patients receive as much water as they desire but they must take a minimum of one liter a day. A minimum of three hours of exercise a day is also required. The fast has a dangerous period during which thrombosis may occur in certain patients and anticoagulants may be required during this critical time. Cholesterol increases during the fast and then decreases as recovery takes place. Acidosis due to extensive fat metabolism occurs between days two and twelve of the fast but then diminishes. A clear cut acidotic "crisis" in which symptoms intensify is associated with the best therapeutic effect. Although blood glucose falls during the most acidotic phase of the diet, it returns to normal by the twentieth to twenty-fifth day of the diet. This therapy has been effective in treating 64% of cases of chronic schizophrenic syndrome without the use of drugs. The clinical appearance of the patients who undergo this treatment is not that of a starving person. The skin colour is good and muscle and skin tone is healthy. At the end of the 28 day fast, a vegetarian diet must be maintained. Cheese and milk are permitted but ingestion of meat, eggs, or fish leads to
relapse. When patients are discharged from the hospital, they are advised to take prophylactic fasts of three to five days each, but not to exceed a total of ten days a month.

The relapse of schizophrenic syndrome due to meat and/or fish ingestion is similar to that in hepatic coma. Meat and/or fish may often precipitate hepatic coma in patients with liver disease due to the high methionine content of these foods. Milk, cheese, and vegetable proteins have very low methionine concentrations. Meat and fish are also restricted from the diets of patients with hepatic coma and they may be fed synthetic diets low in methionine.

The increase in cholesterol in schizophrenics during the therapeutic fast may also indicate an abnormal cholesterol metabolism. Schizophrenics exhibit considerable variations from day to day with occasional gross changes developing at a pace not observed in normal individuals. Serum cholesterol is usually low in the early stages of schizophrenia and abnormal high density lipoproteins have been found in schizophrenics. The effects of antipsychotic drugs on cholesterol metabolism will be considered in detail in the section on drug therapies.

IV. Drug therapies used to treat schizophrenia

A. Phenothiazines

The phenothiazine drugs, which are also termed neuroleptics or antipsychotic tranquilizers, are still the most popular drugs used in the treatment of schizophrenic syndrome and other psychoses. From 1955 to 1965 at least 50 million patients received phenothiazines and more than 10,000 publications have dealt with their actions. Although phenothiazines are highly effective and were a major breakthrough in the treatment of schizophrenic syndrome, significant side effects are associated with their use. The most significant side effects are called extrapyramidal (referring to the neuroanatomical region responsible for these motor effects) and parkinsonian-like syndrome, involuntary muscle movements including abnormal eye movements and facial grimacing and motor restlessness. Most of these side effects can be controlled by dosage adjustment or concomitant administration of certain antihistamine drugs. Phenothiazine and other neuroleptic drugs bind in vitro to a form of the postsynaptic dopamine receptor obtained from the brains of man and other mammals and this reaction of neuroleptic drugs is currently the most popular explanation for the efficacy of neuroleptics in treating this disorder. A tremendous volume of research resulting in numerous monographs has been done on these neuroleptic receptor interactions; however, fashions exist in medical science as in the rest of society, and emphasis on this one aspect of these drugs has drawn attention away from their other interactions.

Chlorpromazine, a commonly prescribed phenothiazine, is a lipophilic drug that is bound to a wide variety of proteins including membranes of red cells, albumin, lipoproteins. The affinity and capacity of lipoprotein binding is at least as high as that of albumin and is equally distributed on high density lipoprotein, low density lipoprotein, very low density lipoprotein and on the chylomicrons. An increase in body weight in man has been consistently noticed as a side effect of chlorpromazine treatment, and it has been demonstrated that chlorpromazine inhibits the hydrolysis of triglycerides by lipases from lung and adipose tissue. In addition, Seppala et al demonstrated that chlorpromazine was an inhibitor of lecithin cholesterol acyltransferase (LCAT) both in vitro and in vivo. Lecithin-cholesterol acyl transferase catalyses the transfer of a fatty acid group from lecithin to cholesterol forming lysolecithin and cholesterol esters (Figure 4). Thus, an effect of chlorpromazine is to diminish the concentration of the powerful detergent lysolecithin by inhibition of lecithin-cholesterol acyl transferase. The phenothiazines and other neuroleptic drugs such as haloperidol are also effective inhibitors of phospholi-pase, which is elevated in many schizophrenics and returns to normal following neuroleptic therapy (Footnote 1).
Figure 1. Toxic products of methionine metabolism.

Figure 2. Dose response curves for the production of coma by NH$_4^+$ in the presence and absence of a subcoma dose of methanethiol (MT) in rats. Reproduced with permission from Zieve et al, / Lab Clin Med 1974;83:16-28.

Figure 3. Dose response for the production of coma by the nonesterified fatty acid octanoate in the presence and absence of subcoma doses of methanethiol (MT). Reproduced with permission from Zieve et al, / Lab Clin Med 1974; 83:16-28.
Figure 4. Formation of lysolecithins and cholesterol esters catalyzed by lecithin cholesterol acyl transferase (LCAT).

