

The Biochemistry of the Schizophrenias

Libuse Gilka, M.D.1

The group of diseases called "inborn errors of metabolism" are usually characterized by an inherited defect of an enzyme catalytic activity leading to a metabolic block with an accumulation of metabolites before and a lack of metabolites behind the block (see Figure 1). The substrate which cannot be properly degraded because of such a block is metabolized on other minor pathways and induces an accumulation of products on these pathways. The accumulation of metabolites on the minor pathways is followed by further metabolic deviations, and frequently causes disturbances in the brain metabolism.

The degree to which our environment (physical, chemical, microbiological, and psychological) is injurious depends on our genetic legacy. As our control of environmental factors and pathogens improves, an increasing proportion of disease becomes endogenous rather than exogenous. Genetic diseases cannot fully be eradicated, but through a knowledge of the resulting biochemical deviations we can devise a rational treatment for such diseases.

A typical representative of an inborn error of metabolism is phenylketonuria, an inborn error of phenylalanine metabolism. In phenylketonuria, an inherited deficiency of an enzyme phenylalanine hydroxylase leads

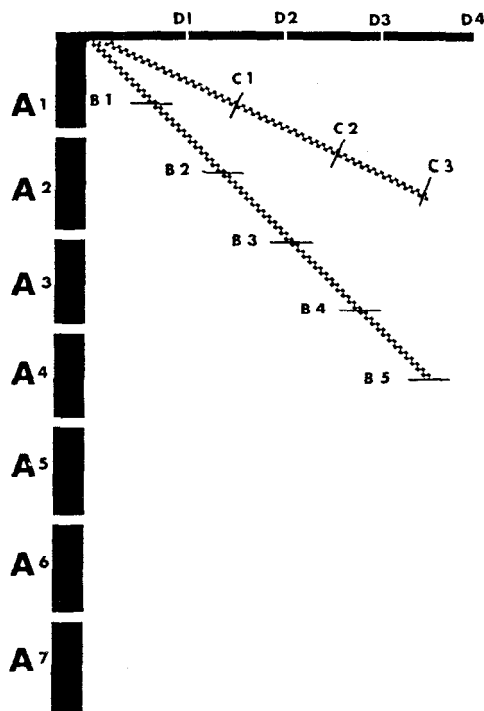
Condensed version of lecture presented at the Eighth Scientific Symposium of Academy of Orthomolecular Psychiatry, Toronto, April 30 - May 1, 1977. to a metabolic block on the phenylalanine-adrenalin pathway, followed by an increased degradation of phenylalanine on minor pathways. The shift of phenylalanine metabolism to minor pathways leads to a lack of tyrosine and its metabolites and an accumulation of phenylalanine derivatives on minor pathways, inducing further metabolic abnormalities and excretion of abnormal phenylalanine metabolites in the urine. Clinically phenylketonuria is characterized by usually severe retardation of mental development. Early dietary restriction of the essential amino acid phenylalanine and supplementation of the missing metabolite, tyrosine, can prevent the shift of phenylalanine metabolism to minor pathways, normalize urinary findings, and prevent mental retardation.

In schizophrenia, high urinary levels of abnormal derivatives of essential amino acid tryptophan have been found, especially during an acute exacerbation of psychotic behavior. Because of the similarity of the biochemical findings between phenylketonuria and schizophrenia—the excretion of abnormal urinary derivatives of essential amino acid phenylalanine in phenylketonuria and the excretion of abnormal urinary derivatives of essential amino acid tryptophan in schizophrenia—the biochemical and genetic studies on schizophrenia, done during the last few decades in North America and Europe, have

