Zinc and Manganese in the Schizophrenias

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First published in Journal of Orthomolecular Psychiatry, Vol. 12, No. 3, 1983

Abstract

The essential trace elements zinc and manganese have been noted as factors in brain disease since the 1920s. The combined use of zinc and manganese in schizophrenia is based on: 1) Increased urinary excretion of copper when both zinc and manganese are given orally; 2) Zinc alone causes a decrease in blood manganese; 3) The double deficiency of zinc and manganese frequently is found in patients with excess copper. The mauve factor (Kryptopyrrole) is known to increase the excretion of zinc and vitamin B_6 (pyridoxine). In children, insufficient levels of zinc and manganese have been associated with lowered learning ability, apathy, lethargy and mental retardation. Hyperactive children may be deficient in zinc, manganese and vitamin B_6 and have an excess of lead and copper. Alcoholism, schizophrenia, Wilson's disease, and Pick's disease are brain disorders dynamically related to zinc and manganese levels. Zinc has been employed with success to treat Wilson's disease, achrodermatitis enteropathica, and specific types of schizophrenia. Manganese is important in the building and breakdown cycles of protein and nucleic acid. For RNA chain initiation, manganese was found to be a better effector than magnesium. Manganese stimulates adenylate cyclase activity in brain tissue. Because cyclic-AMP plays a regulatory role in the action of several brain neurotransmitters, manganese is important in brain function. Owing to the fact that zinc is well absorbed from the gut but manganese is poorly absorbed all diagnostic categories may be harmed by large prolonged oral doses of zinc without manganese. In oral doses manganese occasionally elevates blood pressure in patients over 40 years of age. Zinc alone can lower blood pressure in some hypertensive patients. Chronic use of hydralazine (a manganese chelator) in rats produced manganese deficiency which resulted in convulsions. Low blood and serum manganese levels may play a role in epilepsy possibly by interfering with membrane stability. Prolonged use of pheno-thiazines causes tardive dyskinesia. Phenothiazines might chelate manganese making it unavailable for some presumed function as an enzyme activator.

Historical

The first suggestion that a trace element deficiency might be a factor in mental disease was that of Derrien and Benoit (1929) who found a high level of urinary Zn in a dying porphyric female patient showing abnormal psychiatric symptoms. The first use of a trace element as treatment for schizophrenia was that of Reiter (1927) who found intravenous Mn to be effective. He found that 23/50 patients improved after the injections. Schrijver (1928) gave manganese chloride intravenously to 23 patients with good improvement in three and possible improvement in seven. Helweg (1928) treated 95 chronic schizophrenics, with negative results. Tindinge (1929) used either oral or intravenous Mn in 75 patients and found only one dramatic improvement. Reed (1929) used a control schizophrenic group (30) and found that 18 percent of the controls were discharged from the hospital in one year while 37 percent of the Mn treated schizophrenic patients (30) were discharged. Reed used 2 to 8 ml of a 0.02 molar Mn solution intravenously twice weekly over a period of 15 weeks; followed by a 0.3 g of manganese chloride twice daily by mouth. W.M. English (1929) studied many schizophrenics but had the best results with Mn

in those who had been psychotic only two weeks to three years. Of 38 such patients an increase in body weight, physical improvement and mental improvement occurred in 22 patients. Some of the chronic patients also improved. R.G. Hoskins (1934) used suspended manganese dioxide intramuscularly in 30 patients with only two improved, two worse, and 26 unchanged. Although Hoskins failed to follow the experimental procedure and design of the successful investigators his study triumphed and manganese hydrochloride intravenously was no longer used.

We found in 1968 (Pfeiffer and Iliev) that oral Mn produced a three fold increase in excretion of Cu in schizophrenic patients and that the combination of Zn and Mn was even more effective in promoting urinary Cu excretion. Since many schizophrenics had a Cu overload we used "ziman" drops (10 percent Zn sulfate with 0.5 percent Mn chloride) to reduce their Cu burden. Six drops of Ziman morning and night provides 10 mg of Zn and 3. mg of Mn which is about 3/4 of the estimated daily need - namely 15 mg of Zn and 4 mg of Mn. In 1965 Professor Roger Williams called our attention to the paper of Kimura and Kumura who found the brains of schizophrenics at autopsy to have only 50 percent of the Zn content of control brains. This low level of Zn held constant for the frontal, occipital and hippocampal portions of the brains studied. We know that Zn is essential in the hippocampal portion of the brain where histamine is stored in histaminergic nerve endings. We, therefore purchased an Atomic Absorption Spectrophotometer and analyzed body tissues and juices. We have seen over 15,000 out-patients and each outpatient has had blood serum and hair analyzed for both the trace and toxic elements.

In the period 1966 to 1971 we observed lasting clinical benefit with ziman drops in many patients who had high hair or serum Cu levels and low serum Zn levels. By 1977 we had perfected the method for whole blood Mn determination so we now encounter schizophrenics who initially are high in serum Cu and low in both serum Zn and whole blood Mn. These biochemical abnormalities revert to normal as the patient improves mentally and physically. In our opinion the use of Mn and Zn to reduce the Cu burden of the body and restoration of Zn in the hippocampus allows for a reduction in the need for major tranquillizers in the schizophrenic. In some cases this Cu excess with Zn and Mn deficiency is the only biochemical imbalance.

By 1971 we had objective data showing that mauve positive schizophrenic patients [Kryptopyrroles in the urine - (Irvine et al., 1969)] actually excreted almost twice as much Zn as did schizophrenic patients who were not mauve positive. Kryptopyrrole is an avid aldehyde reacting agent which we have shown to combine irreversibly with pyridoxal phosphate. The new molecule then chelates Zn with the combined product appearing in the urine. The whole syndrome is stress induced so the susceptible patient when stressed, quickly becomes vitamin B_6 and Zn deficient. Armed with this knowledge we can effectively treat the pyroluric patient ("malvaria" of Hoffer and Osmond) and we have written several papers on the signs, symptoms and treatment of pyroluria (Pfeiffer et al., 1974; Pfeiffer and Bacchi, 1975).

By 1977 our method for whole blood Mn was applied to all out-patients both new and old. This revealed that many patients who had been treated with Zn alone had become Mn deficient. With new patients the diagnostic categories with the lowest Mn levels were the epileptic, nutritional hypo-glycemics, pyrolurics and schizophrenics. Zinc is easily and rapidly absorbed from the gut but Mn is poorly absorbed and we don't know at present how to increase the whole blood Mn other than by the administration of large doses of Mn gluconate daily over a long period of time. We have tried all of the presently

marketed oral preparations of Mn. We have not tried parenteral or intravenous Mn as a supplement.

Practical Aspects of Manganese Supplements in Man

The physicians at the Princeton Brain-Bio Center have now had four years' experience in the use of Mn supplements. In the 1977-79 period we noted low blood Mn levels in many of our schizophrenic patients and, therefore, increased the dose of oral Mn using either 10 mg or 50 mg of Mn as the gluconate. To our surprise the blood Mn level in many instances continued to be low or go to a lower level. Most of these patients were receiving 30 mg of Zn as the gluconate morning and night, which in retrospect is a large dose since the body needs only 10 to 15 mg/day. Patients with normal eating habits would require less supplementation since 5 to 8 mg is obtained from a good diet.