Figure 5. Antilipolytic effect of nicotinic acid and rebound effect. Each curve represents the mean response of four dogs injected with intravenous nicotinic acid at doses indicated on each curve. Reprinted with permission from Pereira. J. Lip. Res. 1967;8:239-44.

Figure 6. Antilipolytic effects of propranolol and nicotinic acid on exercise-induced lipolysis. Nicotinic acid was administered before the rest period and after every work period. Work was pedaling a stationary bicycle at a prescribed rate. Each work and rest period was 50 minutes in length. Reproduced with permission from Bulow Scand. J. Clin. Lab. Invest. 1981,41:415-424.
now like to consider the effect of two other drugs used to treat schizophrenic syndrome, propranolol and nicotinic acid, on the production of nonesterified fatty acids and/or lysolecithins.

B. Nicotinic Acid

Nicotinic acid (niacin) is an essential vitamin, a deficiency of which causes the disease pellagra. Pellagra is characterized by three prominent clinical symptoms: dermatitis, diarrhea and dementia (psychosis). Because the psychosis in pellagra is very similar to schizophrenic syndrome, the psychiatrist Hoffer investigated the use of megadoses (ten to hundredfold times the recommended daily allowance) of nicotinic acid for the treatment of schizophrenic syndrome and, based on clinical experience, he and a large number of "non-mainstream" psychiatrists have promoted the use of nicotinic acid to treat and "cure" schizophrenic syndrome. Such treatment was also endorsed by Linus Pauling in a controversial article in Science entitled "Orthomolecular Psychiatry". The use of this vitamin has been extremely controversial because of failures of some studies to confirm the work of Hoffer. In addition to treatment failure with this vitamin by some groups, major criticisms of this drug therapy centre on two issues: (1) no evidence for nicotinic acid deficiency, abnormal requirements for excessive nicotinic acid or abnormal metabolism of nicotinic acid have been established in schizophrenic syndrome; (2) lack of any other strong theoretical basis for its efficacy.

Here I would like to suggest a theoretical basis for both the efficacy claimed by Hoffer, Pauling and their adherents, as well as a rational basis for the treatment failures encountered by others. The anti-lipolytic effect of nicotinic acid has been known for over 30 years but to my knowledge has never been connected with its efficacy in the treatment of schizophrenic syndrome. This effect takes place only at pharmacological and not physiological doses. Figure 5 from shows a typical profile from experiments in dogs obtained after a relatively high dose of nicotinic acid — a dose much larger than that needed to prevent pellagra. Following drug administration there is a sharp decline in plasma nonesterified fatty acids concentrations; however, after the initial decrease in plasma nonesterified fatty acids there is a rebound effect and plasma nonesterified fatty acids rise to values greater than the original baseline values. Similar results have also been obtained in humans. The duration of the suppression of plasma nonesterified fatty acids concentrations is dose dependent. When the dose of nicotinic acid reaches very high levels, the rebound effect can be essentially eliminated even after exercise (Figure 6) which usually causes marked increases in nonesterified fatty acids values. Hoffer and his adherents have always proposed extremely individualized dosage adjustments of nicotinic acid for their patients.

If the efficacy of nicotinic acid depends on the suppression of toxic nonesterified fatty acids while avoiding the rebound effect, then titration of the proper dosage
for each patient would require considerable adjustments to maintain a therapeutic response. Indeed, maintaining therapeutic drug concentrations for drugs such as tricyclic antidepressants, as an example, requires careful adjustments of dosage even when serum concentrations of drugs can readily be measured in the laboratory.

Again, the work of Zieve can be used to clarify some of the clinical results of nicotinic acid treatment of schizophrenics. The toxicity of nonesterified fatty acids is also dependent on ammonia and methanethiol loads. Methanethiol and/or ammonia in certain individuals might be so high that these compounds alone might induce psychosis. There is good clinical evidence to support this possibility. Ananth et al\textsuperscript{26} reported that nicotinic acid was effective in treating psychosis induced in schizophrenics on low doses (1.2 grams per day) of methionine but not high doses (20 grams per day) of methionine.

Nicotinic acid is also used in the treatment of hypercholesterolemia, hypertriglyceridemia, and mixed hyperlipemia. It is a potent suppressor of low density lipoprotein and very low density lipoprotein levels in most hyperlipemic states and is a very effective cholesterol lowering drug. The doses used to treat hyperlipemia are in the same range\textsuperscript{76} as the doses that Hoffer recommends for the treatment of schizophrenic syndrome.\textsuperscript{43, 44}

C. Propranolol

Propranolol is a beta-adrenergic blocking agent which was synthesized in 1964. It is most frequently used as an antihypertensive and antiarrhythmic agent; however, events in Israel in 1969 led to a very important discovery.\textsuperscript{49} A female patient was admitted to an Israeli hospital with severe abdominal pains, reddish colour of her urine, a severe psychosis and laboratory findings consistent with variegate porphyria. Her heart rate reached 180/min. and her blood pressure continued to rise. At the time, a daily dose of propranolol of 160 mg/day was considered to cause maximal beta-adrenergic blockage; however, a propranolol dosage of 400 mg/day was needed to control symptoms. This dosage was regarded as unwarranted and dangerous. Although a reduction in pulse rate and blood pressure by propranolol were expected, a complete disappearance of the abdominal pains and psychosis also occurred. Withdrawal of propranolol caused all previous symptoms to recur and intensify.