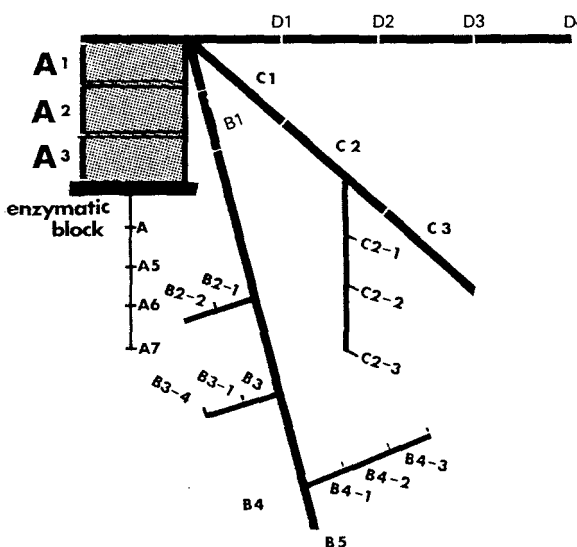
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FIGURE 1

NORMAL METABOLISM



INBORN ERROR OF METABOLISM



been reviewed to elucidate if schizophrenic symptoms, at least in some patients, might be connected with an inborn error of tryptophan metabolism. If so, we can deduce on the basis of principles, valid for all inborn errors of metabolism, a rationale for treatment and prevention of schizophrenia.

A careful analysis and synthesis of these studies confirms that in schizophrenia, at least in most of the chronic schizophrenics, the basic underlying metabolic defect is indeed a metabolic block on the tryptophan-niacin pathway, in most cases apparently due to an inherited defect of an enzyme 3-hydroxyanthranilate-oxygenase, and therefore that the principles valid for the treatment and prevention of inborn errors of metabolism may be applied also in the treatment and prevention of schizophrenia (Gilka,1975).

In normal individuals, tryptophan, an essential amino acid, is metabolized by 75 percent on the dominant pathway tryptophan-niacin into niacin. Niacin is a basic constituent of two very important coenzymes, NAD and NADP, which play a vital

role in the metabolism of the human organism. There have been described more than 100 chemical reactions in the human body dependent on NAD and NADP. NAD and NADP are also important in cell respiration and are structural components of the mitochondria. MAO enzymes are closely dependent on mitochondrial efficiency.

Price and his colleagues (Price et al., 1959) studied tryptophan metabolism in schizophrenia and found that schizophrenics are unable to metabolize tryptophan normally and their urinary levels of niacin degradative products are significantly decreased, but their metabolites proximal to niacin are increased.

The elevation of metabolites proximal to niacin in the urine of schizophrenic patients has also been observed by the other authors (Benassi et al., 1961; Cazzulo et al., 1966).

These studies, similar to the finding that excretion of N-methylnicotinamide is decreased in schizophrenics after loading

with L-tryptophan (Lozovskii, 1962), suggest that in schizophrenia there is a metabolic block on the tryptophan-niacin pathway.

A careful analysis of the results of these studies suggests that this block is due to a decreased activity of an enzyme, 3-hydroxyanthranilate oxygenase (Gilka, 1975).

The deduction that in schizophrenics the metabolic block on the tryptophan-niacin pathway is due to a defect of 3-hydroxyanthranilate oxygenase is further indirectly supported by an observation that sera from schizophrenic patients show a significantly decreased oxidation of 3-hydroxyanthranilic acid (Ehrensvar et al., 1960). This observation points to the conclusion that the activity of the enzyme responsible for this oxidation (i.e., 3-hydroxyanthranilate oxygenase) is apparently decreased.

In schizophrenics the metabolic block on the tryptophan-niacin pathway is followed by a lack of metabolites distal to the block, i.e., a lack of niacin, NAD, and NADP, and a shift of tryptophan metabolism to minor tryptophan pathways.

The suggestion that in schizophrenia there is a block on the tryptophan-niacin pathway leading to a lack of NAD and a shift of tryptophan metabolism to minor indole pathways has already been stressed several years ago by Hoffer (Hoffer, 1973).