When the Zn supplement is reduced to 15 mg a day the blood Mn level will usually rise with a daily dose of 10 to 20 mg of Mn. Note that this dose is two to four times the recommended daily intake.

We are at present studying the factors which may increase the absorption of Mn from the intestinal tract. When normal subjects in the fasting state take 150 mg of Mn as the gluconate (or amino acid chelate) this dose does not cause a significant rise in the serum Mn level over a period of four hours. The eating of a breakfast high in manganese content does not significantly elevate the serum Mn levels. The normal serum level is 1.20 + 0.99 ng/g (ppb). Ninety percent of the blood Mn (normal level, 14.80 ± 3.9 ng/g [ppb]) is contained in the erythrocyte which has a life of 120 days.

The determination of whole blood Mn is useful in our clinic since patients are seen every three to six months. Patients with a blood Mn below 8 ng/g (ppb) slowly develop a macrocytosis as characterized by a high mean corpuscular volume and elevated con puscular hemoglobin. These patients have normal serum folate and vitamin B_{12} levels and the macrocytosis responds to a dietary supplement of Mn with the Zn supplement reduced to a maximum of 15 mg per day.

With Zn alone and sometimes with Ziman Fortified AM and PM, the patient's whole blood Mn will decrease over a treatment period of 4 to 12 months. These low Mn levels can result in depression, intolerance to oral Zn, possible increase in autoimmune reactions and the aforementioned macrocytosis. The finding of a lowered Mn blood level with prolonged Zn supplementation has occurred in psychiatric, arthritic, senile and cardiac patients. Thus all diagnostic categories can be harmed by large prolonged doses of Zn without Mn. With this new concept we have treated problem patients with large oral doses of Mn. In one severely allergic male, age 45 whom we had treated for 15 years, we suggested 50 mg of Mn as the gluconate morning and night. He felt somewhat better with this dose, so he cautiously increased the dose to 100 mg, three times per day. Before starting this dose his blood Mn was 6 ng/g (ppb). After three months of the big dose, his blood Mn was 11 ng/g (ppb). One month later the level was 8.5 ng/g (ppb) and after a year and a half later it was 10.5 ng/g (ppb). Normal is 10 to 20 ng/g (ppb). Physical examination, blood pressure, pulse and chem screen showed no abnormalities. During the period of 300 mg of Mn orally per day he gained 11 needed pounds in body weight and was able to tolerate foods that normally caused severe depressive reactions. With the higher blood levels of Mn this patient now can tolerate small doses of Zn which previously caused severe depression.

Manganese Levels in the Hair of Schizophrenics

Other than the therapeutic trials of Mn in schizophrenics by Reiter and English in 1929, the first demonstration of a possible deficiency of Mn was reported in our sur-

vey in 1974. We found Mn to be low in the hair of schizophrenics, and in males (but not in females) Mn decreased with age. Barlow (1979) found Mn to be significantly lower in the hair of schizophrenics compared to a control population. Bowen (1972) found the Mn in hair of Indonesian children to be normal but protein deficient Indonesian children had a level five times higher. The hair copper level in these same children was two times higher. Perhaps the continuous ingestion of tropical fruits (high in Mn) with a low protein diet might account for the very high Mn level of the protein deficient Indonesian children. Ryan et al. (1978) reported Mn hair levels of both male and female patients diagnosed as multiple sclerotic (MS) to be one-half that of a normal population. The hair Zn levels of the MS patients were not lower than the controls.

Manganese and Tardive Dyskinesia

Excesses of the polyvalent metal ions of manganese, mercury, copper, cadmium and lead all appear to cause malfunctions of the CNS in animals and man. Manganese is unusual among these ions since neurological abnormalities have been associated with both a deficiency and an excess of Mn. Neuroleptic drugs are known to cause tardive dyskinesia in which the patient exhibits involuntary, rhythmic movements of the tongue, lips and facial muscles; sometimes exhibiting abnormal trunk movements or choreoathetoid movements of the extremities. This condition is usually reversible but in the long run may become irreversible in some patients.

In his earlier work with psychiatric patients who developed tardive dyskinesia on neuroleptic drugs, Kunin (1976) tried antiparkinson agents and Rauwolfia to no avail. He then recalled the work of Borg and Cotzias (1972) who reported that phenothiazines form free radicals with manganic (trivalent) ions in vitro. Manganese is found in high concentrations in the extrapyramidal system. He reasoned that phenothiazines might chelate Mn, thus binding it electrochemically, and that this might make it unavailable for some presumed function as an enzyme activator. It seemed plausible that by providing extra dietary Mn the deficiency would be corrected and the dyskinesia might thereby improve. Kunin (1976) found in 15 cases of tardive dyskinesia treated with Mn, seven were completely relieved; three cases were much improved; four were improved and only one was unimproved. Good results followed Mn doses of at least 15 mg and up to 60 mg/day. Niacin, at doses of 100 to 500 mg, was of significant benefit in treating dyskinesia in three of the 15 cases. Mean content of Mn in the hair of a psychiatric patient population averaged 0.8 ppm. The tardive dyskinesia patients averaged 0.46 ppm. It is concluded that Mn appears to be of value in treating many cases of tardive dyskinesia and it may also be of value in preventing the occurrence of dyskinesias.

Manganese and Blood Pressure

In oral doses Mn has not been found harmful, although in patients over 40 years of age Mn supplementation has occasionally elevated blood pressure. The elevated blood pressure returns to normal when Mn is discontinued and Zn alone is used. Zinc is effective in lowering the blood pressure of some hypertensive patients which is reminiscent of some of the early work of Schroeder and his coworkers. Comens (1960), working in Schroeder's laboratory, found that chronic hydralazine (a Mn chelater) in rats produced Mn deficiency which resulted in convulsions. These convulsions were antidoted by Mn but not by potassium, calcium, cobalt, zinc or nickel injections. Comens (1956) also postulated that Mn deficiency could be a factor in lupus erythematosus and other collagen diseases. Two of the side effects of hydralazine therapy, when used to lower blood pressure in man, are arthritis and lupus

erythematosus. An acute rheumatic state occurs in as many as 10 percent of the hypertensive patients treated with hydralazine. From these findings we can conclude:
1) Zn, by antagonizing Mn, may lower the blood pressure of some hypertensives.
2) Zn, when used to treat arthritic patients, should be carefully balanced with adequate Mn to sustain any beneficial effect.
3) Mn may be important in preventing autoimmune reactions.

Manganese and Seizures

Mn deficiency also affects cerebral motor function. Hurley et al. (1963) demonstrated a relationship between seizure activity and Mn deficiency in rats. The seizure threshold was found to be significantly lower in Mn deficient animals. Tanaka (1977) has presented a preliminary report on low blood Mn levels in epileptic patients.