A second patient with severe psychosis, including auditory, visual and tactile hallucinations, was admitted to the same hospital. Since a laboratory result indicated the possibility of porphyria, the patient was treated with propranolol at a dosage of 800 mg/day because of the good response of the first porphyria patient. It was later found that the laboratory result was an error, but, as in other important advances in medicine, it was an important and fortunate error. The patient responded very quickly with a complete recovery. Withdrawal of propranolol led to a recurrence of the psychosis. Based on these initial clinical responses, several other clinical trials were conducted on patients with schizophrenic syndrome, manic depression and postpartum psychosis and very good results were obtained with this drug therapy.\textsuperscript{49}

Although toxicity in schizophrenic patients occurred when propranolol was too rapidly increased, toxicity was well controlled when the dosage was increased more gradually. When the symptoms of schizophrenic patients treated with propranolol remitted, the patients were judged "lucid, alert, and lacked the apathetic, unreactive appearance of many patients who are stabilized on phenothiazine drugs".\textsuperscript{53} Patients in remission who discontinued propranolol had relapses of schizophrenic behaviour which was again controlled when propranolol was reinstituted.\textsuperscript{53}

A larger scale uncontrolled drug trial involving 55 patients was later conducted by Yorkston.\textsuperscript{51} In this study, 29 of the patients were given propranolol only while the rest of the patients were given propranolol in addition to their current neuroleptic drugs (phenothiazines or haloperidol). All schizophrenic symptoms remitted in 28 of the 55 patients. Seventeen of the 29 patients taking only propranolol experienced complete remission of symptoms and 27 of the 29 patients on only propranolol experienced at least moderate
improvement. In addition, two complete remissions were obtained in patients who had been ill for more than 20 years.

Based on the success of the controlled study, a controlled blind study conducted in which either propranolol or a placebo was added to the regular treatment (phenothiazines or other antipsychotic tranquilizers) of 14 patients who had chronic schizophrenic syndrome for an average of 9 years.

Figure 7 shows the results of this clinical trial. The mean score in this figure refers to the score of a standard psychiatric rating test used to evaluate schizophrenic syndrome. The propranolol and placebo groups were not significantly different at the beginning of the trial but the propranolol treated group experienced very significant improvement by the end of the trial. The code used in the blind study was broken after week 12. (5 of the 7 patients in the placebo group were then given propranolol in addition to their regular medication and showed considerable improvement.) Other studies have confirmed the effectiveness of propranolol in managing both acute and chronic adult schizophrenic patients when it was added to the drug regimen of patients who had not responded to phenothiazines or other neuroleptics alone.

Propranolol is a potent inhibitor of lecithin-cholesterol acyltransferase and inhibits the release of nonesterified fatty acids from adipose tissue.

A good example of the antilipolytic effect on both propranolol and nicotinic acid is given in human experiments reproduced from Figure 6. Six normal human volunteers performed exercise for periods of 50 minutes. Blood samples were taken during 10 minute rest periods that were scheduled between exercise ("work") periods. Blood was again sampled after a 50 minute rest period at the end of the last exercise period. Exercise caused a marked increase in plasma nonesterified fatty acids.

Propranolol at a dose approximately 1% of that administered to schizophrenics dramatically decreased plasma nonesteri-

2. Propranolol is also an inhibitor of phospho-lipase A2 (Vanderhock and Feinstein, Molecular Pharmacol. 16, 171-180, 1979).
in both disorders.

VI. Evidence that schizophrenia is a systemic rather than a central nervous system specific disease: Pathological and viral studies.

A. Muscle and enzyme changes

Increased activity of the enzyme creatine phosphokinase (CK) (E.C.2.7.3.2) and aldolase (E.C.4.1.2.7) have been found in the serum of acutely psychotic patients with both manic depression and schizophrenic syndrome.

Chronically psychotic patients did not have any increase in the activity of these enzymes even when they were experiencing an exacerbation of their psychosis which necessitated rehospitalization. Isozyme studies have established the MM isozyme is responsible for the increased CK activity. The increase in CK or aldolase activity was generally present at the onset of a psychotic episode and lasted for five to ten days after hospitalization. The increased enzyme activities ranged up to 50-fold normal limits. No increases in lactic dehydrogenase, acid phosphatase, alkaline phosphatase, aspartate amino transferase, or alanine amino transferase were found in the sera of patients with elevated aldolase or CK.

Since intramuscular injection of drugs may cause elevated CK results, a study excluding psychotic patients who had intramuscular injections was done and confirmed that the elevations were not an artifact induced by injections. In addition, oral pheno-thiazines had no effect on serum CK activities in these patients. Cerebrospinal fluid CK values were normal in acute psychotic patients with increased serum CK values.