The observation of Hoffer (Hoffer et al., 1957) verified by others (e.g., Osmond and Hoffer, 1962; Maslowskii, 1967; Kassay and Pinter, 1969; Hawkins et al., 1970; Saarma and Vasar, 1970), that niacin can improve the condition of schizophrenics, confirms the importance of supplementation of missing metabolites, i.e., niacin, in schizophrenia. In this connection it is interesting to note that all conditions known to be associated with a lack of niacin, i.e., pellagra, nicotinic acid deficiency encephalopathy (Joliffe et al., 1940), porphyria, and all known inborn errors of tryptophan metabolism leading to a lack of niacin (tryptophanemia, kynureninuria, 3-hydroxy-kynureninuria, xanthinuria) (Auerbach and DiGeorge, 1969), and Hartnup's disease (Hersov and Rodnight, 1960) have

mental disturbances as a part of the clinical symptoms. Treatment with niacin was followed in each of the above conditions by improvement or recovery from mental symptoms.

Tryptophan is the only amino acid which contains an indole nucleus. The only pathway leading to a cleavage of the indole nucleus is the dominant tryptophan-niacin pathway. All other minor tryptophan pathways fail to cleave the indole nucleus. Therefore, any metabolic block on the tryptophan-niacin pathways shifts tryptophan metabolism to the other minor pathways and leads to an accumulation of indole compounds.

The abnormally high levels of indole compounds, tryptamine, 5-hydroxytryptamine, and 5-methoxytryptamine in the urine of schizophrenics, have been found by many authors.

A relationship between the rise of indole compounds, especially the urinary tryptamine and the aggravation of schizophrenic behavior, was confirmed by Himwich and Himwich (1970).

Tryptamine, 5-hydroxytryptamine (serotonin), and 5-methoxytryptamine are normal metabolites on minor tryptophan (indole) pathways and, under normal conditions, all of them are degraded by MAO (Zeller, 1967; Spaide et al., 1968). Murphy and Wyatt (1972) were the first to find that MAO activity is decreased in schizophrenics. If MAO activity is decreased, oxidative deamination becomes insufficient, and the further degradation of tryptamine, 5-hydroxytryptamine, and 5-methoxytryptamine must proceed by other metabolic pathways. Transmethylation is the major metabolic alternative to oxidative deamination, especially when MAO is inhibited (Baldessarini, 1962). Accordingly, MAO inhibition in schizophrenics promotes transmethylation of the tryptophan metabolites, tryptamine, 5-hydroxytryptamine (serotonin), and 5-methoxytryptamine, into their psychotomimetic dimethylated compounds, DMT, bufotenin, and 5-MeO-DMT. All these psychotomimetic compounds are degraded by MAO and, therefore, MAO inhibition also

decreases the degradation of these psychotomimetic products (Zeller, 1967; Spaide et al., 1968).

These tryptophan derivatives, DMT, bufotenin, and 5-MeO-DMT, have psychotogenic properties. They can induce an abnormal behavior including hallucinations and catatonia in animals and also in normal individuals (Berlet et al., 1964; Bonhour, 1969; Charalampous and Tansey, 1967; Fabing and Hawkins, 1956; Gessner and Page, 1962; Michaux and Verly, 1963; Smythiesetal., 1967).

A tryptophan load can induce exacerbations of psychotic symptoms in schizophrenics; such exacerbations are accompanied, as are spontaneous exacerbations, by increased levels of psychotogenic tryptophan derivatives, DMT (Tanimukai et al., 1968; Heller et al., 1970), bufotenin (Heller, 1966; Tanimukai et al., 1967; Fischer and Spatz, 1967; Sireix and Marini, 1969; Heller et al., 1970), and 5-MeO-DMT (Tanimukai et al., 1968; Heller et al., 1970).

The insufficient activity of MAO also promotes transmethylation of a catecholamine product, dopamine (3,4-dioxy-phenylethylamine), into its psychotomimetic derivative, 3,4-dimethoxyphenylethylamine (DMPEA). DMPEA has often been found in the urine of schizophrenics especially during acute exacerbations (Takesada et al., 1963; Boulton and Felton, 1966). In animal studies, DMPEA induces a catatonia-like condition and various changes in behavior (Michaux and Verly, 1963; Smythies et al., 1970). In contrast, administration of DMPEA did not produce a psychotomimetic effect in humans (Shulgin, 1964). However, it was shown recently that DMPEA can produce psychotomimetic effects when administered intravenously to normal persons pretreated with MAO inhibitor (Charalampous, 1971), in other words, when the degradation of DMPEA is inhibited. The possibility that schizophrenia may be associated with abnormal methylation of catecholamines and production of a substance like DMPEA was proposed already in 1952 by Osmond and Smythies and Harley-Mason (Osmond and Smythies, 1952; Harley-Mason, 1952).