Sohler et al. (1979) compared blood Mn levels in a group of patients with seizure activity to a control group. Blood Mn levels from control subjects had a mean of 14.8 ng/g (ppb) while serum levels were 1.2 ng/g (ppb). The blood Mn levels were significantly lower in the patients with seizure activity, 9.9 ± 4.9 ng/g (ppb) $p < 0.005$). The clinical significance of the low blood Mn levels remains to be evaluated. In uncontrolled trials we find that Mn is helpful in controlling seizures of both minor and major types.

Both Mn and choline deficiencies are believed to interfere with membrane stability and this could be responsible for facilitating the propagation of seizure activity. We suggest these findings warrant the use of dietary supplements of Mn for the control of seizure activity. The remission of seizures is frequently dramatic. Apparently the essential trace element Mn is a basic, direct legacy from vegetable life to animal life. Tropical fruits are naturally high in Mn with tea leaves the highest. Plants cannot convert the sun's energy without Mn (photosynthesis) and man cannot live without Mn since at least six important enzymes require Mn for normal function. Compared to Zn, Mn is poorly absorbed and both Mn and Zn are rapidly excreted. The absorption of Mn and Cu are equally slow but Cu is sequestered in the absence of Zn and Mn and may cause harmful effects. Because of the slow absorption of Mn the beneficial effects of Mn in man may not be evident for weeks and months. Except for the occasional elevation of blood pressure, oral Mn is without serious side effects. The use of Mn food supplements and foods high in Mn can be tried in some of the diseases which still baffle the medical profession. Patience may provide good rewards with Mn.

Manganese and the "Empty" Basophil

The blood histamine level correlates with the absolute basophil count since most of the blood histamine is contained in the basophils (Pfeiffer, 1972). On all patients we perform both determinations and expect the histamine to be near the mean of 48 ng/ml and the basophil count at about 35 cells per cu milliliter. When the patient is Mn deficient some patients may have a high basophil count, i.e. 75, with a normal or low blood histamine. We call this the "empty" basophil syndrome. The patient responds clinically to an oral Mn supplement and has a rise in the blood histamine level to correlate with the high basophil count. The opposite - a high blood histamine and a low absolute basophil count is usually a laboratory error - frequently we find that the blood was taken late on Friday and the basophils were then counted on Monday. The elapsed time of 48 hours allows disintegration of the basophils.

Summary - Manganese

Although often ignored by nutrition conscious individuals, Mn is an essential trace metal frequently deficient in our diet. A component of at least six known enzymes, Mn is required for efficient sugar

metabolism, for the production of cartilage - a vital structural component of our bodies, and for the manufacture of cyclic AMP - a cellular second messenger.

We know that Mn deficient animals suffer impaired growth, reproductive problems, and a shortened life span. With a severe deficiency, animals cannot stand up because of defective cartilage formation. Humans with low Mn levels can suffer chronic joint pains, particularly in the knees and back. "Growing pains" often disappear when our young patients take adequate Mn with zinc along with their vitamins. And, since the discs between the vertebrae consist largely of cartilage, widespread Mn deficiency might be responsible for the high incidence of back problems in the developed, more carnivorous, world.

In addition, low Mn levels have been associated with epilepsy and schizophrenia. Studies dating back to 1929 indicate that schizophrenics improve with supplementary Mn and our experience with Mn deficient schizophrenics at the Brain Bio Center supports this. We have also discovered that Mn deficient patients may suffer depression which clears up when Mn is included in the treatment program. Seizure patients may respond dramatically to Mn. Deficiency may lead to autoimmune diseases.

We find that patients with either hypoglycemia or diabetes need extra Mn to help normalize blood sugar levels. This isn't surprising since in Mn deficient animals, the insulin secreting cells of the pancreas atrophy - and insulin is the body's crucial regulator of sugar metabolism. Interestingly, low levels of this trace metal during early development may lead to malformation of the ear's vestibular system, the ear's mechanism responsible for maintaining balance. Young children who are slow to walk may require Mn supplements.

Unfortunately, most diets, even the best planned, tend to be deficient in this important trace metal. Our Mn deficient farmlands often produce fruits and vegetables lacking adequate levels. And, many of our frequently eaten foods contain little Mn. For example, meat, even liver, provides little Mn. Foods rich in Mn include nuts, whole grains, spices, legumes, and tea leaves. Tropical fruits such as pineapple, banana, papaya, and mango are particularly good sources. However, patients with low Mn blood or hair Mn levels will need supplementary Mn in addition to a good diet. Fortunately, Mn is well tolerated, even at high doses (up to 300 mg/day). However, occasionally in patients over forty, Mn can raise blood pressure and produce tension headaches. If this occurs, the Mn dose should be stopped until the blood pressure normalizes and the headaches disappear. Dried or fresh tropical fruits and tea can then be used as a source of Mn.

Low Zinc and High Copper in Some Schizophrenics

In 1966, when we found that some schizophrenic patients had low levels of blood histamine, we turned to a study of their Zn and Cu levels as possible factors in the storage and destruction of body histamine. Those patients registering low in histamine were also low in zinc and serum folate and high in serum Cu (Pfeiffer and Iliev, 1972). Occasionally a high Cu level was accompanied by a high serum creatine phosphokinase (CPK) level. Meltzer et al. (1969) have studied serum CPK extensively. In sheep poisoned with Cu, the CPK levels are tremendously high (Thompson and Todd, 1974), so that a high serum Cu level plus increased motor activity may cause a rise in CPK in the occasional schizophrenic. Over a 10 year period we have used folic acid and vitamin B_{12} to treat patients with low serum histamine levels and high serum Cu levels. These two vitamins reduce the need for the large doses of niacin used in megavitamin therapy; the use of folate and vitamin B_{12} in histapenic patients makes reasonable doses of niacin effective. With these nutrients, plus Zn and Mn, the Cu

burden of the patient decreased over a three month period, and the blood histamine level usually rises to a normal level.

Experience in the diagnosis and treatment of large numbers of schizophrenic patients has led us to separate three main biotypes: 50 percent are histapenic (low blood histamine, high serum Cu, low folate), 20 percent are histadelic (high blood histamine, low or normal serum Cu), and 30 percent are normal in Cu and histamine but excrete large quantities of kryptopyrrole in their urine, depleting them of vitamin B_6 and Zn (Pfeiffer, 1975). We have continued to characterize schizophrenia around the histamine axis, accumulating empirical, experimental, and theoretical support for these biotypes. Many biochemical abnormalities have been reported in schizophrenia; rather than being contradictory, much of the previous research supports our classification.