Because of the abnormal increases in CPK MM isozymes in acute psychosis, Meltzer and his colleagues evaluated skeletal muscle biopsies from acute schizophrenics. They found that the muscle cells from these patients had a histological abnormality termed "Z-band spreading" and that muscle biopsy samples alone could be used to distinguish normal and schizophrenic populations using histological criteria.

Elevated CK MM isozymes and abnormal muscle histology have also been reported in Reye's syndrome.

B. Comparison of liver pathology and liver function tests in schizophrenic syndrome, hepatic encephalopathy, and Reye's syndrome

Almost all cases of hepatic encephalopathy occur in individuals with cirrhosis of the liver. The essential morphological features of cirrhosis are increased fibrous tissue, nodular parenchymal regeneration, and derangement of the vasculature. Portal-systemic shunts develop that result in the shunting of blood from the intestine around the liver as a whole or around viable hepatic cells during passage through the damaged liver. The most common causes of cirrhosis are alcoholism and viral hepatitis caused by types A or B hepatitis virus, cytomegalovirus, herpes simplex, rubella, Epstein-Barr virus, and others. Fatty infiltration of the liver is common in alcoholic cirrhosis and may concur with other causes as well especially with hepatotoxins. In Reye's syndrome, fat in the liver usually accumulates in small vacuoles rather than in large cytoplasmic droplets. The most common causes of encephalopathy in a large series of cirrhotic patients in order of decreasing frequency were: azotemia (due to diffusion of urea in the blood into the intestine where it formed ammonia due to the action of intestinal bacteria), drug induction, gastrointestinal hemorrhage (due to ammonia production from purines and proteins in the blood), hypokalemic alkalosis, excess dietary protein (especially meat), severe infection, and constipation.

Severe vomiting is considered an essential clinical symptom to support a diagnosis of Reye's syndrome. This symptom is not usually found in schizophrenic syndrome but is also not usually found in adult hepatic coma either.

Although aminotransferases are elevated in viral hepatitis and in some cases of alcoholism, in subclinical anicteric cases evidence of disturbed hepatic function is obtained by tests such as the hippuric acid function test, serum bile acids, or by an exogenous overload of organic anions such as bromsulphalein (BSP) or indo-cyanine green.

Sourkes has summarized the findings.
on hippuric acid excretion in schizophrenic syndrome. In the initial study in 1938, 100% of all catatonic schizophrenics tested had low rates of hippuric acid excretion. In a repeat test, the initial study was confirmed and it was noted that patients with higher rates of hippuric acid excretion had undergone remission or some improvement. Nine different research groups confirmed the initial studies and established that the hippuric acid excretion rate was correlated with clinical improvement.

Pathological liver findings in schizophrenia date back the the early 1900's and have been emphasized by V. M. Buscaino. Almost 1200 brains of schizophrenic patients have been evaluated by autopsy and similar findings have been obtained by brain biopsy. Neuronal damage is concentrated in the cortex, basal ganglia, and brain stem with involvement of the glial G. A. Buscaino, and a large number of other Italian investigators for over half a century. In retrospect, it appears that the great outburst in knowledge about neurotransmitters and hallucinogens in the 1950's and 1960's drained away interest from this substantial work. I will review just the highlights of a review by V. M. Buscaino. Liver weight was reduced 18% in male schizophrenics and 25% in female schizophrenics. Reduced liver weight is common in post hepatic cirrhosis. Pathological changes were reported in 83% of 207 cases. The most common changes were fatty degeneration and infiltration, vacuolar degeneration, and parenchymatous foci of cell disintegration. Similar pathological changes were found in biopsies from living patients. Over 30 different liver function tests have been reported as abnormal in a high percentage of schizophrenics, including the bromsulphalein retention test, hippuric acid excretion after benzoic acid loading, and a large number of flocculation and turbidity tests.

C. Comparison of central nervous system pathology in schizophrenic syndrome, Reye's syndrome, and hepatic coma.

The pathology of the central nervous system in the schizophrenic syndrome has been documented for over 60 years by a large number of pathologists. Clusters of disintegration have also been reported with nerve fibers with decreased or complete demyelination by numerous investigators. The dissociative behavioural manifestations of the disease have been attributed to the physical disruptions of the nerve pathways which in the normal individual allow for the expression of "appropriate" behaviour. Glial proliferation in the region of the hypothalamus, hippocampus, and other diencephalic structures have been reported. The presence of glial nodules in the brain stem, which were present in seven of eight schizophrenic patients but not in controls have also been reported. The older data is, however, even more convincing than the recent data since the early studies were done many years prior to the advent of antipsychotic tranquilizers; the more recent studies are complicated by possible drug-induced neuropathological damage.

In chronic liver diseases that result in hepatic coma, the neuropathological findings are strikingly similar to those described in schizophrenic syndrome: "The protoplasmic astrocytes increase in number and size, taking on a characteristic appearance identified as the Alzheimer Type II astrocyte. These cells frequently appear in pairs or clusters. These more distinctive cells are more numerous in all parts of the cerebral cortex, the basal ganglia, and brain stem, approaching twice the number seen in patients with chronic liver disease with overt encephalopathy or in normal controls. Similar increases in Alzheimer Type II astrocytes have been observed in chronic hyperammonemia associated with congenital urea cycle enzyme deficiencies or produced in animals experimentally by portacaval shunts, repeated infusions of an ammonium salt, or injections of urease." The same type of astrocytosis also occurs in Reye's syndrome.