As already mentioned, under normal conditions DMPEA, DMT, bufotenin, and 5-MeO-DMT are rapidly degraded by MAO (Charalampous and Tansey, 1967; Zeller, 1967; Spaide et al., 1968), and their final effect requires a critical brain level (Vogel and Horwitt, 1967). Because MAO activity is decreased in schizophrenics (Murphy and Wyatt, 1972) these psychotomimetic compounds accumulate in the brain, and when they reach a critical brain level they induce changes in perception and mental changes.

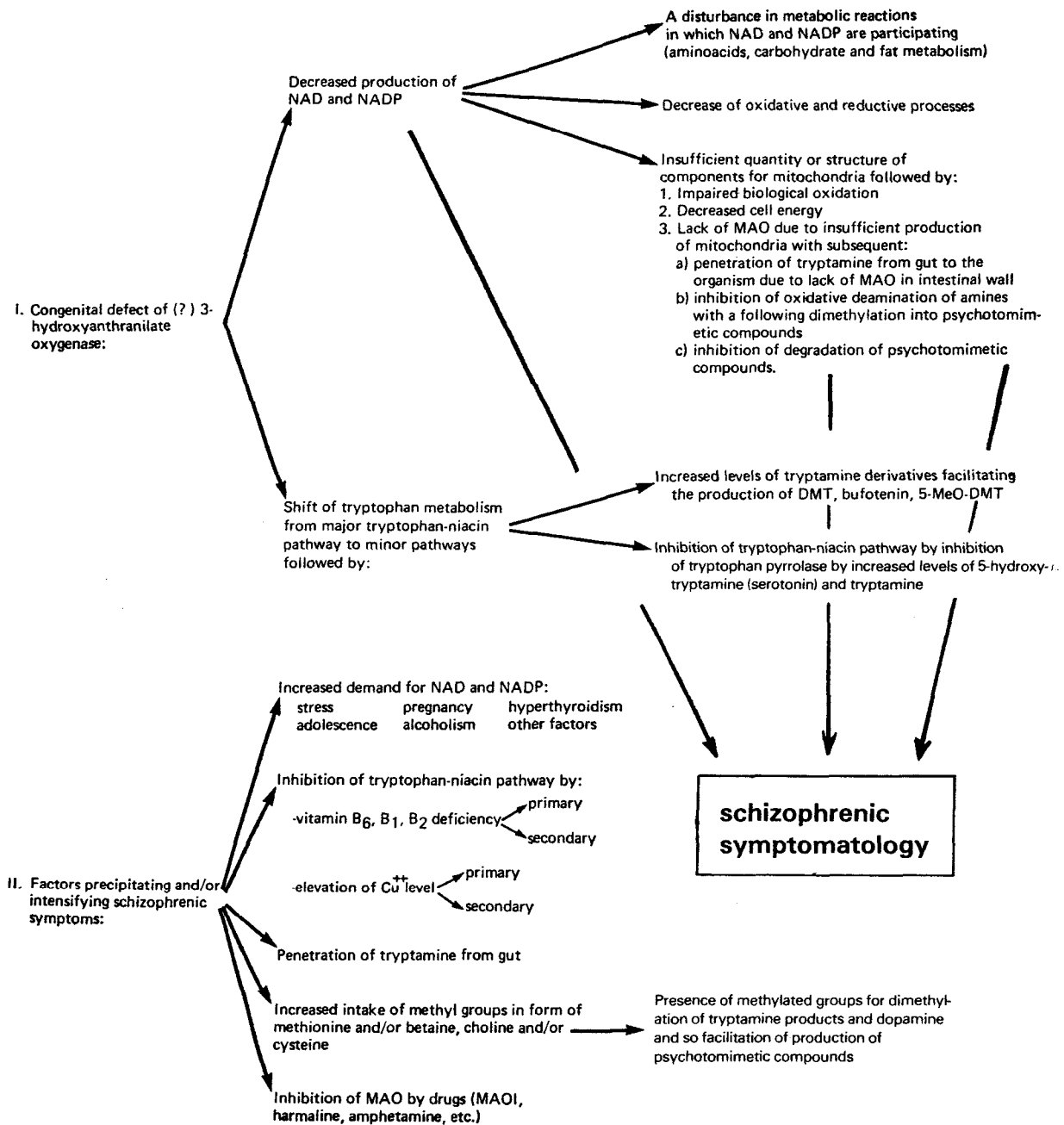
In humans the final response to a psychotomimetic compound depends not only on individual variations in metabolism and excretion of the compound, but also on the subject's personality (Szara, 1961). Differences in personality deeply influence the final response to psychotomimetic drugs; therefore, individuals in the same mental condition may react differently. This response may range from unpleasant and frightening reactions to a transcendental experience with a concomitant deep emotional response (Szara, 1961).

