

# Large Amounts of Nicotinic Acid and Vitamin B12 in the Treatment of Apparently Irreversible Psychotic Conditions Found in Patients with Low Levels of Folic Acid

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Large doses of nicotinic acid (6 grams a day) and vitamin B-12 controlled psychotic conditions of long duration which were clinically found in 36 patients who had shown low folic acid levels as determined by bio-assay. This study leads without a shadow of a doubt to the conclusion that such an abnormality of the folic acid levels was due primarily to deficient nutrition, and the lack of vitamin B-12 and vitamin B3.

The name of folic acid is applied to a number of substances which contain the following chemical groups:

1. Pteridine nucleus
2. Para-amino benzoic acid
3. Glutamic acid.

Pteridine compounds are said to be widely distributed in nature. The substance contained in Folic Acid is 2-Amino 4-Hydroxy-6

Methyl-pteridine joined by a methylene linkage to the amino group of para-aminobenzoic acid. The latter, originally considered a vitamin B, is now regarded as existing in nature. It functions solely as a component of the folic acid group of compounds. Acetyl-paba is found in the blood and urine. The designation of pteroid is applied to the pteridyl-methylene-paba-moiety. The amino group of p-aminobenzoic acid is in peptide linkage with glutamic acid. Folic acid, as it occurs in the liver, is pteroylmonoglutamic acid. It occurs in nature and also in the form of two polyglutamic acid conjugates, containing three and seven glutamic acid residues, respectively.

Pteroylmonoglutamic acid is liberated from these conjugates by enzymes called "conjugases". The active coenzyme form of the vitamin is the tetrahydro-derivative (tetrahydrofolic acid). Because of their lability, these occur naturally only in small amounts, being present mainly in the form of N-5 formyl or N-5 methyl derivatives.

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What information is available concerning the mechanism of biosynthesis of folic acid? What we know has been mainly derived from studies in microorganisms. Folic and tetrahydrofolic acids can be synthesized by most microorganisms (e.g. intestinal bacteria in man and rat) grown on simple synthetic media. There is evidence that, in the presence of ATP and CoA, PABA reacts with glutamic acid to form p-aminobenzoyl-glutamic acid. The latter can react with a pterin to produce pteroylmonoglutamic acid (folic acid). Certain microorganisms require p-aminobenzoic acid for the formation of folic acid, synthesis of which may be blocked by sulfonamide, i.e. by competitive inhibition. This is not the case in animals, including man, which are not known to have an independent requirement for PABA. It is believed that the primary end-product is dihydrofolic acid, not folic acid, the latter occurring in nature only because of the lability of the reduced compounds to oxidation. Dihydrofolate is reduced to tetrahydrofolate by dihydrofolate reductase. Conversion of folic acid to tetrahydro-derivatives is accomplished by folic acid reductase. NADPH is the hydrogen donor of these reactions and ascorbic acid is apparently a requirement.

Tetrahydrofolic acid serves as a carrier of one-carbon units in metabolic reactions involving transfers of these units. These carrier forms differ only in nature of the one-carbon unit (methyl, formyl, hydroxymethyl, forminino) and the site of its attachment to the tetrahydrofolic acid molecule, (N5, N10). Two of the compounds probably exist chiefly as anhydro-derivatives, which are perhaps their active forms, i.e. hydroxymethyl-tetrahydrofolate as N5, N10-methylene-tetrahydrofolate, and formyl-tetrahydrofolate as N5, N10-methylene-tetrahydrofolate.

Administration of pteroylglutamic acid results in increased urinary excretion of tetrahydrofolic acid. The liver and kidneys are apparently active in this process, which is stimulated by ascorbic acid. Conversely, subjects with scurvy (ascorbic acid deficiency) excrete relatively small amounts of tetrahydrofolic acid in the urine, even after administration of folic acid. Moreover, a megaloblastic anemia occurs in

scorbutic monkeys, which is corrected by administration of small amounts of tetrahydrofolic acid more readily than by large amounts of folic acid.

Tetrahydrofolic acid may be liberated from inactive conjugates (polyglutamic acid forms) by enzymes (conjugases) apparently identical with those which liberate pteroylmonoglutamic acid from its conjugated forms.