The low-histamine (histapenic) biotype of schizophrenia is frequently an environmentally produced copper overload with a resultant nutrient imbalance. Patients may be deficient in folic acid, vitamin B_{12}, niacin, Zn and Mn. The biochemical imbalance is characterized by oxidation of amines, low serum folate (Pfeiffer and Braverman, 1979), slowed metabolism (Carmel, 1978), fat accumulation, and decreased mean energy content of the quantitative EEG (Dow, 1971; Goldstein and Sugerman, 1969). Behavioral symptoms in high-copper histapenia include paranoia and hallucinations in younger patients, but depression may predominate in older patients. The patient is usually classified as having chronic or process schizophrenia. Others have found that the administration of folic acid will correct severe psychosis caused by folate deficiency. A 15-year-old girl was found to suffer homocysteinuria and symptoms of "schizophrenia". She was shown to have impaired $N^{5,10}$-tetrahydrofolate reductase activity. Enzyme inactivity caused diminished production of N^5 methyltetrahydrofolate. Methylation of homocysteine was thus impaired, resulting in homocysteinuria. Folate and pyridoxine greatly improved the patient's condition (Barber and Spaeth, 1969). There have been many well-documented reports of other folate-responsive behavioral disorders (Botez et al. 1977; Botez and Lambert, 1977; Carney, 1975).

Folic Acid in Low-Histamine High Copper Patients

We have used folic acid plus vitamin B_{12} for over 12 years to treat histapenic high copper patients who have hallucinations or paranoia in the early years of life or depression in later years. This is effective therapy that augments the effects of zinc, niacin, and vitamin C. With this therapy the serum Cu level is reduced, and the blood histamine rises to the normal range of 40 to 70 ng/ml after five to six months of therapy. The psychiatric symptoms decrease as the biochemical values approach more nearly normal levels (Pfeiffer and Braverman, 1979).

Folic Acid in High-Blood Histamine Normal-Copper Patients

Histadelic (high-blood histamine) patients are characterized by fast oxidation, little fat, long fingers and toes, severe depression, compulsions, and phobias. These patients respond to mild antifolate drugs such as phenytoin and agents that decrease histamine such as calcium salts and methionine in doses one to two g/day. Folic acid makes histadelic patients worse, and even the folic acid in food may cause seasonal depression, which we have termed "salad bowl depression." A reducing diet composed mainly of New Zealand spinach or lettuce has caused depression in some histadelic patients. These examples are obviously dietary extremes, but the patient who is depressed each summer in the salad season may be histadelic. Even the 0.4-mg (400-μg) dose of folic acid in many multivitamins is enough to produce increased depression in

the histadelic patient. When a mildly depressed histadelic patient is given one mg of folic acid per day, a severe agitated depression may result. Therefore, we do not use folic acid in any schizophrenic patient until we know the absolute basophil count or the blood histamine level. Since the blood histamine is contained primarily in the basophils, the absolute basophil count may frequently serve to differentiate histapenic and histadelic patients. Therapy with niacin, folic acid, and zinc-manganese can change a low-blood histamine (histapenic) patient into a high-blood histamine depressed patient (Foreman and Mangor, 1973). This has occurred many times in our experience and is corrected by a reduction in the dose of folic acid or elimination of folic acid for a week and thereafter the use of a smaller dosage. Our usual one to two mg/day dose of folic acid is sufficient for the histapenic high copper patient.

Some of the florid symptoms in the high copper histapenic patient will respond promptly to therapy with folic acid, niacin, vitamin C, zinc, and manganese. The drippy palm syndrome which forces the patient to carry a wad of tissues in each hand to absorb the sweat, responds within one to four weeks to this vitamin-mineral regime. The hypomania, hallucinations, and mind racing are subdued within three to four weeks. In other patients insomnia may be rectified in the same period. The degree of paranoia decreased very slowly, so that full remission may take 12 to 15 months. Relief of paranoia parallels the attainment of a normal Cu level in the blood serum.

The simple histapenia-histadelia concept allows a therapeutic trial of "running for the other goal line." If a patient worsens with folic acid and niacin, this therapy is stopped. Then the history and laboratory data are reviewed, and the patient may be tried on methionine, calcium, and phenytoin therapy to see if this provides improvement. Many allergic patients do not store histamine in their basophils because of antigen-antibody interaction. Thus, our allergic patient may have an abnormally low blood histamine.

Excess copper is the primary imbalance of histapenics. The Cu comes from the drinking water, food, and "vitamins plus minerals," which are overloaded with 2 mg of copper. Diphenylhydantoin (DPH) elevated copper levels (Vasiliades and Sahawneh, 1975). High Cu levels antagonize folic acid through a complex web of trace metal interactions. Pregnant women and young women on the birth control pill will have abnormally low blood histamine levels because of the high estrogen levels. Copper levels also rise with the increase in estrogens. High copper levels increase the activity of histaminase (diaminoxidase), which is a copper-containing enzyme (Jensen and Olesen, 1969; Jonassen, 1976; Torok, 1970). Vitamin C-deficient guinea pigs show progressive rises in serum copper levels.

Pellagrins have elevated serum, hair, and urinary copper levels; skin histidine is low (Rifkind and Heim, 1977; Vasantha, 1970). These return to normal with niacin treatment. Reduced availability of NADH has been reported in folate deficiency. The skin of pantothenic acid-deficient rats has a fivefold increase in copper level, as compared with controls. It has been reported that a single large dose of pantothenic acid effectively lowers the high serum Cu level for a one week period. Plasma concentrations of Zn decrease during pregnancy, whereas Cu levels increase. Zinc and Cu are antagonistic in the human body and probably compete for the same sites on the protein carrier, metallothionine. Histamine is stored in the mast cells and basophils in a zinc-heparin-histamine complex (Kazimiercza and Maslinski, 1974; Keller and Sorkin, 1970).

Zinc and Neural Function

Zinc appears to play a role in axonal transport and neuronal microtubule and tubulin synthesis and assembly (Amos and

Baker, 1979; Baker and Amos, 1978; Larsson et al., 1977; Tamm et al., 1979). Axoplasmic flow and axonal and dendritic transport are responsible for delivery of various macromolecules to distant parts of the neuron. Axonal transport occurs for opiate receptors in rat vagus nerve, and muscarinic cholinergic receptors in vagus sciatic and splenic nerves. Axonal flow may be common to all receptors (Young et al., 1980). Zinc ions induce tubulin to form transport sheets as well as increase the number of neurofilaments. Toxic concentrations of Zn can produce abnormal tubulin aggregates (Gaskin et al., 1978). In segments of rat peripheral nerves immersed in zinc chloride solutions buffered with Zn ions neurotubules are stabilized. Zinc also has an essential role in brain tubulin phosphorylation (Larsson et al., 1977).

Small amounts of zinc $5X10^{-6}$ M stimulate rapid axonal transport of proteins in an in vitro system using frog ganglia and nerve (Edstrom and Mattsson, 1975). Zinc probably stimulates axonal transport by stabilizing rat brain microtubules and ribosomes (Edstrorn and Mattsson, 1975). Zinc, at concentration of $5X10^{-6}$ increased synthesis to 140 percent of the control and protein transport to 175 percent of the control value. In certain concentrations, Zn appears to be important for both protein synthesis and axoplasmic flow. Metal chelation of Zn causes nerve degeneration, while Zn toxicity causes fast axonal transport resulting in a distal concentration of membrane protein which may proceed to defective maintenance of axon terminal structures and loss of function.