Environmental factors (dietary intake of tryptophan and methionine, drug intake, e.g., MAOI, amphetamines, etc.) and endogenous factors (increased metabolism during puberty, stress, lactation, MAO activity, etc.), play an important role in the production and degradation of psychotomimetic compounds. For this reason there is no characteristic or consistent pattern in the urinary excretion of psychotomimetic metabolites in schizophrenia, just as there is no consistent pattern of glycosuria, acetonuria, and glycemia in diabetes.

Basic therapy in the disorders due to the inborn errors of metabolism involves the following therapeutic principles:

1. Replacement of the missing enzyme.
2. Reduction of the accumulated substrate by-products by:
 - (a) Dietary restrictions, e.g., galactose free diet in galactosemia or phenyl-lalanine-restricted diet in phenylketonuria.
 - (b) Inhibition of by-product formation.

FIGURE 2



- (c) Increasing the excretion of accumulated substrate and substrate by-products.
- 3. Supplementation of the missing product.
- 4. Supplementation of vitamins to meet unusual demands for coenzymes and/or for vitamins.
- 5. Special approaches to compensate for the inborn error of metabolism, e.g., phlebotomy to remove the excess iron in hemochromatosis, and

d-penicillamine to remove the excess copper' in Wilson's disease.

In most schizophrenics, especially those with chronic symptoms, the disorder is apparently the result of an inborn error of metabolism—mostly the missing or insufficient activity of 3-hydroxyanthranilate oxygenase. Here, treatment and prevention are based on the same principles that govern the prevention and treatment of

other errors of metabolism due to an enzymatic block.

When applying these general principles, the specific therapy depends on whether the patient has a primary or secondary schizophrenia and whether he is chronically ill, in an asymptomatic interval, or acutely psychotic (Gilka, 1975).

A term, "primary schizophrenias," can be used in those schizophrenics in whom we can detect a metabolic block on the tryptophan-niacin pathway, which has been induced by an inherited enzymatic deficiency. The inherited enzymatic defect on the tryptophan-niacin pathway, expressed clinically in homozygous carriers, seems usually to be due to a deficiency activity of 3-hydroxy-anthranilate oxygenase. The defect induces a metabolic block in the tryptophan-niacin pathway, which leads to a lack of niacin, followed by an insufficient production of NAD and NADP coenzymes and, subsequently, by disorders of the metabolic reactions in which these coenzymes are involved. Also, indirectly, the defect leads to an insufficient production of MAO and inhibition of tryptophan degradation on the minor tryptophan (indole) pathways, with an accumulation of tryptophan intermediary metabolites and formation of dimethylated psychotomimetic compounds.

Clinically, primary schizophrenia is usually characterized by the slow onset of progressive deterioration and a chronic course.

Secondary schizophrenia may be divided into four subgroups according to the basic causative factor: 1. those due to a lack of niacin in persons who are not homozygous carriers of a genetic enzymatic defect on the tryptophan-niacin pathway, e.g., in pellagra; 2. those due to an increased production of tryptamine and its derivatives in the gut, e.g., in the malabsorption syndrome; 3. those due to increased levels of CH₃ groups, e.g., homocystinuria; and 4. those due to decreased enzymatic activity of MAO, e.g., ingestion of amphetamines, or an inherited defect of MAO activity.

