The Effect of Nutrient Supplements on the Biological and Psychological Characteristics of Low IQ, Preschool Children

Unabelle R. Boggs, Ph.D.[1], Allen Scheaf, Ph.D., David Santoro, Ph.D. and Robert Ritzman, R.Ph.

Introduction

Causes of learning and behavioral problems in children are numerous and complicated with interaction between metabolic state and psycho-social environment. Factors known to influence learning ability, behavior and brain development include: nutrition (1-5), genetics (6), toxic metals (7-9), allergens (10, 11), infections (12, 13), social deprivation (14, 15), richness of environmental stimulation (16,17), and history of reinforcement (18). Usual methods of intervention include drugs, behavioral modification, counseling, psychoanalysis, special education, and programs of environmental enrichment. However, these methods neither identify nor alleviate those problems caused by either metabolic disturbances such as specific nutrient needs or toxic metal overload.

Drugs (dextroamphetamine and methylphenidate) reduce hyperactivity but, contrary to popular opinion, do not reduce delinquencies or enhance IQ, academic performance, visual-motor coordination, and emotional adjustment (19, 20). In addition, undesirable side effects of methylphenidate are so pronounced and frequent in preschool children that they are not advised for this age group (21). Behavioral methods are safe and can be very effective. However, their use with the type of subjects employed in the present study or with the severely disturbed requires expensive staff training and constant programming (22).

Early childhood education programs such as Headstart have been shown to raise the IQ and increase academic performance of disadvantaged children. In general, the earlier the intervention and the greater the involvement of the mother the greater the benefit. An extensive two year program of teaching parents how to teach their children raised the average IQ from the low 90's to 107 and decreased school behavior problems (17). One intervention program with low IQ mothers and their infants, starting before six months and continuing to school entry, improved development on a large number of measures and raised IQ over 20 points during the period between 18 months through 7 years (23). However, four years of special education efforts failed to improve basic skills in hyperactive, hypoactive, and

1. 1025 Amelia Ave. Akron, Ohio 44302.

normoactive learning disabled boys who tested at the 20th percentile when first seen and at follow-up. Moreover, the troublesome behaviors common to ten-year-old hyperactive boys were still present at 14 years of age (24).

There is a need for more effective and less expensive means of controlling behavior and increasing mental capacity. Improved nutrient intake could be expected to fill these needs and to improve health in general since adequate nutrient supply is the most fundamental requirement for biological and psychological functioning. No organism can survive without the availability of proper nutrients. Moreover, the level of health of the organism is directly dependent upon the levels of nutrients available.

Numerous studies over the years have shown that the healthy development of an animal or child from conception onward depends upon adequate nutrient consumption. The deficiency of any one of a large number of different nutrients has been shown to cause embryonic and fetal malformations. The greater the deficiency, the more severe the malformations, the larger the number of different kinds of malformations, and the more body structures affected. For example, marginal zinc deficiency in chick embryos causes defective feather barbs. As the deficiency increases the defects progress to muscular weakness, to skeletal and other mesodermal malformations, to neural and endodermal malformations, and to death in very early embryonic stages. Even more severe deficiency prevents ovulation and fertilization (25). Further studies have shown that given normal gross development, various levels of zinc intake can be related to learning ability in rats, with the male being more susceptible to marginal zinc deficiency than the female (26). Zinc deficiency (measured in the hair) has also been shown to reduce growth, appetite, and taste acuity in young humans (27) and to occur frequently in Headstart children (28).

Studies of various cultures suffering from widespread malnutrition have shown that general malnutrition during prenatal and postnatal life leads to retardation of brain development, lowering of IQ, and changes in behavior (1-5). Deficiencies of specific nutrients can also lower IQ as would be expected from animal studies. Paul Gyorgy reported in 1968 (29) that vitamin A deficiency depresses IQ below that caused by multiple deficiencies and semi-starvation. If the level of deficiency is sufficiently severe and timed to inhibit nerve cell formation, the damage cannot be reversed (30). However, several studies indicate that if the neuron formation has not been prevented, mental retardation in both humans and rats caused by prenatal malnutrition can be overcome by proper post-natal nutrition (31).

The first use of a vitamin in treating mental illness in patients without pellagra was in 1939 by Cleckley et al. (32) who successfully treated 19 patients with 100 to 300 mg of niacin. (The National Research Council recommends 18 mg per day for a healthy 154 lb. man in the 23-50 year age bracket and 13 mg for a healthy 128 lb. woman in the same age group.) It was also recognized by others at this time that therapeutic (larger than normal) doses of nutrients are needed to overcome illnesses of various kinds including psychosis (33). In 1957, Hoffer, Osmond and others reported the successful use of three grams of vitamin B3 for treating schizophrenia (34). They, with others, conducted the first double blind studies in psychiatry in which neither the evaluators nor the caretakers knew which patients were receiving experimental treatment (35, 36). In their niacin studies they did extensive follow-up evaluation of patients discharged from the hospital over a five year period in which they evaluated treatment effectiveness on several different levels having to do with perceptual distortions and family and community adjustment. They were thus able to demonstrate that vitamin B3 decreases schizophrenic symptoms in a statistically significant number of patients (37). Likewise, Wittenborn showed that a subgroup of acute schizophrenics improved on a large variety of measures when given three grams of niacin per day for two years (38).

In 1970, Green (39) described a schizophrenia-like syndrome in both children and adults who appeared healthy, having no clinical symptoms but many physical complaints. He called this syndrome subclinical pellagra, since vitamin B3 was able to relieve the symptoms. He found that in 1100 public

school children in Prince Albert, Saskatchewan, 17% showed signs of subclinical pellagra. The incidence of the illness is associated with socio-economic class, with the lower classes having the greatest incidence (40).

Allan Cott in 1971 (41) reported clinical evidence that massive doses of vitamin B3, B6, C, and E decrease the symptoms of schizophrenic children and adults and of autistic children. He also reported that the less disturbed learning disabled child responds to vitamins B3, B6, C, and pantothenic acid within three to six months of treatment. In 1975, Thiessen and Mills (42) reported in a matched control study that these four vitamins, given over a period of a year to learning disabled children with normal IQ, reduced hyperkinesis, sleep disturbance, nystagmus, and certain perceptual dysfunctions. Some basic language skills as measured by four subtests of the Illinois Test of Psycholinguistic Ability (ITPA) were also improved.

The Russian scientists, Dergacev et al. (43), reported in 1970 that high daily doses of orotic acid (1.5g) and folic acid (60 mg) and a medium dose of vitamin B12 (10 *u*g) improved a host of physical and behavioral symptoms of children with various memory disorders. The study included 24 experimental children and 12 control children. The children selected were those unable to remember more than four out of ten words presented to them the previous day. The physical symptoms which improved in all diagnostic categories were: asthenic symptoms (improved first), low body weight, headaches, tiredness, and emaciation. Social and psychological behaviors which improved in all categories were: contact with other children, participation in class, interest, ability to work, concentration, perseverance, responsibility, and self-discipline. Other studies have shown that orotic acid improves memory in animals (44) and protects against amnesia produced by electroconvulsive shock (45).

Pratusevich and Lisitsyna (46) found that a combination of potassium Orotate, methionine, glutamate, vitamins Bl, B2, B6, niacinamide, and pantothenic acid increased short-term memory and blood flow to the brain in normal healthy children. Glutamate, neurotransmitter and stimulator of brain metabolism (47), has long been known to decrease petit mal seizures (48), to increase mental functioning and improve personality in certain mentally retarded individuals (49, 50) and to improve learning in rats (51). Glutamine which is interconverted to glutamate and is more readily absorbed from the intestinal tract than glutamate (52), has been reported to increase IQ in mentally deficient children (53).

Watson (54), Pfeiffer (55), Rimland (56) and Blackwood (57) have reported the need to individualize nutrient supplements for either the mentally disturbed adult or child. In 1965, Watson reported that while certain adults with mental and emotional illnesses benefit from a broad spectrum, nutritional supplementation program, others develop metabolic imbalances with either no improvement or an exacerbation of their symptoms. Pursuing this observation with metabolic studies and a step-by-step evaluation of separate nutrients, Watson discovered that he could divide such individuals into what he called "slow and fast glucose oxidizers." Slow oxidizers particularly benefited from vitamins Bl, B2, and B6 while fast oxidizers are especially improved with pan-tothenic acid, choline, and vitamin E. Other nutrients may play a paradoxical role but to a lesser extent.

Rimland (56) started autistic children on a Recommended Dietary Allowance (RDA) level B-complex with 10 mg of iron and 500 mg of vitamin C, two weeks later added 500 mg of niacinamide and 75 mg of vitamin B6, then three weeks later added 100 mg of pantothenic acid. He found that most children were benefited markedly with such improvements as the clearing of skin problems, normalization of appetite whether excessive or lacking, increased alertness and social awareness, greater calmness, more accessibility, greater fluidity of speech, ,and greater pressure to talk. However, he found that 4 of 190 children became either more wild or more withdrawn on niacinamide and Pyridoxine (B6). He also found, in keeping with Watson's work, that a few children improved dramatically when pantothenic acid was added, while in others this led to deteriorated behavior.

Carl Pfeiffer et al. (55) have reported that

still another set of nutrients may worsen or benefit adult schizophrenics. Histamine in whole blood can be used as an indicator of whether or not folic acid and possibly vitamin B12 should be supplemented. Individuals with low histamine find relief following the intake of vitamin B12 and folic acid over a period of one to three months. However, high histamine individuals may experience exacerbation of their symptoms when taking folic acid. Pfeiffer (58) has also presented the idea that the quantity of urinary kryptopyrrole can be used as an indicator of the need level for vitamin B6 and zinc. Blackwood (57) has supported this by showing that the amount of zinc in hair is inversely correlated with the level of kryptopyrrole in urine.

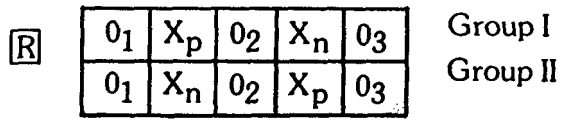
Pfeiffer has conducted metabolic studies . which have led him to believe that copper retention in the brain is a major problem in schizophrenics with low histamine (55). Elevated copper in the blood of schizophrenics had been reported as early as 1956 by Leach et al. (59) and confirmed by Akerfeldt in 1957 (60). Recently, Rudolph (61) reported that copper is also elevated in the hair of schizophrenics and of children with learning disorders. Conversely, Blackwood (57) found that copper in the hair of 73 subjects (with a mixture of ailments including schizophrenia) was not correlated with Hoffer-Osmond Diagnostic (HOD). Test scores suggesting that high hair copper may be related not only to schizophrenia but also to various conditions as is known to be the case with high blood copper (62). Jacob et al. (63) have reported that in rats hair copper and liver copper are highly correlated in direct proportion.

Blackwood (57) has also presented data showing that the metabolic types of Watson and Pfeiffer are separate entities and are found in children as well as adults. Combinations of the types may occur in an individual with superimposition of heavy metal poisoning along with elevated and depressed levels of nutrient minerals in the hair and an assortment of deficiency symptoms which are sometimes consistent with the formulae of Watson and Pfeiffer but sometimes not. Moreover, in the same report she showed that by supplementing individuals reporting mental and emotional symptoms with individualized nutrient regimens (based on hair minerals, metabolic types of Watson and Pfeiffer, and other deficiency symptoms) for periods ranging from one to six months, HOD Test scores were reduced 56% in 21 adults ($p = 0.001$). Another four individuals (three children and one retarded adult) supplemented five weeks improved 76% ($p= 0.05$) as measured by frequently occurring symptoms on Green's Dysperception Test. The present study is similar to the previous study mentioned above but differs in the type of subjects, the measures of effectiveness of treatment, and the experimental design. It was formulated to determine in a controlled manner whether any measures of developmental impairment or behavioral disorders could be improved by the use of multi-nutritional supplements individually prescribed to preschool children at developmental risk.