Zinc is also the most important trace metal in subcellular DNA and RNA fractions. Both DNA and RNA polymerases are Zn metalloenzymes. Zinc's primary importance in nucleic acid metabolism may explain much of its role in neuron maturation and proliferation.

Brain Development and Zinc

Zinc is an essential nutrient in the development of neurons of the normal brain. Rats Zn deficient in prenatal and early postnatal periods (gestational-lactational) develop abnormal brains. In adults rendered Zn deficient only postnatally, abnormal behavior is manifest without demonstrable abnormal structure. Both hippocampal and cerebellar development in rats occur postnatally with the cerebellar cortex acquiring nearly all its cellular constituents and the hippocampus acquiring 85 percent of its neurons during the first three weeks of life (Hurley and Shrader, 1972). Zinc is involved in the maturation and function of the mossy fibre pathway. Histochemical observations indicated increasing levels of Zn in the hippocampal mossy fibre layer after 20 days of age. Between 18 and 22 days hippocampal Zn increased by 35 percent to reach adult levels. Axoplasmic transport of Zn occurs from granule cell perikarya to their terminal boutons (Crawford and Connor, 1972). Zinc deficiency during the critical period for brain growth permanently affects brain function. When this deficiency is imposed throughout the latter third of pregnancy, brain size is decreased, there is a reduced total brain cell count and the cytoplasmic nuclear ratio is increased, implying an impairment of cell division in the brain during the critical period of macroneuronal proliferation (Hurley and Shrader, 1972). In adult life, male rats so treated display impaired shock avoidance and female rats are significantly more aggressive at a high level of shock than adult females whose dams were Zn sufficient during pregnancy (Halas and Sandstead, 1975; Underwood, 1971). Zinc deficient animals are more susceptible to a standard stress.

Zinc deficiency has been shown to impair DNA, RNA and protein synthesis in the brains of suckling rats (Fosmire et al., 1975). Zinc deficiency results in impaired incorporation of thymidine into brain DNA. Incorporation of sulfur into protein is also decreased. Zinc deficiency

also decreases the concentration of total lipid in brain while phospholipids and fatty acids are not affected.

Rat pups suckled for 21 days by dams fed a zinc deficient diet demonstrated impaired body growth and smaller cerebella and hemispheres compared to pups given adequate zinc (Fosmire et al., 1975). A smaller hippocampus and a marked retention of the external grandular layer of the cerebellum are associated with zinc deficiency (Buell et al., 1977). A deficiency of dietary Zn during the suckling period of the rat results in the pups having smaller forebrains, reduced cell numbers, and decreased RNA and DNA (Fosmire et al., 1975). Zinc deficiency in pregnant rats affects pups' liver greater than brain. Livers contain only one-third of the normal amount of Zn. Total brain Zn was spared by comparison. Buell et al. (1977) found that postnatal Zn deficiency in rats results in fewer brain neurons with a decrease in the total amount of DNA. The hippocampus showed similar deficits.

Zinc and Hormones

Zinc deficiency affects hypothalamic pituitary thyroid function. Thyrotropin releasing hormone content was decreased in the zinc deficient rat (Morley et al., 1980). Ultimately triiodothyronine (T3) and thyroxin levels were decreased. The hypothalamic axis susceptibility to Zn deficiency may explain the dynamic relationship between testosterone and Zn. Injections of testosterone or dihydro-testosterone in mice restores normal zinc content (Donovan and Thomas, 1980) while Zn deficiency decreases serum production and delays puberty (Prasad, 1966).

Elevations in hypothalamic Zn concentrations in the rat appear to correlate with the release of gonadotropin releasing hormone and gonadotropins which occurs between proestrus and estrus and after castration, although this, of course, does not establish a causal relation (Merriam et al., 1979). Hypothalamic Zn ions rise with gonadotropin secretions (Merriam et al., 1979; Root et al., 1979). Hypogonadism occurs with Zn deficiency (Caggiano et al., 1969; Prasad, 1966).

Zinc deficiency inhibits essential fatty acid metabolism to prostaglandins (PG) either by blocking linoleic acid desaturation to gamma - linoleic acid or by inhibiting mobilization of dihomo - gamma linolenic acid from tissue membrane stores (Cunnane and Horrobin, 1980). Prolactin and Zn have similar actions on PGE1 formation and prolactin enhances flow of fluid from fetal to maternal compartments (Manku et al., 1975; Manku et al., 1979). Zinc deficiency can result in polyhydraminos (Manku et al., 1979). Opiates may have an effect on PGE1 synthesis which is opposite to that of Zn and there is evidence that reduced PGE1 production (possibly due to an endogenous opioid) may play a role in schizophrenia (Horrobin et al., 1978; Horrobin and Morgan, 1980). An enkephalin degrading amino peptidase from rat brain homogenates is a Zn metalloenzyme(Schnebli et al., 1979). A higher than normal proportion of arachidonate was found in the fatty acids of Zn deficient skin (Bettger et al., 1980). PGE2 and PGF2 have opposing effects on Zn transport and may act as regulators of the intestinal mucosa transport of Zn (Song and Adham, 1979).

Zinc deficiency and thyroid hormone shortage occurring in both cretinism and myxedema have similar signs, ie. retarded growth, reduced appetite and activity, impaired development of skin and hair (Hartoma et al., 1979). Zinc deficiency symptoms may be mediated by excess glucocorticoids since Zn depletion results in elevation of glucocorticoids. Elevated glucocorticoids and Zn deficiency both result in death of thymic lymphocytes (Donovan and Thomas, 1980). A deficiency of nerve growth factor may occur with Zn deficiency. One nerve growth factor is a

small basic protein with three distinct types of sub-units (Vinores and Guroff, 1980). Two molecules of Zn are present in the complex and Zn participates in holding the structure together (Dunn et al., 1980; Pattison and Dunn, 1975). In the absence of Zn the subunits separate. Nerve growth factor is required for the survival and development of certain sympathetic and sensory neurons. It is equally clear that nerve growth factor affects a wide variety of other cells as well. Nerve growth factors are present on the plasma membrane and almost certainly at the synaptic ending as well (Dunn et al., 1980). Nerve growth factor action increased dendritic attachments which requires elevated levels of RNA synthesis, which is Zn dependant.

Zinc and Amino Acids

Zinc deficiency greatly alters amino acid metabolism and balance. Some amino acids have important neurotransmitter functions in the brain. Hsu (1977) studied the effects of Zn deprivation on the levels of free amino acid in plasma, urine, and skin extracts of rats. He found significantly higher concentrations of threonine, leucine, and isoleucine both in the urine and plasma of Zn-deficient animals. Higher concentrations of taurine, glutamic acid, valine, and lysine as well as urea were also observed in the Zn deficient urine. A Zn deficient diet causes anorexia and cyclic feeding behavior in rats. Zinc deficiency causes a significant increase in the brain catecholamines; norepinephrine and dopamine (Wallwork and Sandstead, 1981). Total plasma amino acids are increased (Wallwork et al., 1981). Histidine was especially elevated while plasma glutamic acid was depressed. Histamine from histidine, glutamic acid directly, acetylcholine from choline, serotonin from tryptophan and catecholamines from tyrosine are neurotransmitters affected by dietary control. Changes in amino acid levels in Zn deficiency were affected by abnormalities in amino acid utilization and excretion (Wallwork et al., 1981). Unfortunately, amino acid distribution in the brain of Zn deficient animals has not been studied, although the brain is not as sensitive as some of the tissues described. For example, Zn concentration in the brain is unaffected by marasmus or kwashiorkor (Lehmann et al., 1971).