Based on these principles, valid for any inborn error of metabolism, the following rationale for treatment of schizophrenias due to a block on the tryptophan-niacin pathway can be deduced (Gilka, 1975):

1. Replacement of the missing enzyme

Although 3-hydroxyanthranilate oxygenase has been demonstrated in the yeast *Saccharomyces cerevisiae* (Greenberg, 1969) and has been purified, direct replacement of the missing enzyme is only a theoretical possibility at the present time. However the activity of 3-hydroxyanthranilate oxygenase may be increased by increasing the concentration of its coenzyme, NADPH.

Many enzymes consist of two parts, a coenzyme or nonprotein part, which is usually a vitamin or its derivative, and an apoenzyme—the pure protein part. With a normal concentration of coenzyme, perhaps only 1 percent of the abnormal apoenzyme has combined with the coenzyme. According to the principles of chemical equilibrium, a larger fraction of the abnormal apoenzyme could be made to combine with the coenzyme by increasing the concentration of the coenzyme in the body fluids. If the concentration were increased, for example, one hundred times, most of the apoenzyme molecules might combine with the coenzyme to give a nearly normal amount of active enzyme (Pauling, 1970).

The coenzyme of 3-hydroxyanthranilate oxygenase is NADPH, a reduced form of NADP. Large niacin or niacinamide supplements can increase the niacin level and also the quantity of coenzyme NADPH and thus increase the activity of 3-hydroxyanthranilate oxygenase.

2. Reducing the accumulation of substrate and substrate by-products

(a) By dietary restriction:

(1) Reduced intake of tryptophan and its derivatives (to prevent the accumulation of indole derivatives on minor tryptophan pathways).

(2) Reduced intake of amino acids which are capable of increasing CH₃ and/or SH groups, i.e., reduced intake of methionine,

betaine, cysteine, homocysteine, and choline (to decrease transmethylation processes and prevent activation of N-methyltransferase).

(b) By drugs, which act as acceptors of methyl groups (to decrease transmethylation of indole and catecholamine compounds):

- (1) Phenothiazines (Hoffer, 1970)
- (2) Penicillamine (Ibbott, 1970)
- (3) Niacin and niacinamide (Hoffer et al., 1957)

(c) By increasing degradation of hallucinogenic compounds:

Psychotomimetic compounds are degraded by MAO (Zeller, 1967; Spaide et al., 1968). At present MAO can be replaced only indirectly by niacin supplementation. This increases the quantity of NAD and NADP and restores mitochondrial activity.

3. Supplementation of the missing product

The supplementation of the missing product, i.e., niacin, should be permanent in schizophrenias due to an inborn error of metabolism on the tryptophan-niacin pathway. In other schizophrenias, supplementation is necessary only during periods when the organism cannot produce a sufficient amount of niacin.

4. Supplementation of vitamins to meet unusual demands for coenzymes

Vitamin C is necessary to maintain the activity of 3-hydroxyanthranilate oxygenase which is decreased in most schizophrenics. Vitamin C also stimulates oxidative-reductive reactions which are insufficient in schizophrenics.

Vitamin B1 deficiency increases the permeability of the blood-brain barrier (War-nock and Burkhalter, 1968), and thus penetration of psychotomimetic compounds may be increased.

Vitamin B2 seems to be important in the regeneration of MAO activity because it is retarded in riboflavin deficiency (Wiseman-Distler and Sourkes, 1963).

Vitamin B2 and especially vitamin B6 act as coenzymes in the tryptophan-niacin pathway; an insufficient intake of these vitamins will further

decrease niacin production.

Vitamin B6, the "amino acid metabolism vitamin," is the coenzyme for many reactions involving amino acids.

The demand for vitamins fluctuates in response to the interaction of environmental and internal factors (stress, infection, intake of alcohol, diet, adolescence, pregnancy, etc.), and differs from one patient to another and within the same individual.