Method

Subjects were children attending Head-start nursery schools. The criteria for selection were: (a) high degree of developmental risk, (b) IQ below 80 on the Slossen Intelligence Test (SIT) and (c) willingness of parents to participate in the study. Nine children (eight boys and one girl) were originally selected, each from a different school, from over 400 children. The children acted as their own controls. Each child received a battery of physiological and psychological tests before the beginning of the experiment and at the ends of two experimental periods each of which lasted one month. Exceptions to this generalization are given in the results. During the first experimental period half of the children received nutrient supplements in powdered form and the other half received a placebo (methyl-cellulose). During the second experimental period those children receiving nutrients were switched to placebo and those receiving placebo were placed on supplements. Neither the children nor those evaluating them knew which treatment they were receiving. The experimental design was a randomized, double-blind, cross-over type. It is illustrated below with 0 representing the measures and its number subscript indicating the time of measurement. X_n represents the nutrient treatment and X_p represents

the placebo treatment. The R in the box indicates that the subjects were randomly assigned to the two groups. The group receiving placebo first is called Group I and the group receiving nutrients first is designated Group II.



Criteria for determining possible nutrient need and/or tolerance of specific supplemented nutrients included clinical appearance (e.g. learning disabilities, hyperactivity, poor speech, dry hair and skin, frequent infections) and the following laboratory tests: (a) blood histamine, (b) blood gases (pH, pO_2 [oxygen pressure], PCO_2 [carbon dioxide pressure]) (54, 57), (c) complete blood count, (d) fasting blood glucose and (e) mineral analysis of hair. Those minerals determined in hair were: calcium (Ca), magnesium (Mg), sodium (Na), potassium (K), copper (Cu), zinc (Zn), iron (Fe), manganese (Mn), chromium (Cr), nickel (Ni), lead (Pb), cadmium (Cd), mercury (Hg), and arsenic (As). Histamine in whole blood was analyzed by Bio-Science Laboratories using a modified spectrofluorometric method (64-66). Of the blood gases, pH, PO_2 and pCO_2 were analyzed directly in blood from the heated finger tip using arterialized capillary blood with the aid of an Instrumentation Laboratory Blood Gas Analyzer. The other blood gas values (HCO_3, total CO_2, and H_2CO_3) were calculated. Mineral levels in hair were determined by Bio-Medical laboratory, West Chicago, IL, using an emission spectrometer (ARL Applied Research Lab QA137, Inductive Coupled Plasma Quantometric Analyzer) and an atomic absorption spectrophotometer (Perk and Elmer 403).

Table 1 shows the nutrients and dosages used. Thiamine was omitted or kept low in relation to the level of pantothenic acid when the pH < 7.40 and H_2CO_3 > 1.1. Vitamin A was also omitted from the supplement of these individuals unless they exhibited symptoms of vitamin A deficiency such as dry hair, dry skin, frequent infections. When histamine was above normal, folic acid and vitamin B12 were omitted (57) and larger amounts of ascorbic acid were given since ascorbic acid has been shown to detoxify high histamine (67) in animals. All children received vitamin C as either ascorbic acid or sodium ascorbate. Potassium was omitted when the sodium/potassium ratio was normal and/or both minerals were elevated. Copper, sodium, chromium, and manganese were omitted when the hair levels of these minerals were normal or elevated. Children with elevated lead or cadmium received one tablet per day of a cysteine-lysine-methionine-mineral mixture (68-70) and larger doses of vitamin C, since it has been shown to detoxify lead and cadmium (71).

TABLE 1. DOSAGE RANGE OF NUTRIENTS IN SUPPLEMENT POWDER

Nutrient	Dosage Range
Vitamin A	0 -10,000 IU
Vitamin D	400 - 800 IU
Alpha tocopherol	0 - 400 IU
Thiamine	5 -100 mg
Riboflavin	50-100 mg
Niacin	100 - 400 mg
Pyridoxine	50 -100 mg
Cyanocobalamine	0-0.1 mg
Folic acid	0 - 1 mg
Ascorbic acid	0 - 500 mg
Sodium ascorbate	0 -1000 mg
Calcium pantothenate	0 -100 mg
Choline	0 - 250 mg
Inositol	0 - 500 mg
Calcium in dolomite and bone	210 mg
Phosphorus in bone	47 mg
Magnesium in dolomite	50 mg
Magnesium as protinate	50 -100 mg
Copper as protinate	0 - 2 mg
Chromium as protinate	0 - 0.3 mg
Iron as protinate	10-17 mg
Calcium Orotate	250 mg
Manganese as protinate	0 -1.6 mg
Potassium as protinate	0 - 75 mg
Zinc as protinate	5 -15 mg
Glutamine	500 mg
Protein hydrolysate	3000 mg
Cysteine-lysine-methionine-mineral mix	0 - 1/3 tablet

The nutrients and dosages used were similar to those in previous studies (57). The crystalline or powder form of most nutrients was employed to avoid additives and binders. The placebo consisted of pure methyl cellulose. The powdered nutrients and placebo were placed in small, plastic covered cups. Each child was to receive three doses per day mixed in food. The school administered one or two doses four times a week. The mothers were asked to give the remaining doses. Only two of the mothers consistently

gave all of the nutrients and placebo. When it was learned that a child was not receiving the powder at home, the school gave two doses in a half-day period.

Those tests used to determine effectiveness of treatment on development and behavior were: (a) three subtests of the Illinois Test of Psycholinguistic Abilities (ITPA), (b) Peabody Picture Vocabulary Test (PPVT), (c) Slossen Intelligence Test (SIT), (d) Early Childhood Embedded Figures Test (ECEFT), (e) Early Childhood Matching Familiar Figures Test (ECMFF), (f) Conners' Teacher Questionnaire (CTQ), (g) Conners' Parent Symptoms Questionnaire (CPSQ), (h) observations of attending behavior in the school and (i) mother's reports of her child's speech behavior. Tests (a) through (e) measured the child's response to various questions and were used to determine intellectual development. The higher the score on each of these tests the greater the ability and the less the impairment of development. All of these tests were administered by the same psychologist. The three subtests of ITPA (auditory reception, auditory sequential memory, and visual closure) were selected because these were the only ones appropriate to the abilities of the children in our study.

The early childhood tests, ECEFT and ECMFF, are tests of various aspects of analytical ability which require self-regulated behaviors. They were developed by Banta (72) for preschool children and further researched by Schleifer and Douglas (73) and Schleifer et al. (21).

Conners' Questionnaires (74, 75) are standardized measures of the child's behavior as observed by the parent and teacher. They were assembled for determining the effectiveness of drug treatment in children. The higher the score on these tests the greater the problems. The Parent Symptom Questionnaire consists of a check list of 93 observable symptoms most commonly associated with behavioral disorders of childhood. The parent is given four choices for evaluating the degree of severity of each symptom. The severity is rated from 0 to 3 with 0 being "not at all" and 3 being "very much." Hence, the lowest score possible on the total questionnaire is 0 and the highest score possible is 279. Of the 93 symptoms,

42 were factor analyzed into eight different factors categorized as: conduct problems, anxiety, impulsive-hyperactive, learning problems, psychosomatic, perfectionism, anti-social and muscular tension.

The Teacher Questionnaire consists of a 39-item behavioral symptoms list with the same rating system as in the Parent Questionnaire making 0 the lowest and 117 the highest score possible. The analyzed factors of this test using 31 items are: conduct problem, inattentive-passive, tension-anxiety, and hyperactivity with some inter-correlation between conduct and hyperactivity. The Teacher Questionnaire deals almost entirely with behavior. However, the Parent Symptom Questionnaire covers many more physiological type problems. Out of 93 items in the CPSQ, 25 deal with problems concerning: eating, sleeping, muscular tension, speech, soiling, and various aches and pains. The same parent answered the questionnaire each time with the assistance of the same psychologist, and the same teacher answered the questionnaire each time with each child having a different teacher.

The statistical method for determining the effect of nutrient supplementation on the various measures was analysis of variance. The t-test was used for analyzing the data derived from observations of attending behavior. Statistical significance was set at $p < 0.05$.

RESULTS AND DISCUSSION Descriptive Statistics

Six of the nine originally selected children remained in full participation throughout the study, one girl and five boys. Their mean chronological age at the time of the SIT determination was 56.2 months with a range of 44 to 68 months. Of the three children lost from most of the study, two had high histamine. The child with the highest histamine (14 mg/dl, normal range 4-7) was unable because of vomiting to take placebo, the treatment on which he was first placed. The other child with elevated histamine (8.3 mg/dl) could not be enticed to take either placebo or the nutrients by either the parent, the teacher, or the psychologist. This is of special interest since histamine elevation in

rats leads to taste aversion (76). Of the original nine children, three had high histamine while none had low histamine.

Of the 39 chemical-physiological and intellectual developmental measures made on each of the children, only a few measures were normal in every child. Table 2 shows the means and ranges of the chemical-physiological measures on the nine children before treatment, along with the corresponding normal standard values. Values for six experimental subjects throughout the experimental period are shown in Tables 4 and 5. There were many irregularities in the blood count. Most of the children had less than normal mean hemoglobin and red cells. One boy had suspected thalessemia (77) with a hemoglobin of 10.8 g/dl, erythrocytes 4.1 x $10^6/mm^3$, and abnormal cell morphology (slight hypochromia, slight anisocytosis, slight poikilocytosis) which worsened on nutrients (moderate hypochromia, moderate anisocytosis, moderate macrocytosis). Also, nutrients caused his erythrocytes to increase to 6.2 x $10^6/mm^3$. One child had elevated leukocytes ($13,000/mm^3$). Three children had slightly or markedly elevated lymphocytes with one having 70%. Two children had elevated segmented neutrophils (54 and 56%). No child had elevated stabs, monocytes, or eosinophils.

Of the blood gas measures, the sample mean pH was elevated above normal mean (77). No child had a low pH, while two had an elevated one of 7.46. All of the six experimental children had low or low normal pO_2 and two children had very low pO_2 (56 and 60 mm Hg). All but one of the original nine had low pCO_2 and all but two of these children had low total CO_2.

Hair mineral analysis revealed two predominant abnormalities, high lead and low zinc. Hair has been shown to be a reliable tissue for measuring chronic lead exposure (78) and zinc nutriture (79). All but one of the original nine children had high lead. The one child with acceptable lead (10 ppm) was the suspected thalessemic and the only one with normal pCO_2 levels. However, there was no significant correlation between lead level and pCO_2 or any other blood gas measure (see Table 12). Only one child had normal zinc which belonged to the only girl of the group. Males are known to be more susceptible to zinc deficiency, presumably because of the great demand for zinc by the prostate (80). High cadmium was also present in five of the original nine children. One quite disturbed child who suffered from serious coordination problems, immature and echolic speech, inappropriate and uncontrolled laughing, severe balance problems (twirled in a circle), and extreme nystagmus had very high cadmium (4.4 ppm), high lead (51 ppm), high copper (48 ppm), and low zinc (98 ppm). The toxic metals are known to be additive in their deleterious effects which are exacerbated by various nutrient deficiencies (7, 81). No child at the beginning of the study had abnormal calcium, chromium, nickel, or mercury. However, on the followup analysis at the end of the experiment high mercury (6.0 ppm) was found in the hair of one child.

Initial psychological test scores (shown in Table 3) were quite variable. All had IQ's (SIT) below 80 since this was the primary selection criterion. Only the raw score of the PPVT is given because it was too low to accurately derive IQ in three children. On many of the other tests, the scores ranged from 0 to above average. Our children had lower perceptual field independence (as measured by ECEFT) than other socially comparable children. The mean ECEFT of our group was lower than that of randomly selected lower class black children (72) or lower class white children (73). Also, it was below the mean, 6.5, of a group of "true" hyperactive preschoolers (21). Our children had very low reflectivity or high impulsivity in problem solving as measured by ECMFF. The mean ECMFF of our group was below that of other socially comparable children (72, 73) and also below the group of "true" hyperactives, mean, 4-3 (21). The mean score of all of the ITPA subtests was much below the standardized norms.