Zinc and Behavior

Zinc deficiency in humans is associated with apathy, lethargy, amnesia, and mental retardation, often with considerable irritability, depression and paranoia (Prasad et al. 1978). Caldwell et al. (1973) have shown that the rats born to mildly Zn deficient mothers are mentally retarded and do not learn as well as rats from Zn supplemented mothers. Prior to the above studies Caldwell and co-workers observed a significantly inferior learning ability, as measured by water maze and platform avoidance conditioning tests, in the surviving offspring of mildly Zn-deficient mothers, compared to similar rats from Zn-supplemented mothers. These effects of Zn deficiency were subsequently confirmed and extended (Halas and Sandstead, 1975; Sandstead et al., 1972; Sandstead et al., 1977; Underwood, 1971). Colleagues visiting Iran and Egypt are told that 30 percent of the young children are slow learners. It may not be a coincidence that these areas of the world which have been farmed for centuries no longer have much available Zn in the soil (Prasad, 1966). Hesse et al. (1979) have found that adult rats chronically deprived of dietary Zn do not behave as hippocampal intact animals; the evidence suggests that the deficiency alters the electrophysiological properties of normally Zn rich hippocampal mossy fibers (Hesse, 1979). The behavioral characteristics of these animals differed from controls and were substantially parallel to those reported for animals with excess glucocorticoids, i.e., impaired passive avoidance, open field activity and maze alternation

(Hesse et al., 1979). Zinc deficient rats show latency in the platform box test, cul de sac and retrace errors, and open field errors (Caldwell et al., 1973; Sandstead et al., 1972; Sandstead et al., 1977). Zinc deficient rats (Bradford et al., 1981) show significant differences in stereotypic behavior (grooming licking) and motor function (rapid changes in position, backward locomotion and rapid jerky movements). These behavioral abnormalities correlated with high levels of striatal catecholamines.

Zinc ions can mimic ouabain when injected intraventricularly and can produce epileptic seizures in rats. Serum zinc levels in treated epileptics are significantly decreased as compared to age and sex matched controls (Barbeau and Donaldson, 1974). In contrast, elevated Zn levels (possible B_6 deficiency?) in serum have been found in baboons moderately sensitive to photically induced seizures (Alley et al., 1981). The hippocampus is implicated in epileptic seizures (Silfvenius et al., 1980). Zn may also have an important role in transmitter release on the basis of the inhibitory effect on Na-K ATPase (Barbeau and Donaldson, 1974). Seizures which occur after burns of the skin are possibly due to Zn or Mn deficiency caused by excess demands of tissue regeneration (Hughes and Cayaffa, 1973). Zinc and Mn are important for normal otolith formation and, therefore, necessary for normal balance. Disperception can occur during deficiency states and Zn has been useful in otology (Ruggles and Linquist, 1976). Henkin et al. (1975) have noted that one of syndromes of acute Zn loss is cerebellar dysfunction. Zinc supplementation following Zn deficiency reverses excessive emotionality (Pfeiffer, 1975). Each of three major phenothiazines increases the total brain zinc uptake in all animals tested, more in rats than in mice (Czerniak and. Haim, 1971). The following regional changes were detected in rat brains. Occipitotemporal cortex, thalamus and hippocampus became more zincophilic, the thalamus especially under chloropromazine and the hippocampus under perphenazine treatment. Zinc deficiency clearly alters behavior through both primary and secondary metabolic pathways.

Brain Content of Zinc and Disease

McLardy (1973) observed a 30 percent deficit of Zn brain content in early onset schizophrenics and chronic alcoholics. Other researchers have observed a decrease in hippocampal Zn in schizophrenics (Kimura and Kumura, 1965). Zinc deficiency elevates catecholamines in rat brain (Bradford et al., 1981; Wallwork and Sandstead, 1981) and zinc deficiency with dopamine excess might be a frequent biological dyad in schizophrenia.

Lead displaces Zn from the hippocampal mossy fiber system (Bushwell and Bowman 1979; Niklowitz and Yeager, 1973). Rabbits exposed to lead-poisoned water have uniformly elevated frontal cortex, cerebellar, and hippocampal lead. Copper, iron, and Zn are significantly decreased in these regions. The decrease in Zn was most significant in the interior hippocampus.

Staton et al. (1976) have also described Zn deficiency-Cu excess presenting as schizophrenia. In the Wilson's disease patient only Zn uptake is increased since Cu is already overloaded (Aaseth et al-, 1979). It is clear that brain Zn content changes during disease states and that brain Zn deficiency is possibly dynamically related to schizophrenia, alcoholism, Wilson's disease and lead poisoning.

Excess Zinc

Zinc excess appears to have almost no brain toxicity, although patients show some significant somatic effects (Pfeiffer et al., 1980; Snyder, 1979). Zinc has very little toxicity measured by morphological and histochemical changes occurring in the brain of rats fed 100 mg of zinc oxide (via gastric tube) Kozik, 1979; Kozik et al., 1980). The

rats developed minor degenerative changes of neurocytes (vascularization) along with moderate proliferation of the oligodendroglia and of undifferentiated subependymal glial cells. Cerebral activities of acid phosphatase (elevated in prostatic cancer), ATPase and acetylcholinesterase were found, while increased activity of thiamine pyrophosphatase was observed. The activity of carbonic anhydrase, a Zn enzyme, normally increases with age but was lower than normal in white matter from Krabbe disease and adrenoleukodystrophy (Lees et al., 1980).

Pick's disease is a degenerative dementia with onset in the 5th to 7th decades, characterized by apragmatism, stereotyped gestures, bizarre behavior, decreased speech leading to complete mutism, prefrontal signs and in some cases, pyramidal and extrapyramidal signs. Morphologically, its most characteristic form consists of atrophy of the temporal and frontal lobes, with gliosis and demyelination. In addition, two types of pathological changes in the neuronal bodies are observed: argyrophilic inclusions and neuronal ballooning. The lesions in Pick's disease are observed initially in the hippocampus, and subsequently extend to the temporal, insular and orbitofrontal cortex, and sometimes even to the parietal cortex. The hypothesis of an excess of Zn in patients with Pick's disease is supported by postmortem hippocampal Zn measurements (Constantinidis et al., 1977; Constantinidis and Tissot, 1980). Hippocampal Zn is higher in Pick's disease than in Alzheimer's disease or controls. Similarly, the blood cells and urine of patients with

Pick's disease contain more Zn than those of patients with Alzheimer's disease or controls. Zinc chelators (Disulfiram, calcium EDTA) increase urinary excretion of Zn. This increase is greater in patients with Pick's disease than in patients with Alzheimer's disease (Constantinidis and Tissot, 1980).