5. Special approaches

The correction of hypoglycemia, found in many schizophrenics, by a sugar-free and low-carbohydrate diet and by avoiding food to which the patient is sensitive increases the recovery rate.

Phenothiazines can alleviate psychotic symptoms in both primary and secondary schizophrenias:

(a) They are potent agents of oxidative reductive reactions (Domino, 1965) and are useful in those schizophrenias where these processes are decreased.

(b) Phenothiazines affect permeability (Domino, 1965; Quastel, 1965) and therefore may prevent the penetration (Poldinger, 1967) of tryptamine and other tryptamine products and DMPEA into the brain. It is not yet known whether this changed permeability also prevents the removal of psychotomimetic compounds from the brain, and keeps niacin and niacinamide from entering the brain.

(c) Chlorpromazine accumulates selectively in the mitochondria and acts at all steps of the electronic transport chain (Domino, 1965), which in schizophrenics is impaired owing to a lack of NAD and NADP.

(d) Chlorpromazine, in large doses, prevents transmethylation (Hoffer, 1970) and in this way the production of di-methylated psychotomimetic compounds.

(e) Phenothiazines prevent transmethylation of niacinamide to N-methylnicotin-amide (Hoffer, 1970), and thus increase the quantity of NAD and NADP.

(f) Chlorpromazine increases the quantity of NAD and NADP (Burton et al., 1958) also by increasing the activity of tryptophan pyrrolase (Kusch and Heinrich, 1963).

(g) Phenothiazines increase the excretion

of serotonin and thus prevent the formation of bufotenin and 5-MeO-DMT.

An effective treatment of schizophrenia depends on determining all factors that are interacting in an individual case; therefore each schizophrenic should have tests of tryptophan metabolism, determination of MAO activity, and other biochemical tests. Ultimately, the effective treatment of schizophrenia depends on the assessment of all the factors, chemical and otherwise, which are interacting in an individual case. Ideally, the following biochemical examinations should be done because they may demonstrate the underlying abnormalities in schizophrenia:

- (1) Testing of tryptophan metabolism, especially the tryptophan-niacin pathway, tryptophan-loading test, and determination of urinary tryptamine.
- (2) Determination of MAO enzyme activity.
- (3) Determination of CH₃ and SH levels.
- (4) Detection of psychotomimetic dimethylated compounds: DMPEA, DMT, bufotenin, and 5-MeO-DMT.
- (5) Examination of carbohydrate metabolism.
- (6) Special examinations, e.g., mauve factor, testing for cerebral allergies, etc.

In schizophrenia the regular testing of urine for tryptamine can detect its increase, indicating the accumulation of indole derivatives and the production of psychotomimetic compounds, which is followed by an exacerbation of psychosis. Thus, regular testing of urinary tryptamine can serve—as does detection of acetone in the urine of diabetics—as an indicator of imminent psychotic exacerbation and enable the start of proper prophylaxis immediately. An increased excretion of tryptamine in schizophrenics appears to be the most sensitive indicator of alterations of indole excretion as well as imminent behavioral exacerbations (Himwich and Himwich, 1970). Regular daily estimation of urine for tryptamine in schizophrenics might predict the activation of psychosis, because the tryptamine rises approximately one day before the behavior worsens.

Ideally, if the patient could determine his urinary tryptamine level daily (similarly as diabetics test for sugar and acetone in urine), immediate treatment given with each increase in urinary tryptamine might prevent exacerbation.

Tryptophan-loading test with determination of niacin, 5-HT, 5-IAA, and 3-IAA, and measurement of activity of MAO and 3-hydroxyanthranilate oxygenase might also detect clinically latent carriers. Early prevention of shift in tryptophan metabolism in these individuals by restriction of dietary tryptophan and methionine intake and by supplementation of niacin may prevent the formation of psychotomimetic compounds and thus prevent the development of psychosis in these genetically predisposed individuals.