Why are the astrocytes a major site of central nervous system pathology in schizophrenic syndrome, hepatic coma, and Reye's syndrome? It has been found that the astrocytes contain glutamic dehydrogenase and glutamine synthetase, enzymes that catalyze the detoxification of ammonia. The astrocytes are interposed between the capillaries and the neurons and
the astrocytes appear to be metabolically involved in regulating the environment of the neurons.

The anatomic location of the astrocytes gives maximal exposure to toxic substances in the blood.

D. Abnormal reproductive function in schizophrenics and liver disease.

As early as 1919, it was reported that male schizophrenics had abnormal testes and a low androgen: estrogen ratio was reported in male schizophrenics. Abnormal androgen: estrogen ratios have also been found in males with severe liver disease. Testicular biopsies on male schizophrenics have given mixed results. In one study, no abnormalities were reported. In another, pathological features similar to those found in patients with infertility were found. In a third, a unique form of tubular atrophy was found in schizophrenic males.

E. Other diseases in which psychosis is a common clinical symptom and in which detergents play an important role.

If a derangement of nonesterified fatty acids and/or lysolecithin metabolism is a contributing factor in schizophrenic syndrome, then it would be expected that schizophrenia-like symptoms would be present in other disease states in which these detergents are elevated.

The term pancreatic encephalopathy was introduced by Rothermich and Von Haam to describe a syndrome of agitation and confusion, sometimes with hallucinations and clouding of consciousness, dysarthria, and changing rigidity of the limbs in association with acute pancreatitis. In acute pancreatitis, lysolecithins and non-esterified fatty acids are elevated due to the excessive release of lipases and phospho-lipase from the pancreas.

F. Possible significance of age of onset and comparison with hepatic porphyrias

Torrey has reviewed the age distribution of schizophrenic syndrome and the following material is drawn from this source. Schizophrenic syndrome in 75% of all cases begins between the ages of 15 and 25. The incidence of childhood schizophrenic syndrome is less than one-twentieth that of adult schizophrenic syndrome. In general, the younger the age at onset, the poorer the prognosis. Persons who are diagnosed over the age of 30 are likely to have a good prognosis. The diagnosis of schizophrenic syndrome is rare after age 40. Statistics compiled in 1899 on the age at onset are the same as the statistics today. Males who develop this syndrome are, on the average, five years younger than females with this disease. Men with this syndrome have a poorer prognosis, on average, than women with this syndrome. The age at onset coincides with the age range in which steroid sex hormones reach maximal values and has led some researchers to conclude that the disease may be triggered by the secretion of these hormones.

The hepatic porphyria, acute intermittent porphyria, bears some similarities to schizophrenic syndrome. Acute intermittent porphyria is inherited as an autosomal dominant disease with highly variable clinical symptoms. The age at onset is usually after puberty, suggesting a steroid induction and, indeed, an attack may be induced by estrogen administration. There is defective testosterone metabolism in males in this porphyria as in schizophrenic syndrome and the liver function test, the bromsulphalein retention test, is abnormal in acute intermittent porphyria as in schizophrenic syndrome. Abnormal lipoprotein metabolism occurs in both diseases and constipation is common in both.

Neurological manifestations are common. Abdominal pain and psychiatric problems including hallucinations may occur in this porphyria. The psychiatric symptoms and abdominal pain may be treated successfully with chlorpromazine. The biochemical defect in this disease is a deficiency of the enzyme that converts porphobilinogen to uroporphyrinogen I. In the liver, this deficiency leads to increased inducibility of aminolevulinic acid synthetase by drugs or steroid hormones. The disease is diagnosed by an increase in porphobilinogen, a porphyrin precursor. A substance termed "kryptopyrrole" has been isolated from the urine of 50% of schizophrenics and it has been suggested that this compound may be produced by an abnormality in porphyrin metabolism.
G. Toxic substances in schizophrenic syndrome

In my previous article,\textsuperscript{1} evidence for the toxic involvement of unsaturated long-chain, saturated short- and medium-chain nonesterified fatty acids and lysolecithins in Reyes syndrome was examined.

The major points of the previous article are: (1) nonesterified fatty acids and lysolecithins at concentrations found in body fluids such as serum can denature a wide range of proteins because of their detergent properties; (2) the toxicity of nonesterified fatty acids to cellular organelles such as mitochondria and to experimental animals is very highly correlated to the protein-denaturing properties of different nonesterified fatty acids; (3) in Reye's syndrome, in which the most extensive research on nonesterified fatty acids has been done, the nonesterified fatty acids that are most significantly elevated are the short- and medium-chain (C\textsubscript{6} to C\textsubscript{12}) saturated nonesterified fatty acids and the long-chain (C\textsubscript{16} to C\textsubscript{22}) unsaturated nonesterified fatty acids. These nonesterified fatty acids are the same ones which are the most effective protein denaturants and are also those most effective in coma induction; (4) the increased nonesterified fatty acids in Reye's syndrome associated with viral disease appear to be predominantly derived from a phospholipase-catalysed conversion of lecithins to lysolecithins and nonesterified fatty acids, significant because lysolecithins are also very effective protein denaturants.