Zinc and Schizophrenias

The schizophrenias are biochemically numerous, so the simplistic term "schizophrenia" should be avoided. At least seven different biochemical imbalances can produce clinical symptoms which are indistinguishable by the so-called research diagnostic criteria for simplistic schizophrenia. As an example, Wilson's disease, a Cu overload disorder, can be marked by psychosis and hallucinations. Oral zinc has an antagonistic effect on the reabsorption of Cu in the gastrointestinal tract and, for that reason, is considered valuable in the treatment of this disease (Hoogenraad et al., 1978). We have already mentioned the work of Derrien and Benoit (1929), and Kimura and Kumura (1969) who suggested or found Zn to be involved in mental disease. In 1967 Pfeiffer and Iliev reported low blood histamine levels in schizophrenic patients histamine is stored with zinc. A definite percentage of psychiatric patients have been found to have the chemical kryptopyrrole in their urine. Kryptopyrrole reacts avidly with all aldehyde chemicals, including pyridoxal (Pfeiffer et al., 1974). The resulting kryptopyrrole-pyridoxal complex by chelating Zn produces a Zn deficiency as well as a severe pyridoxine deficiency. These patients, whom we have termed pyroluric, respond for the most part to vitamin B_6 and Zn therapy (Pfeiffer and Bacchi, 1975; Pfeiffer, 1976). Pyroluria is a form of schizophrenic porphyria, similar to acute intermittent porphyria where both pyrroles and porphyrins are excreted in the urine in excess (Braverman, 1978). Both Zn, ALA dehydratase, vitamin B_6 , and ALA synthetase, are important co-factors in the pyrrole porphyria-heme pathway.

Evans (1980) found that rats absorb one and one-half times as much dietary Zn if given vitamin B_6 . Specifically 71 percent of dietary Zn was absorbed when the animals were given 40 mg of the vitamin per kilogram of diet. Only 46 percent of the Zn was absorbed when two mg of vitamin B_6

per kilogram were given (Evans and Johnson, 1980). This effect may be due to vitamin B_6's role in the tryptophanpicolinic acid pathways.

Practical Aspects of Zinc Supplements in Man

The physicians at the Princeton Brain Bio Center (PBBC) have had 15 years of experience in the use of trace element dietary supplements since Zn therapy was started in 1967. In 1968 we found in man that Zn plus Mn was more effective than Zn alone in eliminating Cu via the urinary pathway. Approximately one half of the patients coming to the PBBC have a Cu overload as shown by blood serum or hair analysis. Molybdenum and occasionally d-penicillamine are used with Zn and Mn to control Cu overload. The Zn recommendations are based on our experience in 70,000 clinic visits of over 15,000 patients wherein the blood, Zn, Cu, Fe and Mn were determined at each visit. In many patients blood aluminum, molybdenum, lead and rubidium were also determined. Oral Zn salts are readily and equally well absorbed (Sohler and Pfeiffer, 1980). So called "chelates" (Zn added to amino acid digests) have no advantage and are more costly. The surgeons, pioneering in the use of adequate Zn for wound healing, introduced the 50 mg Zn (as the sulfate) tablet. The actual weight of Zn as the sulfate ($ZnSO^4.7H^20$) is 220 mg. The body needs only 15 mg of elemental Zn per day so this original 50 mg tablet is too large and may produce nausea and diarrhea. The use of Zn, 15 mg (as the gluconate) should be standard. This lower dose seldom produces nausea if taken with food. For children, infants and senile patients a liquid preparation of Zn plus vitamin B_6 and ziman (Zn plus Mn) with vitamin B_6 are available from either Willner Chemists, New York City or Bronson Laboratories, LaCanada, CA.

Immediate side effects of dietary Zn supplement may be occasional nausea, more than normal sweating, intolerance to alcohol and transient worsening of depression of hallucinations. All of these reactions respond to lessening of the dose or taking the 15 mg of Zn with food. The immediate effect of Zn may be a decrease in serum iron level. With 15 mg of Zn this is rare and is usually self-corrective so that iron supplements are not needed, (No iron therapy unless serum iron level drops below 50 mcg percent!). Continued massive doses of Zn, up to 5000 mg per day decreased both serum Cu levels and ceruloplasmin levels in one female patient (Pfeiffer et al., 1980). This was corrected by the daily use of Theragran-M which contains 2 mg of Cu. Patients on Zn supplements may have more persistent visual after-images and the time for dark adaptation of the eyes may be prolonged.

The most insidious effect of excess Zn over a period of years is the reduction of blood Mn, 90 percent of which is contained in the erythrocytes. This produces macrocytosis (increased mean cell volume [MCV] and mean cell hemoglobin [MCH]) when the blood Mn level falls to less than 8 ppb (normal 15 ppb). Low blood Mn levels may accentuate depression, allergies, and seizure activity in epileptics. Manganese is poorly absorbed from the intestine and, while only 5 mg is needed per day, the patient may need as much as 300 mg of Mn as the gluconate to attain the normal blood level of 15 ppb. Zinc dietary supplements increase grand mal seizures in epileptics so Mn supplements should be started initially and Zn cautiously added one month later when the blood levels of Zn, Mn, and Cu are known.

The reduction in Mn may be beneficial in older patients in that long term oral Zn will lower blood pressure probably as a result of lowered Mn levels. One antihypertensive drug, hydralazine, is a Mn chelating agent which lowers blood pressure and blood Mn levels. Manganese orally in susceptible older patients may produce hypertensive headaches which subside when the

Mn is discontinued. One of the side effects of hydralazine therapy is lupus erythematosis, an autoimmune disease. Thus, prolonged large doses of Zn may, by lowering Mn levels, increase the patient's susceptibility to autoimmune reactions.

We postulate that some part of the cerebral side effects of Zn supplementation are mediated by the mobilization of Cu from storage in liver and muscle. With Zn by mouth the serum Cu may increase for a period of one to three months before falling to a normal level, With d-penicillamine therapy and Zn/Mn supplements this does not occur. In some instances such as severe paranoia, or retinal disease, the prompt decision to start therapy with d-penicillamine plus Zn and Mn can be justified. The use of Zn and Mn with vitamin B_6 makes d-penicillamine therapy safe because as a chelator d-penicillamine removes Cu, Zn and Mn. The loss of taste with d-penicillamine is a sign of Zn deficiency.

Drug Flood Syndrome

Patients who come to the Princeton Brain Bio Center on large doses of neuroleptics may get very sleepy when Zn and vitamin B_6 are used in treatment. This is the effect of the neuroleptic on a brain made more normal and the dose of neuroleptic should be rapidly reduced. For example, 40 mg of haloperidol can be reduced to 5 to 10 mg at bedtime. The patient's affect improves with the Zn and vitamin B_6 so that the parents may suggest that the neuroleptic dose is too large.