Conners' questionnaires have not been standardized in terms of normal or optimal scores although he has shown significant differences between children visiting a psychological clinic and a control group (74) and has shown good test-retest reliability (75). Our purpose for the questionnaires was not to diagnose but to detect behavioral change resulting from the nutrients. However, the factor scores give an idea of the

types of behavior most troublesome. This is best revealed in the percents of the highest possible scores since the factor scores are based on different numbers of items. The Parent Symptom Questionnaire showed that impulsive-hyperactivity and aggressive-conduct problems were the most troublesome at home with learning problems third. No antisocial behavior was reported which is not surprising because of the age of the children. The Teacher Questionnaire revealed inattentive-passive as by far the greatest problem at school with hyperactivity next in importance.

Thus, our data show that known provokers of learning disability were present in our children, namely, low zinc (26) and elevated toxic metals, particularly lead (7). Even marginally elevated lead (23 ppm) and cadmium (1.72 ppm) in the hair have been reported as predictive factors in learning disabled children with normal scores on the PPVT (82).

Lead poisoning in children is associated with old housing and is most prevalent in black and Puerto Rican children (7, p 133). Eight of our nine original children were black or partially black and five of the six experimental children were black. Early exposure to lead results in hyperkinetic-aggressive behavior (7) which were the behaviors most frequently observed by our mothers. Likewise, the after-effects of lead toxicity in children are reported to include a dulling of the intelligence (7), a characteristic of our children, who also exhibited behaviors characteristic of rats exposed to long term, low levels of lead. Young rats thus exposed over-reacted in an open field test and were unable to perform a difficult learning task (83) which are behaviors consistent with the extremely low ECMFF scores of our children.

Figure 1 shows that hair zinc level in our children was closely related to intellectual development. The intellectual development score given here is the sum of six of the seven intellectual test scores obtained on each child before nutrients and at the end of the experimental period. The scores were summed because the intellectual tests were all designed to measure various aspects of intellectual development with the score being positively associated with higher functioning. PPVT raw scores were not included because of two missing values, and one point on the graph represents data from one child who later dropped from the experiment. It is obvious from Figure 1 that zinc levels in the hair were positively correlated with intellectual levels.

Effect of Nutrient Supplements

The effect of nutrient supplements on blood values is shown in Table 4 for the two groups. The only measure that consistently changed with nutritional supplements was pO_2 which increased in every child on nutrients. However, analysis of variance failed to show significance $F(2, 17) = 3.01$, $p = 0.106$. There was no consistent pattern in pH change but on nutrients it increased markedly in the suspected thalessemic (from 7.415 to 7.53 and back to 7.410 on placebo).

Table 5 shows the follow-up hair minerals. In contrast to other measures, mineral analyses were made only before and after the experimental period because of the slow growth of hair. There were two statistically significant increases in hair minerals. Zinc, $F(l, 11) = 11.13$, $p = 0.029$, and manganese, $F(l, 11)= 10.67$, $p= 0.031$. Magnesium also increased in the hair of every child with gain amounts ranging from 3 to 90 ppm. Iron and cadmium increased in five of the six children, while lead, copper, nickel, chromium and calcium increased in four of the six. No mineral decreased in more than half of the children. The one child who had a large decrease in iron (75 ppm) also had a substantial decrease in copper (29 ppm) and a slight decrease in cadmium (0.3 ppm).

Increases in either blood or hair minerals can be due to either increased intake or metabolic loss from tissues. For example, increase in zinc intake has been shown to increase zinc levels in blood (84) and hair (79, 85). Levels of lead in hair correspond to past levels of exposure to lead in the environment (78, 86). Lead will accumulate in the body when the level ingested exceeds the level excreted (7, p.52). It deposits in the tissues clearing the blood after a period of time with 90% being deposited in the bones and 10% in other organs (7, p.59). Thus, soft tissue and bone act as storage reservoirs for minerals. Lead deposited in tissue can be mobilized by chelating agents (7, pp. 260-

263). Consequently, the increased hair zinc levels found in our study could be expected to be due to increased dietary intake while the increased lead and cadmium levels could be due to either or both increased exposure or excretion stimulated by amino acids (68, 70) and ascorbic acid (71) and iron (87), zinc (88), and copper (89). Although calcium and iron reduce lead absorption, they do not increase its excretion (90). Provided toxic metal exposure did not increase or that the increase in nutrients reduced their absorption, then those children with greater toxic metal tissue levels would be expected to show increases in hair levels from a short treatment period while those with a lower burden would exhibit a decrease in these toxic metals.

The follow-up intellectual scores are shown in Table 6. Following nutrient intake, every child increased in SIT IQ (gain scores: 3,7,23,37,4,5) and in PPVT raw score (gain scores: 6, 4, 10, 3, 4). However, because of variable changes on placebo, this improvement in intelligence was not significant; $F(2, 18)=2.88$, $p= 0.114$. PPVT was not analyzed because of one missing value in each group. The IQ gain scores on placebo were: 7, 19, -20 in Group I and -33, -3,3 in Group II. The PPVT gain scores on placebo were 10 and -4 in Group I and 19 and -1 in Group II.

A graph of the total intellectual score in relation to experimental treatment for each child is shown in Figure 2. Four of the children improved intellectually on nutrients. One child (the suspected thalessemic) failed to improve on nutrients but did improve on placebo following nutrients, and the sixth child improved only slightly on nutrients with a slightly larger improvement on placebo following nutrients. Two of the three children in Group I lost developmentally on placebo previous to nutrients. The first child in Group I was not tested, except for SIT IQ, previous to receiving placebo. Child #4 (first child in Group II) who showed the greatest improvement in intellectual development on nutrients (59 points) was the only child who showed a large decrease in elevated copper, lead, and iron in his hair, suggesting a lower lead burden than the other children with lead. He also exhibited a large increase in zinc (68 to 173 ppm). These four minerals are known to interact (89, 90). Hence, their

change toward normalization after nutrients coincident with improved intellectual development suggest a multiple nutritional improvement and toxic metal decrease effect on intelligence of a greater magnitude than those cases where the lead or other toxic metal burden was still present.

Figure 3 suggests that failure to show greater improvement in intellectual development from nutritional supplements was due in large part to the heavy burden of toxic metals and the failure of zinc to increase in the body in the boys but not in the girl or not to the same degree. The toxic metal burden (Table 7) at pretest and post-test was calculated by summing the deviations from the normal means of lead, cadmium, and mercury in the hair. The total toxic metal burden was calculated by adding the second toxic metal burden to the change in the toxic metal burden between the first and second determinations, in order to take into account both the level and the change in toxic metal burden. This value was assumed to be a measure of detriment to intellectual development. On the other hand, the level and change in level of zinc were judged as beneficial factors (Table 8). Consequently, the deviation of zinc from the normal mean of the second determination plus the change in zinc deviation multiplied by 10 ("zinc benefit score") was subtracted from the total toxic burden to give a "toxic metal risk factor." This then was plotted against the change in total developmental scores from the first to the third score as shown in Figure 3.

The two children in Group I who lost in intellectual development during the placebo period (Figure 2) showed a large increase in toxic metal burden (Table 7). Their loss in development, however, was apparently reversed by the nutrients. Child #2 (the only girl) who had an extremely high toxic risk factor and a high zinc benefit score showed a net intellectual gain of 33 points, putting her gain in relation to toxic risk factor out of line with the boys. Sex differences in learning disability and in body zinc content (80, 26) have been previously reported.

The third and sixth children had very small net gains in development. Both had a high total toxic metal burden and both had negative zinc benefit scores. The first and

fifth children had similar moderate gain scores and similar risk scores, but for different reasons. The first child had a high toxic metal burden but also a high zinc benefit score, while the fifth child had a moderate to low toxic burden and a moderate to low zinc score. The fourth child, with the very high net gain score, was the only child with a zero toxic burden and a moderate zinc score.

The effect of nutrient supplements on behavior in the school observed by the teacher is shown in Table 9. General behavior indicated by the total CTQ score improved dramatically on supplements in both groups and lost most of the improvement within a month on placebo (see Group II). The treatment effect was highly significant, $F(2,17) = 33.36$, $p=0.00013$. The factor scores revealed an even larger proportionate but less significant improvement in hyperactivity, $F(2, 17)= 11.96$, $p=0.004$, with 81% improvement in inattentive-passive behavior approached significance, $F(2,17)=3.35$, $p= 0.088$. Although four of the six also improved in conduct and tension-anxiety, the mean improvement was not significant.

Parent observations likewise revealed significant improvement in behavior (Table 10). Again the Group II children lost some of their improvement on placebo but less than that measured by the CTQ. The reduction in the total CPSQ score was significant, $F(2, 17) = 5.08$, $p = 0.0387$, and reduction in the learning problems approached significance, $F(2,17) = 3.50$, $p=0.081$. However, contrary to the classroom situation, the parents did not report statistically significant improvement in impulsive-hyperactive behavior although none reported a worsening in these behaviors and five of the six reported some benefit.

One mother in each group reported greater improvement in behavior on placebo than on nutrients. The mother in Group I, who reported an improvement of 64 points on placebo, was a child abuser. Her involvement in the study plus assistance from social workers may account for the phenomenal improvement on placebo that she observed. The child in Group II whose mother reported more improvement on placebo following nutrients was the suspected thalessemic. Direct behavioral observations showed

that nutrients improved attentiveness significantly (Table 11). The number of times the child was and was not attending to a classroom activity in a ten minute period was counted at ten second intervals. The number of times on-task was counted for three experimental children and for seven other children in the classroom who served as non-treated controls. Table 11 shows that the experimental children in the pretreatment period were attending significantly less often than the control children. On nutrients the experimental children increased their attending behavior to that of the control children and maintained this behavior on placebo following nutrients.

Similar results were found in the observation of non-attending behavior. Table 11 shows the number of times off task for four children selected from the original nine experimental children. The one child in Group I who was the only girl in the study and the only child with normal zinc exhibited a low level of non-attending behavior which did not change on either placebo or nutrients. The two children in Group II and the one child who was unable to take placebo and thus served as a non-treated control exhibited high distractibility. The two boys who received nutrients first improved dramatically and maintained the improvement on placebo while the non-treated control continued his high level of non-attending behavior throughout.

Speech abnormalities were most frequently mentioned by the mothers as the greatest problem of their children. Table 12 gives the mothers' reports on the children's speech at the three observational periods. The reports suggest improvement on nutrients with continued improvement on placebo for those who received nutrients first. Also, the two questions in the CPSQ regarding speech (stuttering and hard to understand) indicated improvement for the three children whose mothers reported these problems. Before nutrients the total score was 7 while after nutrients the total score was 2.

The suspected thalessemic improved more in behavior at home and intellectually on placebo following nutrients than on nutrients. The fact that the blood pH increased markedly, the red cell count increased above normal, and red cell abnormal morphology

worsened on nutrients suggests that the nutrient formula contained something that was temporarily detrimental in some but not all respects, since the teacher observed improvement in behavior on nutrients. The mother reported verbally that the child was more calm on nutrients and the child liked the effect of the nutrients better than that of the placebo (Table 12). Since this child was on a total supplementation formula including iron because of his low hemoglobin, two possible explanations come to mind. One is that supplemental iron is toxic to a thales-semic (91). Thus, iron would have been detrimental provided he was indeed a thales-semic. Another possible explanation is that the "fast oxidizer" nutrients, particularly pantothenic acid, choline, and vitamin E could have pushed him into a serious "slow oxidizer", causing his pH to become elevated. However, the improvement in behavior in school, the increased calmness reported by the mother, and the preference for the nutrients expressed by the child all mitigate against the second explanation.