A voluminous body of research to demonstrate toxicity of body fluids from schizophrenics exists in the literature and has been reviewed by Buscaino\textsuperscript{8} and Sourkes.\textsuperscript{6} These phenomena induced by body fluids or extracts of body fluids from schizophrenic patients include: induction of electroencephalogram and behavioural changes in rats, disturbance in web construction in spiders, decreased rope-climbing speed in rats and toxicity to cells in tissue culture. A major deficiency of these studies is that no attempts to biochemically identify the toxic substance(s) were performed. Recent work summarized in my previous article\textsuperscript{1} shows that lysolecithins and nonesterified fatty acids denature enzymes and binding proteins, disturb the function of subcellular organelles such as mitochondria, interfere with normal organ function of the heart, liver and lungs and cause electroencephalogram changes in experimental animals. The cellular toxicity of schizophrenic serum was investigated by Fedoroff and Hoffer.\textsuperscript{7} A very high proportion of sera form schizophrenic patients were extremely toxic (4+) to L cells. Interestingly, sera from patients admitted for surgery exhibited toxicity similar to the sera from schizophrenics. The investigators concluded that (1) the cause of the toxicity of serum from patients in both groups may be similar or identical, possibly related to some stress mechanism or (2) that in each group the serum toxicity may be due to different substances, only the end result (toxicity) being similar. Since methanethiol, nonesterified fatty acids, and ammonia are all toxic substances, these agents might well account for the toxicity of body fluids from schizophrenics. Although many of the toxicity studies were replicated in other laboratories, not all laboratories could confirm each study. Methanethiol and ammonia are both volatile substances and would be difficult to preserve unless great precautions were taken. If these substances are indeed the major toxic substances in body fluids from schizophrenics, it would be very difficult to replicate each toxicity study because the toxic substances would be present at different concentrations in each serum and would be preserved to different extents in each serum. Differential stabilities of toxic factors from schizophrenic body fluids have been reported.\textsuperscript{98} The blood factor modifying rat behaviour has been reported to be so unstable that it must be immediately stored under hydrogen; storage under nitrogen or air leads to irreversible decomposition.\textsuperscript{98} However, the serum factor toxic to tissue cells retains toxicity after months of freezing and storage.\textsuperscript{98} Methanethiol would form disulfide bonds with blood proteins unless stored under hydrogen, whereas lysolecithins and nonesterified fatty acids are stable under frozen storage.

Other evidence supporting the existence of toxic substances in schizophrenic syndrome comes from transfusion studies.\textsuperscript{98} Remission from schizophrenic syndrome has been obtained for as long as a month.
by the transfusion of blood from normal people. Conversely, infusion of schizophrenic blood into normal volunteers produced schizophrenic symptoms but others could not replicate the results of these experiments.

Although not every toxicity study has been replicated in every laboratory, the sheer volume of studies reporting toxicity of body fluids from schizophrenics convinces me that this work should be carefully considered. The recent finding of elevated serum phospholipase A₂ in serum from schizophrenics (Footnote 1) gives additional support for these early studies. Lysolecithins are the predominant toxic material produced by phospholipase A₂ that is the active component of cobra and rattlesnake venoms.

VII. Possible Viral Connections

Viral infections have often been associated with schizophrenic syndrome. Increased incidence of schizophrenic syndrome followed the 1918 influenza epidemic. Encephalitis due to herpes simplex virus, influenza virus, cytomegalovirus, and encephalitis lethargica often produce schizophrenic syndrome. Herpes simplex encephalitis is the most common nonepidemic viral encephalitis in the United States, is not a seasonal disease, and affects all ages. Fifty to seventy percent of untreated patients die. A brain biopsy is the only definitive method of diagnosis. Since virology studies are rarely done for psychiatric admissions, the possibility that viral infection may be responsible for some cases of schizophrenic syndrome remains.

Since phospholipase may also be released by disruption of cell membranes by viral infection, phospholipase may be a common mediator of the encephalopathy produced in both viral encephalitis and schizophrenic syndrome.