Vitamin B_6 (Pyridoxine) Toxicity

An occasional patient will show high hair and high serum Zn levels with elevated spermidine and low erythrocyte GOT activity. We postulate that these patients have vitamin B_6 deficiency and cannot utilize the Zn present until adequate vitamin B_6 is provided. With vitamin B_6 therapy the high Zn level drops to normal. Doses of 1000 mg of vitamin B_6 each morning are well tolerated but oral vitamin B_6 in doses of more than 2000 mg may produce tingling or numbness of toes and fingers. This indicates the need for reduction in the vitamin B_6 dosages. With lower doses of vitamin B_6 the numbness is relieved.

The beneficial effect of Zn, Mn and vitamin B_6 in pyroluria, is important since this defect extends through many diagnostic categories. The most urgent need is for daily supplements in those children now labelled mentally retarded, learning disabled, minimal brain damaged, autistic, dyslexic and hyperactive, For this purpose some philanthropic foundation might wish to make available at cost (or free of charge) a simple supplement consisting of the daily need for Zn and Mn, namely 15 and 4 mg respectively plus 25 mg of pyridoxine (vitamin B_6). The patients could be used as their own controls and other vitamins could be used as placebo medication for the first two weeks of medication while the basic behavioral observations are being made

Signs of Zinc Deficiency

In order to diagnose Zn deficiency of the brain, peripheral signs of Zn deficiency must be recognized. These are: white spotted fingernails, cutaneous striae, nasal polyps, amennorhea, impotency, tinnitus, abdominal pain, stuttering, poor dental enamel, loss of taste, frequent infections, depression, insomnia, disperceptions and hallucinations.

Signs of Zinc and Vitamin B_6 Deficiency

Zinc is needed for phosphorylation of pyridoxal to make pyridoxal phosphate so adequate vitamin B_6 should always be given with Zn. Patients without dream recall are vitamin B_6 deficient and vitamin B_6 deficiency is the basic nutrition deficit in Carpal Tunnel Syndrome and Chinese Restaurant Syndrome (Folkers et al., 1981). Double deficiency of Zn and vitamin B_6 , as in pyroluria, may cause the following: no

dream recall, sweet breath and body odor, morning nausea, crowded upper incisors, splenic pain, pallor with itching in sunlight, constipation, achy knees, amennorhea, impotency, seizures, disperceptions, hallucinations, amnesia, paranoia, eosinophilia, lymphocytosis, high bilirubin, and low immune globulin A (Pfeiffer, 1974). We have found a deficiency of Zn and B_6 in all girl families we have treated also.

Summary - Zinc in Schizophrenia

The mauve factor (kryptopyrrole) depletes patient of both Zn and vitamin B_6 (pyridoxine) because the pyrrole combines with pyridoxal and then with Zn to produce a combined deficiency. These patients suffer from "pyroluria", a familial disorder which occurs with stress.

Pyroluria is treated by restoring the vitamin B_6 and Zn so that this double deficiency is corrected. A dose of vitamin B_6 which results in daily dream recall (a normal phenomenon) as well as a Zn-Mn supplement are given daily. One should increase the daily AM dose of vitamin B_6 (up to 2-0 g/day) until dream recall occurs.

With Zn, Mn and vitamin B_6 therapy the pyroluric patient may start to respond in 24 hours and certainly some progress is noted within one week. However, total recovery may take three to four months. The biochemical imbalance and symptoms will usually recur within one to two weeks if the nutritional program is stopped (Pfeiffer, 1974).

Pyroluria may occur together with other imbalances such as histapenia, histadelia, high Cu or cerebral allergies and in these instances progress will be slower. Low histamine patients are typically overstimulated with thoughts racing through their minds making normal ideation difficult. Low histamine children are hyperactive while often healthy in other respects. Serum Cu levels in these patients are abnormally high. Since Cu is a brain stimulant and destroys histamine, the elevated serum (and presumably brain) Cu level probably accounts for many symptoms, including the low blood histamine level.

The treatment program consists of the administration of Zn, Mn, vitamin C, niacin, vitamin B_{12}, and folic acid. The rationale underlying the treatment is that folic acid in conjunction with vitamin B_{12} injections raises the blood histamine while lowering the degree of symptomatology. Zinc and Mn allow for the normal storage of histamine in both the basophils and the brain. With this treatment the high blood Cu is slowly reduced and symptoms are slowly relieved in several months time. Zinc and Mn with vitamin C remove Cu from the tissues. The largest tissues of the body, namely the liver and muscles, are flushed of their Cu first so the serum Cu may rise to aggravate mental symptoms. If this occurs then the dose of Zn should be reduced for a two week period. Excess Cu may be acquired from commercial vitamins and minerals or drinking water flowing through copper pipes. Distilled water may occasionally be needed to reduce Cu intake.

David et al. (1976) found significant lead in the hyperactive child but at a level less than that of lead poisoning. We find similar levels of lead and high levels of Cu which is also a CNS stimulant. We believe that with a high Cu level, any lead level above the age of the child is suspect. These patients are also Zn, and vitamin B_6 deficient. With adequate Zn and vitamin C both the lead and Cu levels return to normal within a period of six months and the hyperactivity is decreased. These children frequently have an elevated serum uric acid level which may indicate that the heavy metals are adversely affecting the kidneys. Excess Cu usually comes from the drinking water and lead exposure may be from air pollution (traffic), contact with the printed page, etc. Zinc deficiency occurs with faulty eating habits.

Epilogue

Nutrients at their best can be smart drugs that know exactly where to go and

what to do. In contrast, other drugs are nonspecific and go everywhere, with the molecules wandering aimlessly, producing unwanted side actions. Nutrients at worst have no therapeutic effect, and are either incorporated or excreted by the usual metabolic disposal systems. Drugs at worst can be rapidly fatal or chronically disabling, as in tardive dyskinesia. Nutrients are slow in relieving symptoms, but when effective the relief is more permanent. Drugs may have the impact of a bulldozer, so both the patient and the therapist know that the drug is working. The slow onset of action of nutrients makes rigid experimental design difficult. If the patient is used as his own control, the placebo must then be given initially rather than after the nutrient treatment.

The advantages of nutrient treatment are inherent in the accumulated knowledge needed to use the nutrient. Usually a study of the patient indicates that a specific defect might be present: sometimes this can be assayed by objective tests. If these tests indicate a deficiency, then the rigid statistical trials which are frequently applied to therapy become meaningless. Scientists discovered the therapeutic effect of the various B_{12} vitamins Without a double-blind test because the objective tests were numerous and the biochemical insight was extensive. We hope that such biochemical tests will lead to better insight and treatment of the Schizophrenias. Biological science can only give us progress reports: it is doubtful whether the final word will ever be spoken or written in our slow conquest of the schizophrenias.

Acknowledgements

This paper could not have been written without the expert help of Elizabeth H. Jenney, M.S., Marie Arcaro, B.A., Eric Braverman, B.S. and Barbara Aston, M.S., Nutritionist.

We acknowledge financial assistance from the following families: Thomas Peters, Stephen Kahn, John Davenport and A.N. Spanel and The Pine Level Foundation.

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