Several lines of evidence suggest that there was a residual beneficial effect of the nutrients which carried over into the placebo period. (1) The degree of misbehavior measured by both the CTQ and CPSQ did not return to as high a level on placebo following nutrients as was observed before nutrients were given. (2) Improvement in development on nutrients was sustained during the placebo period by the child who experienced the largest developmental gain. (3) Increase in attending behavior was maintained on placebo following nutrients. (4) Speech improvement on nutrients continued on placebo. It is a well known principle of nutrition that growth depends upon adequate nutrient intake, and physical growth coincides with intellectual growth. It is thus to be expected that the intellectual gain produced during nutrient supplementation would be sustained during the placebo period, which was shown to be the case. However, the behavioral improvements were not sustained during placebo intake, suggesting that behavior is dependent upon different metabolic processes than intellectual ability as measured by intelligence tests. Growth derives from the formation of new complex molecules suggesting that intellectual development is also dependent upon the formation of complex molecules. On the other hand, behavior is labile, indicating that behavior is dependent upon labile metabolic processes in which compounds are constantly being formed and broken down, a characteristic of neurotransmitters. Since behavior was more dependent upon nutrient intake than intellectual development, the cushion of complex molecules did not appear to sustain the maintenance of good behavior.

In the realm of neurotransmitters, there are those that are dependent upon sustained nutrient intake and upon high energy molecules which are in turn dependent upon oxygen consumption. The glutamate-gamma aminobutyrate pathway is such a system. It uses a major portion of the oxygen consumed by the brain (47). Whether this is the major contributor to the misbehavior of the children in this study is a matter of conjecture.

Correlation

Pearson Product Moment correlations coefficients were determined on all the measures ignoring treatments. The values on two of the children who refused nutrients were also included. Therefore, most of the correlations were based on 20 cases, except those involving hair minerals which were based on 14 cases. Scatterplots revealed several curvilinear relationships. The data were thus transformed to log and reciprocal values and Pearson Product Moment correlation coefficients were recalculated on log-log and reciprocal-reciprocal data. Only the significant ($P < 0.05$) coefficients are presented in Tables 13 and 14. Level of significance was determined from two-tailed test table in which r had been converted to t for n from 3 to l02 (df=n-2).

Table 13 shows the intercorrelations between the various intellectual and behavioral measures along with chronological age. Chronological age correlated most highly with auditory reception, using reciprocal data which gave the highest coefficient. Children between 44 and 55 months of age scored 0, whereas after 55 months there was a steep rise in the auditory reception score. Transforming the scores to reciprocal increased the coefficient from 0.561 to 0.831. Similar but less marked increases in coefficients were

found for PPVT and ECMFF. Data transformation did not increase the already high correlation coefficient between age and ECEFT. Age correlated positively with intellectual measures but negatively with behavioral measures, except muscular tension. The positive correlations of age with intellectual measures and muscular-tension were much higher than the negative correlations with other behaviors. The highest negative correlations between age and behavior were with perfectionism in the home and hyperactivity at school. Impulsive-hyperactivity at home also negatively correlated with age but less so. In summary the older the child, the higher certain of its intellectual scores, the less hyperactive its behavior at home and school but the greater its muscular tension at home.

Those intellectual and behavioral measures which did not correlate with age were: auditory sequential memory, visual closure, IQ, CPSQ and CTQ totals, aggressive conduct problem at home and school, anxiety at home and school, learning problem, and psychosomatic at home and inattentive-passive at school. The failure of IQ to correlate with age agrees with numerous other studies. Also, the failure of CPSQ aggressive conduct and CPSQ anxiety to correlate significantly with age while several of the other CPSQ factor scores did correlate with age are in keeping with Conners' work (74). However, the significant correlation of CTQ hyperactivity with age in this study was not in agreement with Conners' observations (75) who reported that none of the CTQ factor scores correlated significantly with age in an older group (mean age 117.5 months).

All of the intellectual measures correlated highly with every other intellectual measure, which could be expected since all of these tests are measuring various aspects of intellectual development. The highest correlation was a curvilinear one between auditory reception and ECMFF. Reciprocal transformation increased the correlation from 0.727 to 0.908.

Of the correlations between intellectual measures and behavior measures, only auditory sequential memory failed to correlate significantly with at least one behavioral factor score. However, there were many behavioral scores which did not correlate significantly with any intellectual score, namely: CPSQ and CTQ totals, CPSQ and CTQ conduct problem, CPSQ impulsive-hyperactive, and CTQ inattentive-passive. Anxiety at home and school and psychosomatic and muscular tension at home correlated positively with intellectual development, i.e. the more advanced the intellectual development the greater these problems. On the other hand, learning problems and perfectionism at home and hyperactivity at school decreased with increase in intellectual scores.

The intercorrelations among the factor and total scores of the parent and teacher questionnaires showed that those behaviors which worsened with increase in intellectual development were all intercorrelated significantly although CPSQ anxiety did not correlate with psychosomatic or CTQ tension-anxiety and it correlated negatively with muscular tension. Also, its correlations with intellectual measures were not highly significant. On the other hand, CPSQ muscular tension, psychosomatic, and CTQ tension-anxiety were all rather highly intercorrelated, with the highest correlation existing between muscular tension and psychosomatic. These correlations suggest that the anxiety factor in the two questionnaires are measuring two different sets of behaviors. The questions in the CPSQ which were grouped into the anxiety factor dealt more with fear than did those in the CTQ. Five of the seven questions in the anxiety factor in the CPSQ contained the word "afraid" while only one of the six questions in the CTQ tension-anxiety factor mentioned fear.

Biological correlates of the two anxiety factors were also different (Table 14). CPSQ anxiety-fearfulness correlated negatively and curvilinearly with pH and red cell morphology and positively with eosinophils. (Reciprocals increased the coefficient from -.380 *to* -.502 for pH and from -.379 to -.460 for rbc morphology). Also, CPSQ anxiety-fearfulness was the only behavioral score which failed to correlate with any mineral (Table 14). CTQ tension-anxiety correlated positively and curvilinearly with pCO_2, total CO2, phosphorus, and cadmium. It correlated linearly with two types of leukocytes (segmented neutrophils and lymphocytes),

potassium and iron. Both anxiety measures correlated with at least one blood gas measure and two blood count measures. Some of the biological correlates of muscular tension and psychosomatic were shared with each other and with the anxiety measures. All correlated with a leukocyte, suggesting an immunological problem underlying four behavioral disturbances which increased with intellectual development; i.e. anxiety at home and school and muscular tension and psychosomatic at home.

One intellectual measure (ECMFF) correlated positively with each of the three highly intercorrelated behavioral measures which worsened with higher intellectual function. No biological measure was common to ECMFF and the intercorrelated behavioral measures. Although phosphorus correlated positively with ECMFF, CTQ tension-anxiety and muscular tension, it failed to correlate significantly with psychosomatic. Magnesium correlated positively with ECMFF, muscular tension, psychosomatic and IQ. IQ in turn correlated positively with CPSQ anxiety.

Of the three intercorrelated behavioral problems which improved with increase in intellectual development (CPSQ perfectionism, CPSQ learning problem and CTQ hyperactivity), two (learning problem and perfectionism) correlated positively with lead and copper and two (learning problem and CTQ hyperactivity) correlated negatively with erythrocytes. Copper, lead and erythrocytes also correlated with certain of the intellectual measures in the expected directions. In other words, increase in copper and lead in the hair coincided with decrease in certain aspects of intellectual development and increase in certain behavioral disturbances, while increase in red blood cells coincided in the opposite direction with these particular aspects of intellectual development and behavior. It is interesting that copper, lead and erythrocytes are interrelated biologically in that lead suppresses hematopoesis in proportion to the level of copper in the diet; the higher the copper the less the suppression (89).

Hyperactivity observed by the teacher was also quite different from that observed by the parent. The CPSQ hyperactivity questions differed from those in the CTQ in that CPSQ contained a question on perser-vation and one on early awakening which CTQ did not have. CPSQ impulsive-hyperactivity did not correlate significantly with any intellectual measure, whereas CTQ hyperactivity correlated highly and negatively with ECEFT, ECMFF, and IQ and it correlated significantly with auditory perception. The correlation between CTQ-hyper-activity and ECEFT was the highest correlation found between an intellectual and a behavioral measure. Banta, who developed ECEFT for children younger than five years, found that ECEFT correlated most highly with Task Competence ratings showing that ECEFT demands attention, persistence, and task motivation (72). These correlations between CTQ hyperactivity and measures of intellectual development show that CTQ hyperactivity is also a measure of various intellectual abilities in this age group at this level of functioning.

The biological correlates of CTQ hyper-activity, CPSQ impulsive-hyperactivity and intellectual measures also suggest a difference between hyperactivity observed at home and school and that CTQ hyperactivity measured intellectual development. Of the nine biological correlates with CTQ hyperactivity, only two (manganese and nickel) failed to correlate with an intellectual measure. Zinc correlated most highly with CTQ hyperactivity and also correlated linearly with every intellectual measure. Log transformation increased r for zinc and auditory sequential memory and for each of the other biological correlates of CTQ hyperactivity except phosphorus and erythrocytes. Figures 4 and 5 show the scatterplots between CTQ hyperactivity and zinc and magnesium. There is an apparent hyperbolic relationship in each case, with the highest zinc and magnesium levels being associated with a lack of hyperactive behavior.

The biological correlates of CPSQ impulsive-hyperactivity were fewer in number than those of CTQ hyperactivity and totally different. The H2CO3, erythrocyte morphology, and lead correlations with CPSQ impulsive-hyperactivity were curvilinear in that transformations of the data increased r. The correlations with lead and H2CO3 were positive and that with erythrocyte morphology was negative; i.e. the higher

the hair lead, the more acid the blood, the more impulsive and hyperactive the behavior in the home, while the more abnormally shaped the erythrocytes the better the behavior. The latter unexpected relationship was largely due to one child (the suspected thalessemic) whose erythrocyte morphology was abnormal at all three testings and who also had a consistently low CPSQ impulsive-hyperactive score. However, two other children (one in each of the two experimental groups developed abnormal red cell morphology on nutrients and simultaneously had a lower CPSQ impulsive-hyperactive score. Normal morphology (score of 0) was reported for all other testings. Nevertheless, red cell morphology correlated significantly with three of the other CPSQ subscores suggesting that a general improvement in behavior in the home was associated with changed osmotic pressure in the blood of three children.

Other correlations also suggest that acid-base balance was important in behavior with the more alkaline condition being more beneficial. The higher the pH, the higher the HCO_3, the lower the pCO_2, the lower the H_2CO_3, the better the behavior at both home and school. The correlations were consistent with the Henderson-Hasselbach Equation

$$pH \propto \log \frac{[HCO_3]}{[pCO_2]}.$$

Metabolic acidosis is well known to be associated with various toxic conditions, although none of the children could be classified as being in what is generally considered metabolic acidosis. However, the results suggest that when the alkaline reserve is more adequate to compensate for tendency toward metabolic acidosis, the behavior was better. Randolph has long used a mixture of sodium and potassium bicarbonate to treat acute allergic reactions (92). Also, alkalization of women in labor with sodium bicarbonate has been shown to be clinically beneficial and to give a better acid-base balance to the infant (93).

CPSQ impulsive-hyperactivity also correlated highly and negatively with glucose. Neither reciprocal nor log transformations increased r. The scatter plot between CPSQ impulsive-hyperactivity and glucose is shown in Figure 6. These data show that glucose levels below 95 mg/dl for these children were associated with a greater degree of impulsive-hyperactivity behavior in the home. This is in contrast to usually considered normal levels which go as low as 70 mg/dl. The impulsive-hyperactivity score decreased slightly in each of the five children who had this problem when on nutrient supplements (-1, -1, -1, -3, -8). Only the child abusing mother reported a decrease on placebo. However, there was no relationship between glucose levels and CTQ hyperactivity, which responded dramatically to supplementation. Thus, CPSQ impulsive-hyperactivity and CTQ hyperactivity were distinguished by their different degrees of response to nutrient supplements and by their different psychological and biological correlates.

An adequate glucose level in the blood is necessary for cellular energy and CO2 production, which in turn plays a vital role in acid-base balance. Even minimal interference with energy production could be expected to alter those body functions which most depend upon energy supply. Much has been written about the emotional and physical effects of hypoglycemia (94). The correlations in this study are in keeping with these contentions in that those behaviors which were related to glucose and blood gas levels centered around problems with impulsivity, hyperactivity, anxiety, tension, perfectionism, psychosomatic complaints and school conduct rather than with inhibition of intellectual development. The correlations of misconduct in the school discussed later fit into this generalization in an interesting way.