Summary

The detailed analysis and synthesis of the biochemical and genetic studies on schizophrenia done during the last two decades in America and Europe indicate:

- (1) Schizophrenia belongs to the group of disorders called "inborn errors of metabolism."
- (2) The clarification of schizophrenia as an inborn error of metabolism enables us to deduce on the basis of principles valid for all inborn errors of metabolism a rationale for treatment and prevention of schizophrenia, and a rationale for detection of latent carriers.
- (3) In almost all schizophrenics the underlying metabolic defect is due to an inborn error of tryptophan metabolism, but in a small percentage of schizophrenics the underlying metabolic defect is due to an inborn error of methionine metabolism or other factors, e.g., an inherited defect of MAO enzyme.
- (4) Schizophrenic symptomatology results from a wide spectrum of biochemical disorders which lead to a decreased production of niacin and/or accumulation of psychotomimetic compounds.
- (5) The primary defect in most schizophrenics is a metabolic block on the tryptophan-niacin pathway (in most patients due to a decreased activity of 3-hydroxy-

anthranilate oxygenase) which leads to a decreased production of niacin and, secondarily, to a metabolic shift to minor indole pathways leading to increased production and accumulation of psychotomimetic compounds.

(6) Psychotomimetic compounds—DMPEA (3, 4-dimethoxyphenylethylamine), bufotenin (5-hydroxy-N, N-dimethyltryptamine), 5-MeO-DMT (5-methoxy-N, N-dimethyltryptamine), and DMT (N,N-dimethyltryptamine) together with a lack of niacin induce clinical manifestation of schizophrenia in genetically predisposed individuals.

(7) Environmental factors (stress, drugs, alcoholism, vitamin deficiencies, food, etc.), and endogenous factors (e.g., increased metabolism in puberty, lactation, etc.), play an important role in the development of schizophrenic symptomatology.

(8) The biochemical pattern, moment by moment, reflects the interaction between environmental and endogenous factors and the underlying pathogenic mechanism (e.g., a defect of 3-hydroxyanthranilate oxygenase in primary schizophrenia, or the secondary inhibition of this enzyme by increased Cu⁺⁺ levels in porphyria). For this reason there is no characteristic or consistent pattern in the urinary excretion of psychotomimetic metabolites.

(9) An effective treatment of schizophrenia depends on determining all factors that are interacting in an individual case, and therefore each schizophrenic patient should have tests of tryptophan metabolism, determination of MAO activity, and other biochemical tests, suggested in this paper.

(10) The regular testing of urine for tryptamine can detect its increase, indicating the accumulation of indole derivatives and the production of psychotomimetic compounds, which lead to an exacerbation of psychosis. Thus, regular testing of urinary tryptamine can serve—as does detection of acetone in the urine of diabetics—as an indicator of imminent psychotic exacerbation and enables one to immediately start proper prophylactic treatment.

(11) From general principles valid for all inborn

errors of metabolism, the rationale for treatment of schizophrenia appears to be:

(a) dietary restriction of the product which is insufficiently metabolized: in schizophrenia—a dietary restriction of tryptophan.

(b) supplementation of missing products: in schizophrenia—administration of niacin.

(c) prevention of formation of byproducts: in schizophrenia—prevention of formation of psychotomimetic compounds by administration of phenothiazines and related compounds plus a restriction of amino acids yielding CH₃ and SH groups, and ideally, administration of the enzyme monoamine oxidase.

(d) increased demand for vitamins: in schizophrenia—increased demand for vitamins B₁, B₂, B₃, B₆, and C.

(12) The clarification of schizophrenia as an inborn error of metabolism enables us also to deduce the biochemical screening tests (e.g., loading test with tryptophan with determination of niacin, 5-HT, 5-HIAA, and 3-IAA; and measurement of the activity of MAO and 3-hydroxyanthranilate oxygenase) to detect possible carriers in family members of a schizophrenic patient.

(13) By the early detection of the carriers, proper dietary management (i.e., restriction of tryptophan and CH₃ and SH groups), and supplementation of missing metabolites (i.e. niacin), we might prevent formation of psychotomimetic compounds and therefore hopefully clinical manifestations of schizophrenia in the genetically predisposed individuals; similarly, as by proper dietary treatment we can at the present time prevent mental retardation in children with phenylketonuria and enable their normal development.

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