Summary

A summary of biochemical and clinical findings in hepatic coma, Reye's syndrome, and schizophrenic syndrome is given in Table 1. Hepatic encephalopathy and/or Reye's syndrome can be caused by drugs, viral infection, inborn errors of metabolism involving ammonia or fatty acid metabolism, toxic environmental substances, excessive ingestion of meat and/or fish containing high concentrations of methionine or constipation. Zieve has developed convincing clinical and experimental animal evidence that hepatic encephalopathy is due to a combination of the methionine metabolite methanethiol, ammonia, and nonesterified fatty acids. Lysolecithins are as toxic as nonesterified fatty acids due to their detergent effects. Ingestion of animal proteins with high methionine content causes relapse of diet-treated schizophrenics. Methionine causes induction of acute psychosis in schizophrenics but can be reversed by the antilipolytic drug nicotinic acid if the dose of methionine is not too high. Two other drugs that have been proven to be highly effective in the treatment of schizophrenic syndrome, the phenothiazines and propranolol are potent inhibitors of lysolecithin production because of lecithin-cholesterol acyltransferase and phospholipase A₂ inhibition. These drugs are also inhibitors of adipose tissue lipolysis. Fasting, which depletes much of the body fat, initially exacerbates schizophrenic symptoms but eventually "cures" this disorder in the majority of patients. Prophylactic fasts are necessary to prevent relapse.

VIII. A Plan of Action for Improved Treatment of This Disease

1. The fasting and exercise treatment for schizophrenic syndrome used in the Soviet Union should be critically examined by a representative clinical and research team from the United States and if favourable, similar clinical trials should be established in the United States and elsewhere.

2. The use of propranolol, nicotinic acid, and antipsychotic drugs should be tested in conjunction with dietary therapy of the disease. The naturally occurring substance CDP choline is a phospholipase inhibitor that has proven very effective in the treatment of acute pancreatitis" and might prove equally effective in treating the patients with schizophrenic syndrome who have elevated phospholipase.

3. New tests for the total detergent activity
## Table 1
Summary of Clinical and Laboratory Findings in Schizophrenia, Reye's Syndrome and Hepatic Coma

<table>
<thead>
<tr>
<th>Biochemical or Clinical Features</th>
<th>Reye's Syndrome</th>
<th>Schizophrenic Syndrome</th>
<th>Hepatic Coma</th>
</tr>
</thead>
<tbody>
<tr>
<td>May be precipitated by viral infection</td>
<td>Yes 1, 10, 15, 16</td>
<td>Yes 11-14</td>
<td>Yes 3, 89, 90</td>
</tr>
<tr>
<td>Hallucinations and/or psychotic behaviour</td>
<td>Yes 3, 4</td>
<td>Yes 2</td>
<td>Yes 3, 10, 89</td>
</tr>
<tr>
<td>Elevated blood ammonia</td>
<td>Yes 10, 18</td>
<td>Yes 9, 17, 19</td>
<td>Yes 3</td>
</tr>
<tr>
<td>Abnormal metabolism of nonesterified fatty acids</td>
<td>Yes 1, 10</td>
<td>Yes 21-23</td>
<td>Yes 58</td>
</tr>
<tr>
<td>Elevated CPK MM isoenzyme in serum</td>
<td>Yes 87</td>
<td>Yes 83,84</td>
<td>?</td>
</tr>
<tr>
<td>Abnormal muscle histology</td>
<td>Yes 88</td>
<td>Yes 85,86</td>
<td>?</td>
</tr>
<tr>
<td>Abnormal sensitivity to methionine administration</td>
<td>Not tested</td>
<td>Yes 25-29</td>
<td>Yes 3, 58, 59</td>
</tr>
<tr>
<td>Elevated serum phospholipase</td>
<td>Yes 20</td>
<td>Yes (Footnote 1)</td>
<td>?</td>
</tr>
<tr>
<td>Central nervous system damage involving astrocytes in the cerebrum basal ganglia, and brain stem</td>
<td>Yes 18</td>
<td>Yes 8, 9, 37, 39</td>
<td>Yes 3, 91</td>
</tr>
<tr>
<td>Body fluids may be toxic to various biological systems</td>
<td>Yes 1, 16</td>
<td>Yes 5-8</td>
<td>?</td>
</tr>
<tr>
<td>Abnormal androgen metabolism</td>
<td>Not applicable</td>
<td>Yes 92</td>
<td>Yes 90</td>
</tr>
<tr>
<td>Abnormal electroencephalograms</td>
<td>Yes 15</td>
<td>Yes 40</td>
<td>Yes 89</td>
</tr>
<tr>
<td>Abnormal liver size and/or liver pathology</td>
<td>Yes 1, 3, 15</td>
<td>Yes 6, 8, 9</td>
<td>Yes 3</td>
</tr>
<tr>
<td>Insensitivity to painful stimuli</td>
<td>? 37,55</td>
<td>Yes 3</td>
<td>Yes 3</td>
</tr>
<tr>
<td>Associated with and/or exacerbated by severe constipation</td>
<td>? 2</td>
<td>Yes 3, 89</td>
<td></td>
</tr>
<tr>
<td>Abnormal liver function tests</td>
<td>Yes 15, 16</td>
<td>Yes 6, 8, 9, 30-34</td>
<td>Yes 3, 90</td>
</tr>
<tr>
<td>Fatty infiltration of the liver</td>
<td>Yes 1, 10, 15</td>
<td>Yes 8, 9</td>
<td>Yes 90</td>
</tr>
<tr>
<td>Severe vomiting</td>
<td>Yes 15, 16</td>
<td>No</td>
<td>Usually no 10</td>
</tr>
<tr>
<td>Symptoms exacerbated by ingestion of meat</td>
<td>?</td>
<td>Yes</td>
<td>Yes 3, 68</td>
</tr>
</tbody>
</table>

* Reference numbers are given for each of the features included in the table.
of serum should be developed and used for monitoring therapy in clinical research groups. Lysolecithins, phos-pholipase, nonesterified fatty acids, lecithin cholesterol acyltransferase, total cholesterol, cholesterol esters, me-thanethiol, ammonia, porphyrin meta-bolities, and the bromsulphalein reten-tion test and/or other liver function tests should be used in a large clinical trial at admission and during therapy including therapies mentioned above in (1) and (2).