Conduct problems observed by the parent were both different from and similar to those observed by the teacher. Differences might be expected since the behaviors specified on the two questionnaires were expressed differently. CTQ asked about sullenness, temper outbursts, stealing, lying, cheating, quarrelsomeness, and destructiveness; whereas CPSQ asked about bullying, bragging, meanness, sassiness to grownups, fighting, picking on other children and blaming others for his mistakes. Nevertheless, they significantly correlated linearly with each other, neither correlated with a developmental measure nor with age, and both

correlated with CTQ total. The behavioral correlations were different in that CTQ conduct correlated only with CPSQ conduct and CTQ total, but CPSQ conduct problems correlated highest with CTQ tension-anxiety and next highest with CPSQ learning problem, and with CPSQ perfectionism.

Likewise, there were differences and similarities in the biological correlates of the conduct problems. Both correlated with a type of leukocyte. CPSQ conduct problem linearly correlated highly and positively with segmented neutrophils (segs) and negatively with lymphocytes, while CTQ conduct problem curvilinearly correlated negatively with monocytes. The correlation between CPSQ conduct problem and segs was the highest correlation ($r = 0.740$) between a behavior and a blood count measure. The larger the number of segs the worse the misconduct. Figure 7 shows the scatterplot between CPSQ misconduct and total neutrophils. The percentage of segs and stabs were summed since both are neutrophils and the number of stabs was small. The shaded area shows the normal range for children of the age of our subjects. The trend toward greater misconduct with increase in neutrophil percentage is apparent within the normal range but is even more pronounced when the neutrophil percentage is above normal. The highest misconduct score was that of the child whose mother abused him in the beginning of the experiment and who had an elevated neutrophil count, although the degree of his misconduct was out of line with the degree of neutrophil elevation. Nevertheless, the misconduct of this child decreased with decrease in neutrophil percentage both of which were progressive throughout the study (% neutrophil = 54, 47, 41; CPSQ misconduct = 17, 8, 5).

Lymphocyte percentage was also correlated with misconduct in the home. Lymphocytes are the predominant leukocytes in children of this age. Figure 8 shows the scatterplot between lymphocytes and CPSQ misconduct. Again the shaded area shows the normal range for lymphocytes. There were values both above and below normal and a marked trend toward greater misconduct with decreasing lymphocyte percentage. The better conduct was associated with high normal and above normal lymphocytes. The abused child's CPSQ conduct problem score before the treatment was even more out of line with the other CPSQ misconduct scores than it was in the neutrophil scatterplot. This outlyer reduced the r value for the lymphocyte-CPSQ misconduct correlation. These data suggest that immunological factors) underlay misconduct in the home of the children as a group and that this misconduct was exacerbated in the abused child by the treatment of his mother.

Whether the predominance of either of these two types of leukocytes was due primarily to the health of the immune system or to the differences in the types of provoking stimuli cannot be discerned from these data. However, the fact that the number of leukocytes was not related to misconduct or to any other psychological measure except muscular tension would suggest the former to be more likely, since a return of lymphocytes to the blood stream after elevated neutrophils is a characteristic of recovery from bacterial infection, whereas a persistence of elevated neutrophils is indicative of chronic infection, i.e. a failure of the immune system to deal with the infection (95). Also, there is research showing that cell-mediated immune function is suppressed by chronic exposure of animals to either lead (96) or cadmium (97) and zinc deficiency in both animals and people (98).

The conduct problem at school appeared to be associated with a different aspect of immunological response and with acid-base balance or cellular respiration. It correlated negatively with monocytes but most highly with nickel, and nickel correlated even more highly with monocytes ($r=0.80$). Monocytes constitute a part of the large scavenger cells of the body but are also involved in both humoral and cell-mediated immunological reactions (99). Their relationship to nickel is not understood although it suggests that nickel is somehow involved in cellular immunity. The fact that nickel increases in the blood and neoplastic tissues of people with cancer and in the blood of people with various skin disorders (100) supports such a relationship.

Another association between nickel and school misconduct was their mutual correlations with HCO_3 and total CO_2. School conduct problems correlated negatively with

HCO3 and total CO2 which correlated (positively) with Ni (r=0.528 and 0.522). Nickel is known to enhance glucose metabolism including its oxidation to CO2 as well as its incorporation into fats and glycogen and to be associated in function with insulin (100). Monocytes are related to insulin in that they contain receptors for insulin (101) and glucagon (102) and their cytotoxic capacity is closely related to glycolysis (103). The major source of total CO2 and HCO3 in the blood is from oxidation of glucose and cellular respiration.

School misconduct failed to correlate with phosphorus, although a scatterplot revealed a decided negative relationship when the two values of child #3 who had extremely high cadmium and low phosphorus are omitted (Figure 9). Cadmium and phosphorus have also been shown to be interrelated in bone metabolism (104). This is important because phosphorus was very highly correlated with HCO_3 ($r = 0.773$) suggesting that hair phosphorus reflects oxidative phosphorylation. Blackwood (57) found previously in a larger, older, normal-IQ population that hair phosphorus significantly correlated negatively with total CO2.

Inattentive-passive (a behavior not measured at home) was the greatest behavioral problem at school (Table 3). Its only biological correlates were zinc and stabs. The zinc correlation was very high and was a negative curvilinear relationship (Figure 10) showing that zinc below 150 ppm was associated with rapidly increasing inattentive-passive behavior. However, the most surprising finding was revealed by scatterplot which showed a close relationship between manganese and inattentive-passive behavior, both of which responded to nutrient supplements. Figure 11 shows the scatterplot. Only one point on the lower curve represented a prenutrient value. Consequently, higher manganese levels after nutrient supplements were associated with less withdrawn, daydreaming behavior.

The levels of manganese after nutrients were much higher than usual. Since the nutrient supplements either did not contain manganese or contained it in very small amounts (Table 1), the significant increase in hair manganese could not be attributed to the addition of manganese in the supplements. It must therefore be due to a metabolic loss of either an accumulation of manganese in the tissues prior to supplements or to an increase in the rate of manganese turnover. Since dietary zinc has been shown to reduce manganese in the tissues (88), the increase in hair manganese could have been due to the zinc supplements, suggesting that zinc improved inattentive-passive behavior by reducing tissue manganese. Pihl et al. (105) found that hair manganese was higher in a sample of learning disabled children than in non-disabled siblings or in mentally retarded children. Perhaps the normal did not have an accumulation of manganese whereas the retarded did, but were unable to clear their tissues of this metal. On the other hand, the learning disabled had a manganese accumulation but were clearing their tissues because of higher zinc intake or for other unknown reasons. If this were true then the retarded and learning disabled would frequently have an abnormality involving enzymes which are activated by manganese or a metabolic blockage causing manganese buildup which is released by zinc.

Intellectual development also negatively correlated with histamine. Five measures of intellectual development (the three ITPA subtests, IQ, and CTQ hyperactivity) significantly correlated with histamine blood levels. Figure 12 shows the scatterplot between histamine and the total intellectual development score. Whether histamine played a direct role in inhibiting intellectual development is unknown from this study. However, histamine is a known neurotransmitter (106) and elevated or depressed brain histamine achieved through intraventricular injection or antihistamine agents have been shown to alter several behaviors (107). It is also possible that the deleterious effect of elevated histamine was through its action in the immune response, since histamine has been shown to modulate cellular immune reactions (108). It seems more likely that histamine played an indirect role in the retardation process, since histamine elevation in the blood can be achieved through a variety of toxic substances (e.g. bacterial endotoxins or toxic chemicals) and conditions (e.g. irradiation) (67). Moreover, the correlations with the intellectual development measures

were not extremely high although significant, suggesting a secondary relationship.

Among the biological measures, histamine was inversely proportional to zinc, calcium and magnesium and failed to correlate significantly with any other measure. The #6 child (see Figure 2), who appeared to be most affected by elevated histamine, had the lowest pretreatment total developmental score, showed the least change in intellectual development and maintained a high histamine level throughout (11, 12, 9.1 mg/dl). This child also had a low zinc benefit score (Table 8) and a high toxic metal risk factor, 12.4 (see Figure 3), but by no means the highest. Since vitamin C has the function of lowering elevated histamine (67, 109), an increase in his vitamin C level could have been expected to lower his histamine. Even so, had his intellectual level improved with increase in vitamin C and thus lowered histamine, the improvement could still be more related to lead toxicity than histamine since vitamin C also detoxifies lead (71), but this does not exclude the possibility that part of lead's effect on the brain is mediated via histamine, although there is no known evidence of such a possibility.

Conclusions

Of the various nutrients administered, zinc was the only one that was proven to have been deficient and beneficial. This does not mean, however, that other nutrients were not beneficial, only that they were not proven either deficient or beneficial. Nevertheless, the toxic metals are known to interfere with metabolism and to compete with nutrient divalent metals. Since supplementation with various nutrients has been shown to overcome in part these adverse effects, it would be reasonable to suspect that nutrients other than zinc would have played a beneficial role in the improvement in behavior and intellectual development demonstrated in the children in this study.

As pointed out earlier, nutrient supplements have been reported to be helpful in various conditions in the absence of toxic metal overload or proven deficiencies,. These results contradict the classical interpretation of the action of cofactors in enzyme function, i.e. the all-or-none response of an enzyme requiring a cofactor. Increasing the supply of the cofactor does not increase the activity of the enzyme. However, the all-or-none rule does not apply to all enzymes. The activity of certain enzymes has been shown to be regulated by factors which modify their three dimensional structure. One such enzyme is glutamic dehydrogenase which catalyzes the reversible amination of alpha-ketoglutaric acid to form the amino acid L-glutamate with the equilibrium constant favoring amino acid synthesis (110). This enzyme contains four atoms of zinc and requires the coenzymes derived from niacin for activity. Steroid hormones reduce enzyme activity by causing desegregations of the enzyme; whereas diphosphopyridine nucleotide (a niacin containing coenzyme) and the essential amino acids L-leucine, L-isoleucine, and L-methionine will overcome this inhibition. L-glutamate is a neurotransmitter and is a precursor to several other neurotransmitters (47). Reduction in the formation of glutamate would therefore result in reduced levels of a number of neurotransmitters with expected changes in behavior. Since a stressed individual produces more adrenal cortical steroid hormones than a non-stressed one (111), it is possible that supplementation with zinc, niacinamide, and protein hydrolysate all provided more adequate functioning of glutamic dehydrogenase and more adequate levels of the resulting neurotransmitters. This is only one example of how various nutrient supplements could have produced desirable behavioral and intellectual changes which would not necessarily be related to toxic metal overload or to classical nutrient deficiency.

Another possibility is that the glutamine supplementation increased the cellular level of glutamate in the brain and thereby increased memory since glutamate receptors have been shown to be the mechanism by which the telencephalic brain remembers semantic stimuli (112). Memory of this nature is of a long lasting type and therefore would be expected to be involved in IQ and other intelligence test scores. This study did not demonstrate low glutamate levels in the brain, but since these were low IQ children, it would not be unreasonable to suppose that they did. Likewise, one would have to assume that increase in glutamate level

whatever the mechanism of doing so would increase intelligence but not modify behavior since the behavioral changes were not sustained..

Summary

This study showed beneficial effect of nutrient supplements on the behavioral disturbance and intellectual development of low IQ, preschool children. It demonstrated the relationship between various biological measures and psychological test scores. It indicated that toxic metal overload prevented greater intellectual improvement than would otherwise have been achieved.