Under average dietary conditions, adults excrete 2.0 to 6 microns of vitamin B-12 daily in the urine and 130 to 550 microns in the feces. The total amount excreted is four to seven times that contained in the diet (40 to 90 microns), the major portion obviously being contributed by intestinal microorganisms.

## FUNCTIONS OF FOLIC ACID AND VITAMIN B<sub>12</sub>

Tetrahydrofolates are the active cofactors in metabolic reactions involving one-carbon units. These include formyl (CHO), hydroxymethyl (CH<sub>2</sub> OH), methyl (CH<sub>3</sub>), and forminino (CH=NH) groups. These are attached to the N atoms at the 5 or 10 positions of the pteroyl structure or both. Tetrahydrofolic acid is therefore concerned in several important reactions involving one-carbon units. These include interconversion of glycine and serine, biosynthesis of purines, and synthesis of methyl groups for formation of methionine and thymine. Methyltetrahydrofolic acid provides the methyl group for these methylation reactions but its transfer to homocystine to form methionine involves also vitamin B-12-

## CLINICAL CONSIDERATIONS

We have chosen 36 patients, 20 male and 16 female, of an average of 40. During more than ten years they have been suffering from protacted signs of mental illness, i.e. psychotic depression, auditory hallucinations, tremendous irritability to physical stimuli particularly increase in sound, insomnia, epileptic like seizures and alteration of metabolism of antiepileptic

treating agents and others, specifically phenylhydantoin, phenytoin, primidone, ethanol, barbiturates, and estrogen.

Simultaneously, we organized a controlled group of individuals supposed to play the role of patients who were actually completely free of illness, particularly epilepsy and gastrointestinal disorders, stomach ulcers or anomalies of the ovarian system. In other words, our control group had no history either of psychiatric or medical illness of any sort. It goes without saying that these findings were corroborated by our medical associates during the many medical check-ups to which our volunteers submitted themselves.

Fasting serum folates were scrutinized twice a week. A scrupulous surveillance of their diets was carried out at regular intervals. Alcohol was completely eliminated from the diet. Blood samples were analyzed by different techniques which are too specialized to be described in detail in this short note, though one most commonly used was known as the technique of Archibald which, as you know, uses a radiosotopic competitive binding method. Diet habits institutionalized by culture and personal habit were assessed generally in terms of scaling rates of 3 to 4 elements as such.

1. Subjective history of anorexia.
2. Recent and progressive history of weight loss, objectively confirmed.
3. All kinds of information directly obtained from the relatives, particular pertinent to gastrointestinal disease, history of excessive alcohol ingestion or more than often use of estrogen compounds.

Returning to our list of patients, it was found that the chemotherapy associated with folate deficiencies was altered, including, for example, the finding of pyramidon, ethanol and estrogens. On the other hand, 0.5% of patients who were on oral contraceptives showed the massively low level of folate corresponding to 1.2 ng of folate. This significant lowering of plasma folate levels appears to confirm the study of other investigators. In a case cited in

the literature, a woman on oral contraceptives who had 1.1 ng of folate level, became temporarily blind. She regained the vision after the reinstatement of adequate folate nutrition.

**RESULTS OBTAINED:**

After three months of administration of nicotinic acid and vitamin B12 to these patients, 75% had shown an increase in folate of 85% whereas after one year, the folate level was normal and the most extraordinary thing of all was that all the mental symptoms had disappeared. The patient's nutrition had notably improved which could be stated by their weight increases of between 5 to 15 lbs. The patients showed increased appetite and strength. Six patients who had a history of daily epileptic seizures, resumed their normal behavior, including physical tranquility, lack of tremors and unadulterated memory operation. Another symptomatic element also notably absent was insomnia and distractability, lack of nervousness and an obvious *joie de vivre*.

**CONCLUSIONS:**

Whereas most of the investigators who had dedicated their efforts to the study of mental illness correlative to low folate levels, have concluded that this derangement of folic acid metabolism can only be explained by intrinsic enzymatic operations with complete exclusion of the interference of nutritional factors, the present study shows in all its evidence that this position is untenable. It becomes quite clear that the operations leading to the disappearance of mental signs in our patients who showed re-elevation of folic acid levels had an extrinsic source of causation, namely a clear-cut nutritional basis.

As in other papers written by us, we continue in this one defending a non-reductionistic approach in the course of the elaboration of our biological theories referent to crucial areas of organismic metabolism.