4. Serologic tests for viruses associated with schizophrenic syndrome including herpes simplex, cytomegalovirus, influenza, and encephalitis lethargica should be done in all acute onset psychoses cases lacking an organic etiology at admission in a large clinical trial. Titer should be done at the time of admission and two weeks later to assess acute infection. Virus culture and perhaps even brain biopsy should be done on patients with significant rising titers.

5. A frozen serum bank for future biochemical or microbiological follow-up should be established for important experimental groups. At least ten 1 mL aliquots of serum drawn at admission, during therapy, and at discharge should be set aside.

6. The cooperation of foundations such as The National Alliance for the Mentally Ill and The American Schizophrenic Association should be solicited to provide public pressure for funding the necessary research to end this disease. As recommended by Torrey," a dramatically increased share (50% or more) of the federal mental health research budget should be devoted to schizophrenic syndrome research.

7. The diagnosis and treatment of schizophrenic syndrome should be main-streamed into the medical community and separate psychiatric institutions for treatment of this disease should be gradually eliminated as treatment of this disease becomes the province of internal medicine instead of psychiatry and/or psychiatrists treating schizophrenic syndrome are given advanced training in internal medicine.

8. Drug manufacturers should explore the development of alternative drug therapies for the treatment of this disease.

References


22. Mueller PS: Plasma free fatty acid response to insulin in schizophrenia. *Arch Gen Psych* 1962; 7:140-6.


Synergistic Effects of Metabolites in Schizophrenia

60. Zieve L, Doizaki WM, Lyftogt C: Brain methanethiol and ammonia concentrations in experimental hepatic coma and coma induced by injections of various combinations of these substances. / Lab Clin Med 1984; 104:655-64.
71. Bichel M: Binding of chlorpromazine and imipramine to red cells, albumin, lipoproteins and other blood components. / Pharm Pharmac 1975; 27:733-8.
75. Pereira JN: The plasma free fatty acid rebound induced by nicotinic acid. Lipid Res 1967; 8:239-44.
Addendum

After this manuscript was reviewed by several of my colleagues, I realized that there were several issues that need to be clarified.

First, coma is the end stage symptom of classic hepatic encephalopathy. In the beginning stages of classic hepatic encephalopathy, subtle personality changes or peculiar behaviour may be the only clinical symptoms that occur. I am not suggesting that most cases of schizophrenic syndrome are incipient cases of classical hepatic encephalopathy. Schizophrenic syndrome is a special type of hepatic encephalopathy. Schizophrenic syndrome has a distinctive pattern of incidence that suggests a steroid induction during adolescence that is similar to hepatic porphyrias. The clinical manifestations of schizophrenic syndrome bear little resemblance to a "full-blown" metabolic encephalopathy. Indeed, the diagnosis of this disorder depends on full orientation, intact memory, and cognition. However, the stuporous condition of some catatonic individuals, including the documented decreased sensitivity to pain, is similar to patients with classical hepatic encephalopathy prior to the development of coma. The hepatic porphyrias could be classified as hepatic encephalopathies and yet coma is not the usual end result of these disorders either.

Second, I emphasize that the evidence is overwhelming that phenothiazines do have an effect on dopamine receptors. However, I do not think the evidence that schizophrenic syndrome is a defect in dopamine receptors is at all convincing. Phenothiazines are inhibitors of many enzymatic reactions that may be unrelated to their therapeutic effects. Phenothiazines control both the psychotic behaviour and abdominal pain in the hepatic porphyria, acute intermittent porphyria. This disease is completely biochemically characterized and there is no evidence for a defect in dopamine metabolism in this disease. Ly-solecithins and nonesterified fatty acids denature all proteins. However, proteins differ widely in their susceptibility to these detergents and it is possible that observed changes in dopamine receptors induced by phenothiazines may be indirectly mediated by the antilipolytic effects of these drugs. Reduction of denaturing detergents would allow renaturation of dopamine receptors that might be unusually susceptible to detergent concentrations. The evidence cited in this paper demonstrate convincingly an alteration in the structure of serum proteins in schizophrenic syndrome. There is no reason to believe CNS proteins would not also be altered.

Third, I have found a dangerous tendency of current workers to discount much of the older literature, simply because it is old. The true meaning of research is to critically examine all previous work and then to integrate current findings with older work. I was deeply concerned that since many of the older investigators have died, retired or are nearing retirement, a whole era of research might be lost forever due to ignorance of or a lack of respect for the pioneering investigators in this field.