TABLE 2. PRETEATMENT PHYSIOLOGICAL MEASURES

Measure	Unit	Experimental		Normal Range	
		Mean	Range		
Blood					
Histamine	mg/dl	7.5	4.2 - 14	5.5	± 1.5
Fasting glucose	mg/dl	86	70-99	92.5	± 22.5
Hemoglobin	g/dl	11.9	10.5 -13.9	12.6	± 2.3
Erythrocytes	$10^6/mm^3$	4.28	3.26 - 4.77	4.6	± 0.6
Leukocytes	$10^6/mm^3$	7.8	5.4 - 13.8	7.8	± 3.0
Stabs	%	0.4	0-2	8	± 3
Seg. neutrophils	%	38	27-56	38.5	± 11
Lymphocytes	%	53	33-70	46	± 15
Monocytes	%	4.8	0-9	4.7	± 5
Eosinophils	%	2.6	0-5	2.8	
Basophils	%	0.3	0-2	0.6	
pH		7.43	7.40 - 7.43	7.40	± .05
pO_2	mmHg	71	56-79	87.5	± 12.5
pCO_2	mmHg	31	25-35	40.5	± 5.5
HCO_3	meq/l	19.3	17-22	24	± 2
Total CO_2	mM/I	20.5	18-23	25	± 2
H_2CO_3	meq/l	1.0	0.8 - 1.7	1.0	
Hair					
Calcium	ug/g	304	157 - 447	561	± 218
Magnesium	ug/g	31	16-73	89	± 53
Sodium	ug/g	289	9-835	249	± 123
Potassium	ug/g	144	6-420	98	± 66
Copper	ug/g	24	11-49	24	± 10
Zinc	ug/g	87	50 - 136	141	± 27
Iron	ug/g	38	17 - 123	32	± 20
Manganese	ug/g	2.2	1.7 - 5.3	1.14	± .81
Chromium	ug/g	0.9	0.3 - 1.6	0.86	± .23
Phosphorus	ug/g	140	87-199	140	± 38
Nickel	ug/g	0.56	0.1 - 2.1	1.1	± 1.1
Lead	ug/g	40	10-63	7	± 7
Cadmium	ug/g	1.7	0.3 - 4.4	0.85	± 0.85
Mercury	ug/g	0.3	0.1 - 1.6	1.3	± 1.3

TABLE 3. PRETREATMENT PSYCHOLOGICAL MEASURES

Measure	N	Mean	Experimental Range	% Possible	Highest Possible	Normal Standard
Intellectual						
IQ(SIT)	9	63.2	53-77			100 ± 10
PPVT raw score	7	16	7-32			47 ± 8
ECEFT	7	5.9	0 -14			8.3 ± 2.9
ECMFF	7	2.7	0-12			4.2 ± 1.9
ITPA						
Auditory Reception	7	5.6	0 -17			18.5 ± 2.5
Auditory Seq. Memory	7	8.6	2-33			17 ± 2
Visual Closure	7	4.6	0-16			12.2 ± 2.2
Behavioral						
CPSQ						
Total score	8	68	16-96	24	279	
Conduct problems	8	6.6	1-17	29	21	
Anxiety	8	3	0-9	14	21	
Impulsive-hyper	8	8.4	1 - 14	35	24	
Learning problem	8	2.8	0-6	23	12	
Psychosomatic	8	2	0-7	13	15	
Perfectionism	8	1	0-3	11	9	
Antisocial	8	0	0	0	12	
Muscular tension	8	1.3	0-3	10.8	12	
CTQ						
Total score	8	27	23-50	23	117	
Conduct problems	8	6	2-12	15	39	
Inattentive-passive	8	8.4	3 -14	47	18	
Tension-anxiety	8	4	0 - 9	22	18	
Hyperactivity	8	6.1	1-12	34	18	

TABLE 4. EFFECT OF NUTRIENT SUPPLEMENTS ON MEAN BLOOD MEASURES*

	Group I			Group II		
Measure	**Pretreat.**	**Placebo**	**Nutrient**	**Pretreat.**	**Nutrient**	**Placebo**
Blood Count						
Erythrocytes	4.245.25	4.93		4.20	5.70	4.93
Leukocytes	8.70 9.27	7.6		6.63	8.73	7.33
Hemoglobin	11.87	12.37	11.87	11.07	11.67	12.2
Stab	0.0	0.0	0.0	0.7	0.0	1.7
Seg. neutroph.	36.7	41.0	30.0	35.7	42.3	41.7
Lymphocytes	55.3	48.7	49.0	57.0	48.7	48.0
Monocytes	2.0	6.3	6.7	5.3	8.0	6.3
Eosinophils	3.3	4.0	5.3	1.0	0.7	2.0
Basophils	0.7	0.0	0.0	0.3	0.3	0.3
Blood Gases						
pH	7.42	7.40	7.40	7.45	7.48	7.41
pO_2	70.0	69.0	75.3	67.7	77.3	65.7
pCO_2	30.1	30.3	30.6	30.7	27.7	32.3
HCO_3	18.47	18.03	18.47	20.17	19.3	19.9
H_2CO_3	0.97	0.8	1.0	1.0	1.07	1.0
Total CO_2	19.7	19.1	19.3	21.2	20.1	20.9
Histamine	5.8		5.1	7.4	7.2	6.9
Fasting glucose	77.30	86.7	86.0	89.7	91.7	91.7

***N = 3**

TABLE 5. EFFECT OF NUTRIENT SUPPLEMENTS ON MEAN HAIR MINERALS*

	Group I		Group II	
Mineral	**Before**	**After**	**Before**	**After**
Phosphorus	130.7	115.3	170	180
Calcium	287	616	314	336
Magnesium	26.3	64	38.7	83.7
Sodium	451	510	359	787
Potassium	211.7	100	181	169
Copper	24	36	26	18
Zinc	116	200t	78	137t
Manganese	2.7	4.5t	2.2	5.3t
Iron	24.7	61.7	55.7	54
Chromium	0.57	0.97	1.17	1.3
Nickel	0.10	1.47	0.67	1.43
Lead	40.7	66.3	36.3	37.3
Cadmium	2.07	5.57	1.07	1.57
Mercury	0.60	2.07	0.30	0.57

* N = 3; t p<.05

TABLE 6. EFFECT OF NUTRIENT SUPPLEMENTS ON MEAN INTELLECTUAL MEASURES*

		Group I			Group II	
Measure	**Pretreat.**	**Placebo**	**Nutrient**	**Pretreat.**	**Nutrient**	**Placebo**
IQ (SIT)	75.7	77.7	88.7	55.7	61.3	60.0
PPVT raw score	17.0(2)	25.3	32.0	10.5(2)	14.0(2)	23.0(2)
ECEFT	5.0(2)	6.0	9.3	7.0	7.7	7.7
ECMFF	4.0(2)	4.3	4.3	3.0	3.7	4.3
ITPA						
Auditory reception	8.5(2)	8.3	10.3	6.3	8.3	10.0
Auditory seq.memory	20.5(2)	6.3	18.0	4.3	6.3	9.3
Visual closure	8.0(2)	6.0	10.7	2.7	3.0	4.7

*N = 3 in all groups except where indicated by parenthesis (2).

TABLE 7. TOXIC METAL BURDEN*

Child	**Pretest toxic burden**	**Posttest toxic burden**	**Change** toxic burden**	**Total toxic t burden**
Group I				
1	3.31	11.45	8.14	19.6
2	3.09	16.54	13.45	30.0
3	10.53	15.22	4.69	19.9
Group II				
4	8.35	4.17	-4.18	0.0
5	-1.14	2.27	3.41	5.7
6	3.74	7.21	3.47	10.7

* Toxic metal burden = $\frac{\text{ppm Pb - 7 ppm Pb}}{\text{7 ppm Pb}} + \frac{\text{ppm Cd - .85 ppm Cd}}{\text{0.85 ppm Cd}} + \frac{\text{ppm Hg - 1.5 ppm Hg}}{\text{1.5 ppm Hg}}$

** Change = 2nd toxic burden - 1st toxic burden

† Total toxic burden = Change + 2nd toxic burden

TABLE 8. ZINC BENEFIT SCORE

Child	Pretest Zinc* Deviation	Posttest Zinc* Deviation	Change** Zinc Deviation	Zinc Benefit f Score
Group I				
1	-0.19	0.79	0.98	17.6
2	-0.03	0.62	0.65	12.7
3	-0.30	-0.16	0.14	-0.2
Group II 4	-0.52	0.23	0.75	9.8
5	-0.37	0.00	0.37	3.7
6	-0.45	-0.31	0.14	-0.17

* Zinc deviation = $\frac{\text{ppm Zn - 141 ppm Zn}}{\text{141 ppm Zn}}$

** Change = Posttest Zn dev. - Pretest Zn dev.

† Zinc benefit = (Change in Zn dev. + Posttest Zn dev.)10

TABLE 9. EFFECT OF NUTRIENT SUPPLEMENTS ON BEHAVIOR OBSERVED BY TEACHERS

		Group I			Group II		
CTQ	Pretreat.	Placebo	Nutrient	Pretreat.	Nutrient	Placebo	N
Total score	32	33.3	12*	36	17.3*	31.7	3
Conduct problem	6	6.3	2.7	5	3.3	6	3
Inattent-passive	5.3	5.7	3.3 t	9	4t	6.3	3
Tension-anxiety	5	3.3	1.7	4.7	2.3	4.0	3
Hyperactivity	5.3	7	1.3*	5.3	0.7*	5.3	3

* P < 0.005 t P = 0.088

TABLE 10. EFFECT OF NUTRIENT SUPPLEMENTS ON BEHAVIOR OBSERVED BY PARENTS

		Group I			Group II		
CPSQ	Prctrcat.	Placebo	Nutrient	Pretreat.	Nutrient	Placebo	N
Total score	86.3	64.3	51*	54	36*	42	3
Conduct problem	9.3	6.3	4.3	4	4	5	3
Anxiety	6	5.3	3	0	0	0	3
Impulsive-hyper.	11.7	9	8	7	3.3	5.3	3
Learning problem	3.7	3	1.7 t	2.7	1.7 t	0	3
Psychosomatic	1.7	1.3	0.7	3.3	2.3	1.7	3
Perfectionism	1.7	1.7	1.7	0.3	0	1	3
Muscular tension	0.7	0.7	0.7	3	2	3	3

* P = 0.038 t P = 0.08

TABLE 11. OBSERVATION OF ATTENDING BEHAVIOR

Observation	1	2	3
Treatment	Pretreatment	Times on	Nutrients	Placebo
task	37.7 ± 12.7*	N	53.7 ± 10.1	59.7 ± 0.6
3			3	3
Treatment	None	Times on task	None	None
59.6 ±1.1	N	7	57.6 ± 3.5	58.1 ± 2.4
			7	8
Treatment	Pretreatment	Times off	Placebo 7 1	Nutrients 6 1
task	9	N		
1				
Treatment	Pretreatment	Times off	Nutrients	Placebo 0 2
task	28	N	0.5	
2			2	
Treatment	None	Times off task	None	None
23	N	1	24	41
			1	1

P = 0.01 t-test difference pretreatment and no treatment at first observation

TABLE 12. MOTHER'S DESCRIPTION OF CHILD'S SPEECH

Group I

Child	Pretreatment	Placebo	Nutrients
1	Poor speech.	Better speech.	Better Speech.
2	Slurred speech often, to self as before.	Spells of talking different,	Definite improvement, talks to self. talks
3	Unable to hold conversation, talk resembled 18-24 mo. child.	No change.	Talking more, holding conversation.

Group II

Pretreatment	Nutrients	Placebo
4 Poor speech, no sounds.	Speech better.	Talking better, more clear.
5 Poor speech, repeated speech. what he says makes more sense, it's not random now, before could not tell what he was talk- phrases as before.	Speech improving, talks more, talking non-stop, child said the thing, wanted real thing next time,	Doing better, wanting to read, second powder was not the real ing about, asking questions repeatedly now, but not
6 Poor speech, can't sit still to hold conversation.	Talking more, saying more words, able to recognize more of	Talking more,
what he says.		

TABLE 13. INTERCORRELATIONS BETWEEN INTELLECTUAL & BEHAVIORAL MEASURES

	Aud. Recep.	Aud. Seq. Mem.	Vis. Closure	IQ	PPVT	ECEFT	ECMFF	Total	Conduct P.	Anxiety	Impul.-Hyp.	Learn. prob.	Psychosom.	Perfection.	Musc. tens.	Total	Conduct p.	Inatt.-pas.	Tens.-anx.	Hyperactive	Chron. Age
Intellectual																					
Aud. Recep.	1.00																				
Aud.Seq. Mem.	.536	1.00																			
Visual Clos.	.740	.842	1.00																		
IQ	.547	.652	.566	1.00																	
PPVT	.771	.559	.799	.647	1.00																
ECEFT	.778	.488	.720	.511	.811	1.00															
ECMFF	.908	.63.	.798	.563	.809	.822	1.00														
CPSQ																					
Total	...	...	...	...	...	...	...	1.00													
Conduct p.	...	...	...	...	...	...	...	.636	1.00												
Anxiety	...	...	...	.492	...	...	...	.468	...	1.00											
Impul.-hyp.	...	...	...	...	...	...	...	.752	...	.569	1.00										
Learn.prob.	...	...	...	...	...	-.606	...	.539	.589	...	...	1.00									
Psychosom.	...	...	...	.455	...	...	...	.573	.482	...	...	...	1.00								
Perfection.	-.566	...	...	...	...	...	...	-.606	.471	.443	.562	...	...	1.00							
Musc. tens.	.61	...	.450	...	...	.492	.604	...	...	-.517	...	.723	...	...	1.00						
CTQ																					
Total	...	...	...	...	...	...	...	.442	...	...	...	...	...	...	...	1.00					
Conduct p.	...	...	...	...	...	...	...	.454	...	...	...	...	...	...	...	.527	1.00				
Inatt.-pas.	...	...	...	...	...	...	...	.516	...	...	...	...	...	...	...	.761	...	1.00			
Tens.-anx.	...	.564	...	...	...	...	...	.509	.604	...	...	.561	...	...	.523	...	...	.455	1.00		
Hyperactive	-.478	...	...	-.602	...	.724	.625	...	...	...	...	...	...	...	...	.710	...	.447	...	1.00	
Chron. Age	.831	...	...	...	.633	.700	.660	...	...	...	-.452	...	-.585	.698	...	...	...	...	...	-.523	1.00

N = 20 Underlined coefficients are those in which data were transformed to log or reciprocal values.
All correlations are significant at $p \leq 0.05$.

TABLE 14. CORRELATIONS BETWEEN PSYCHOLOGICAL AND BIOLOGICAL MEASURES

	Aud. Recep.	Aud. Seq. Mem.	Vis. Closure	IQ	PPVT	ECEFT	ECMFF	Total CPSQ	Conduct P.	Anxiety	Impul.-Hyp.	Learn. prob.	Psychosom.	Perfection.	Musc. tens.	Total CTQ	Conduct p.	Inatt.-pas.	Tens.-anx.	Hyperactive	Chron. Age
Blood*																					
pH																					
pO_2																					
pCO_2			.462																		
HCO_3																					
Total CO_2																					
H_2CO_3																					
Hemoglobin	.466								.484		.501		.481				-.486		.444		
Erythrocy																	.490				
Leukocytes						.529	.485					-.453		.605	-.444	.465					
Stabs															.622			.553			
Seb. Neutr.			.546						.740						.476				.572		
Lymphocyte									-.646						-.482				-.476		
Monocytes																	-.501				
Eosinophil										.475											
Basophils																					
Ery. morph.								-.799	-.494	-.460	-.633	-.456									
Histamine	-.488	-.651	-.486	-.504																	
Glucose								-.634			-.817			-.670							
Hair **																					
Calcium		.629	.570																		
Magnesium				.590			.658						.554		.533						
Sodium					.563										.685						
Potassium																					
Copper	-.654	.689	.679	.826	.682	.735	.539	.639				.643		.730							
Zinc	.669						.616														
Iron					.556		.633									-.791		-.781			
Manganese																					
Lead	.670					-.576		.765			.657			.617		-.546					
Chromium																					
Nickel																	-.722				
Mercury																					
Cadmium																			-.544	-.634	
Phosphorus	.722					.536	.828							.575	.580				.592		.627

* N = 20 except for histamine and glucose which had N of 19.

** N = 14

Underlined coefficients are those in which data were transformed to log or reciprocal values.

All correlations are significant at p *S* 0.05.

Figure 1. Scatterplot showing relationship between zinc content of hair and intellectual development as measured by the sum of six intelligence tests.

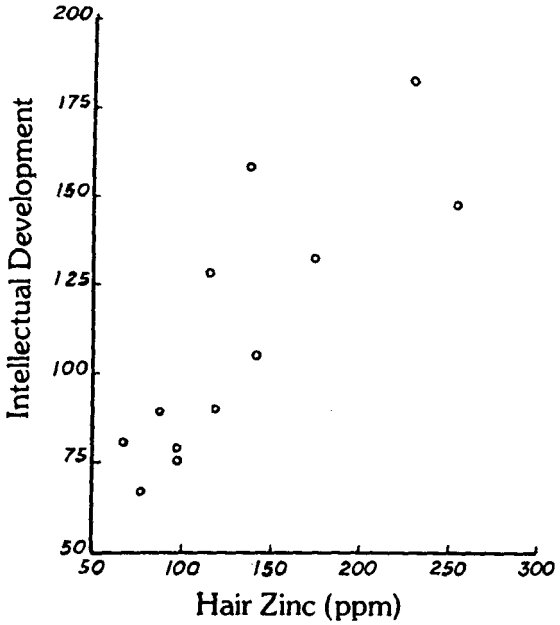


Figure 2. Intellectual development as measured by the sum of six intelligence tests of individual children before treatment, on placebo (P) and on individualized multi-nutrient supplements (N).

Figure 3. Toxic metal risk factor, calculated from the mineral content of hair of children before and after taking individualized nutrient supplements, in relation to intellectual development as measured by the sum of six intelligence tests.

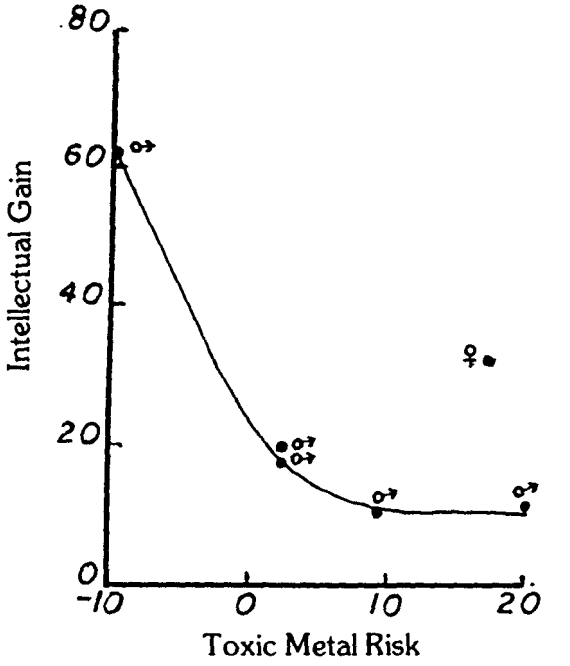
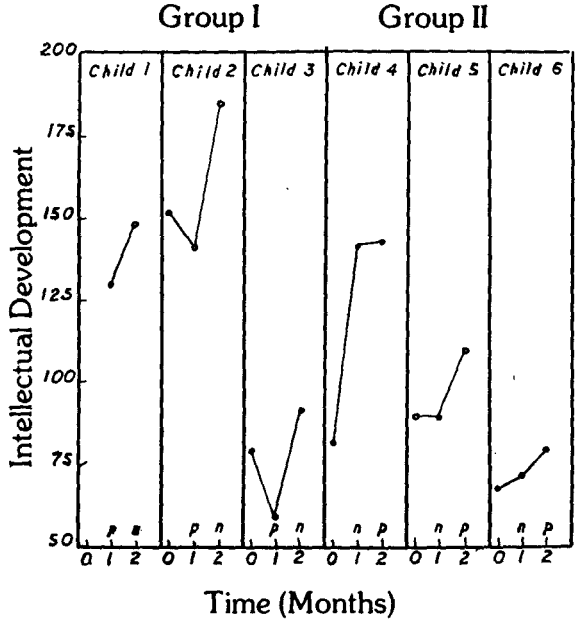


Figure 4. Scatterplot showing relationship between hyperactivity in the school and hair zinc content. CTQ (Conners Teacher Questionnaire).



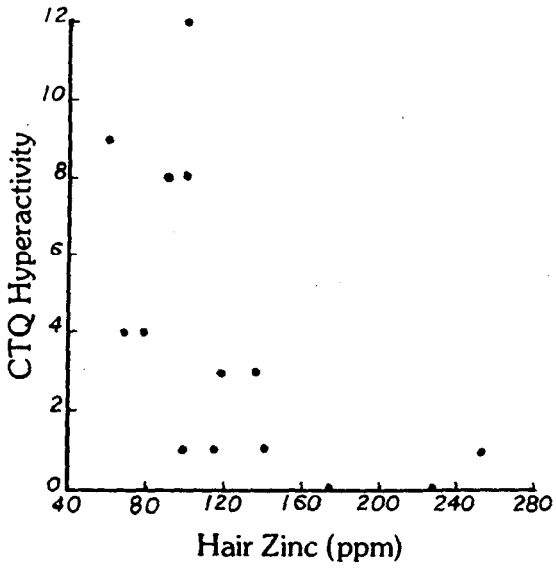


Figure 5. Scatterplot showing relationship between hyperactivity in school and magnesium content of hair. CTQ (Conners Teachers Questionnaire).

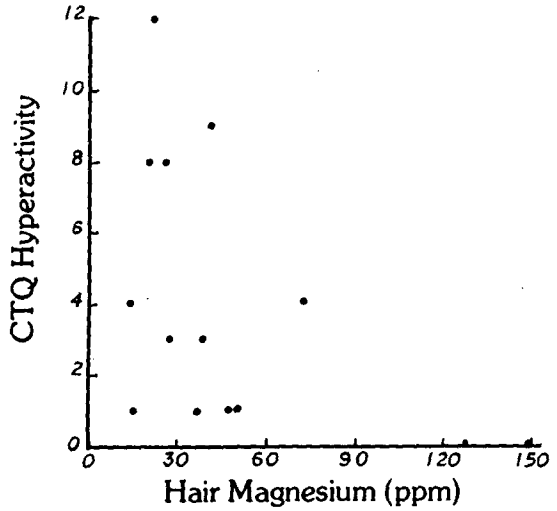


Figure 6. Scatterplot between impulsive-hyperactivity in the home and fasting blood glucose level. CPSQ (Conners Parent Symptom Questionnaire).

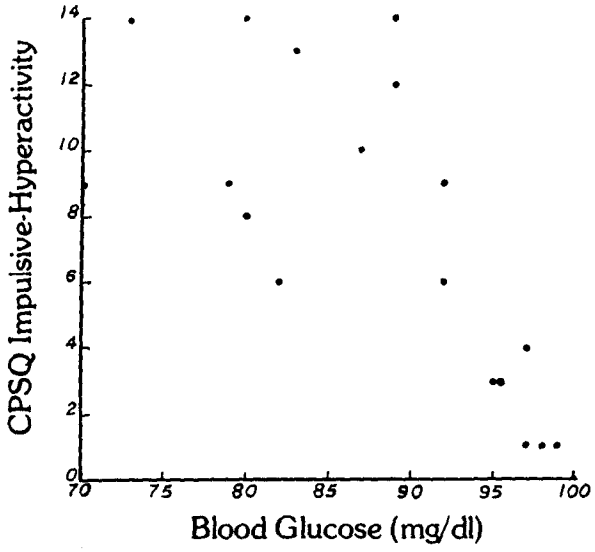


Figure 7. Scatterplot between misconduct in the home and the summed percentage of segmented neutrophils and stabs in the blood. CPSQ (Conners Parent Symptom Questionnaire). • Abused child by mother who reported misconduct.

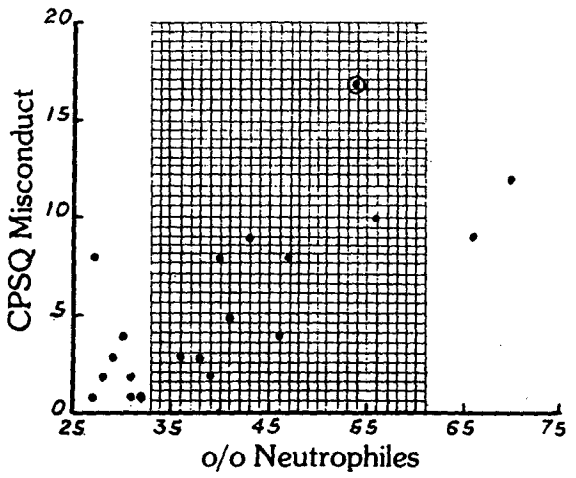


Figure 8. Scatterplot between misconduct in home and percentage lymphocytes in the blood. CPSQ (Conners Parent Symptom Questionnaire). • Abused child by mother who reported misconduct.

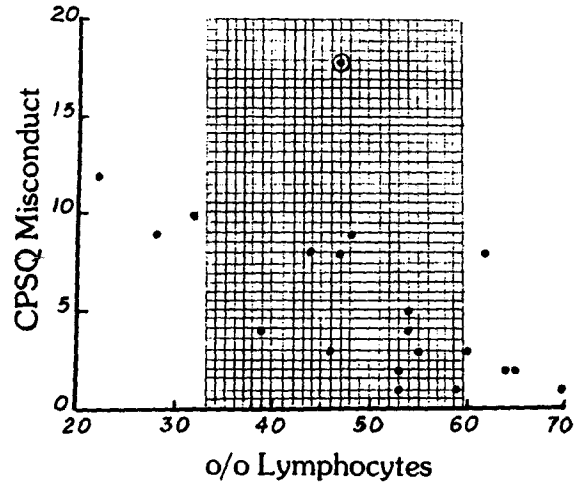


Figure 9. Scatterplot between misconduct in the school and phosphorus content of hair. CTQ (Conners Teacher Questionnaire). • Samples with cadmium from child #3.

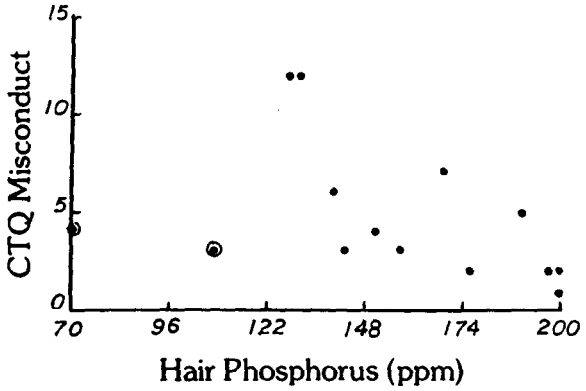


Figure 10: Scatterplot between inattentive-passive behavior in the school and zinc content of hair.

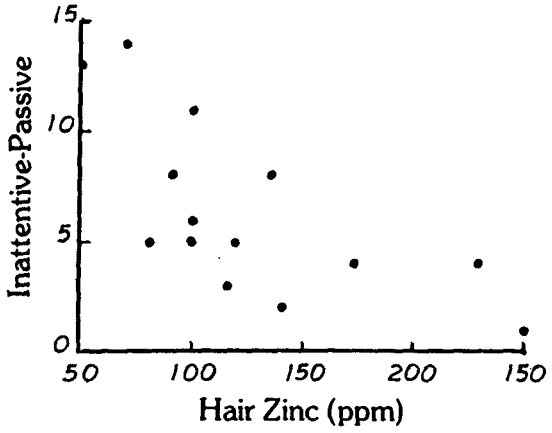


Figure 11. Scatterplot between inattentive-passive behavior in the school and manganese content of hair. • Samples taken before nutrient supplments and • samples taken afterwards.

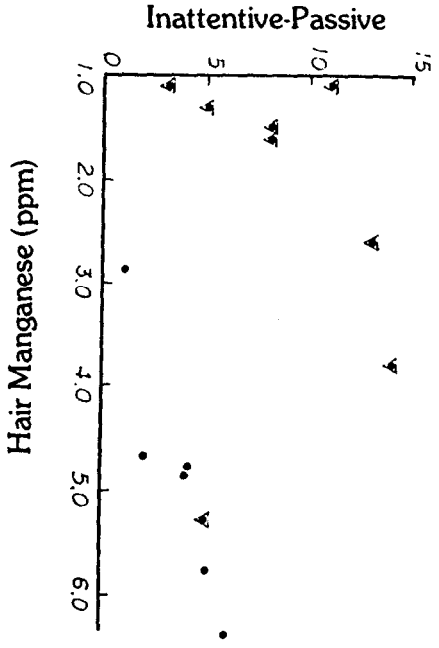
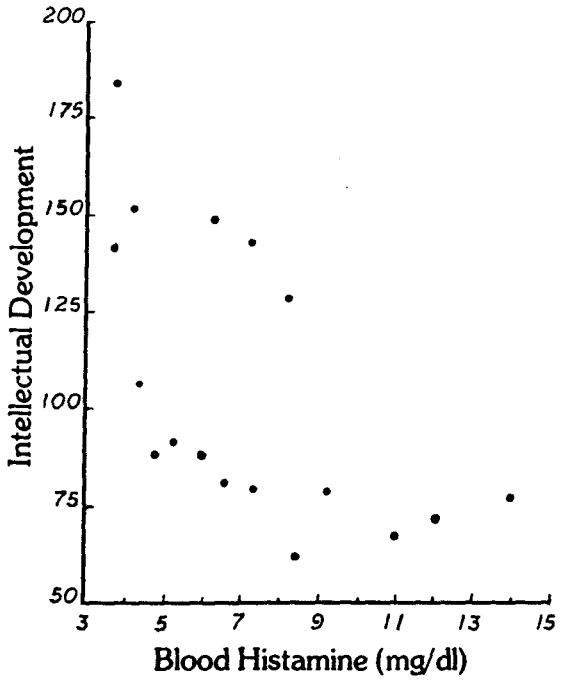


Figure 12. Scatterplot between histamine content of blood and intellectual development as measured by the sum of six intelligence tests.



References

1. Reviewed in E.A. Schneaur: The Malnourished Mind. Anchor Press/Doubleday, Garden, NY, 1975.
2. M. Winick and P. Rosso: Brain DNA synthesis in protein-calorie malnutrition. Protein-Calorie Malnutrition, Ed. R.E. Olson, Academic Press, NY, 1975, pp 94-101.
3. D.S. McLaren, U.S. Yaktin, A. Kanawati, S. Sabbagh and Z. Kacli: The relationship of severe marasmic protein-energy malnutrition and rehabilitation in infancy to subsequent mental development, ibid., pp 108-11.
4. Reviewed in several articles in Nutrition and Mental Functions, Ed. G. Servan, Plenum Press, NY, 1975.
5. Extensive bibliography in J. Brozek: Nutrition, malnutrition, and behavior. Annual Review of Psychology, Annual Reviews, Inc., Palo Alto, CA, 1978.
6. J.B. Stanbury, J.B. Wyngaarden and D.S. Fredrickson (Ed.): The Metabolic Basis of Inherited Disease, McGraw-Hill, 1972,3rd Edition.
7. Reviewed in Airborne Lead in Perspective, National Academy of Science, 1971, pp 157-164.
8. D. Bryce-Smith and H. A. Waldron: Lead, behavior and criminality. The Ecologist 4, No. 10, 1974.
9. B. Weiss: The Behavioral Toxicology of Metals, Fed. Proc. 37(l):22-27,1978.
10. T.G. Randolph: Demonstratable role of foods and environmental chemicals in mental illness. Jap. J. Allergology 23(7):445-457, 1974.
11. M.M. Singh and S.R. Kay: Wheat gluten as a pathogenic factor in schizophrenia. Sci. 191:401-402, 1976.
12. Reviewed in D.C. Gajausek: Unconventional viruses and the origin and disappearance of Kuru, Sci. 197(4307):943-960, 1977.
13. J. Hotchin and R. Seegal: Virus-induced behavioral alteration of mice. Sci. 196(4290):671-675,1977.
14. H. Harlow and M.K. Harlow: Social deprivation in monkeys. Sci. Am. 207:136-144, 1962.
15. R.H. Barnes: Dual role of environmental deprivation and malnutrition in retarding intellectual development. Am. J. Clin. Nut. 29(8):912-917, 1976.
16. F.H. Palmer: The effects of early childhood intervention. Presented at Annual Meetings Am. Assoc. Adv. Sci., Denver, 1977.
17. Mark Rosenzweig: Environmental complexity, cerebral change, and behavior. Am. Psychol. 21:321-332, 1966.
18. F.J. McGuigan: Experimental Psychology, A Methodological Approach, Prentice-Hall, Inc. Englewood, NJ, 1968, p 177.
19. G. Weiss, E. Kruger, U. Danielson and M. Elman: Effect of long-term treatment of hyperactive children with methyl phenidate. CMA J. 112:159-165, 1975.
20. H. Rie, E. Rie, S. Stewart and J.P. Ambuel: Effects of Ritalin on underachieving children: a replication, Am. J. Orthopsychiatry 46(a):313-322, 1976. 322, 1976.
21. M. Schleifer, G. Weiss, N. Cohen, M. Elman, H. Cvejic and G. Kruger: Hyperactivity in pre schoolers and the effect of methylphenidate. Am. J. Orthopsychiatry 45(l):38-50, 1975.
22. Reviewed in J. Hall and R. Baker: Token economy systems; breakdown and control, Behav. Res. & Therapy 11:253-263, 1973.
23. H.L. Garber: Intervention in infancy; a developmental approach. The Mentally Retarded and Society, Eds. M. Begab and J. Richardson, Univ. Park Press, Baltimore, MD, 1975, pp 267-303.
24. P.T. Ackerman, R.A. Dykman and J.E. Peters: Teenage status of hyperactive and nonhyperactive learning disabled boys, Am. J. Orthopsychiatry 47(4):577-595,1977.
25. D.L. Blamberg, U.B. Blackwood, W.C. Supplee, G.F. Combs, Effect of zinc deficiency in hens on hatchability and embryonic development. Proc. Soc. Exp. Biol. Med. 104:217-220, 1960.
26. E.S. Halas, M.C. Rowe, O.R. Johnson, J.M. McKenzie and H.H. Sandstead: Effect of intrauterine zinc deficiency on subsequent behavior, Trace Elements in Human Health and Disease, Eds. A.S. Prased and D. Oberleas, Academic Press, N.Y., vol. 1,976, pp 327-343.
27. K.M. Hambidge, C. Hambidge, M. Jacobs, J.D. Baum, Low levels of zinc in hair, anorexia, poor growth, and hypogeusia in children, Pediat. Res. 6:868, 1972.
28. K.M. Hambidge, P.A. Walravens, R.M. Brown, J. Webster, S. White, M. Anthony and M.L. Roth: Zinc nutrition of preschool children in the Denver Head Start program. Am. J. Clin. Nutr. 29:734-738, 1976.
29. P. GySrgy: Protein-calorie and vitamin A malnutrition in Southeast Asia, Fed. Proc. 27:949-953, 1968.
30. M. Winick and P. Rosso: Brain DNA synthesis in protein-calorie malnutrition, Protein-Calorie Malnutrition, Ed. R.E. Olson, Academic Press Inc., 93-102, 1975.
31. R.E. Frisch: Present status of the supposition that malnutrition causes permanent mental retardation, Am. J. Clin. Nutr. 23:189-192, 1970.
32. H.M. Cleckley, V.P. Sydenstricker and L.E. Geeslin: Nicotinic acid in the treatment of atypical psychotic states associated with malnutrition. J. Am. Med. Assoc. 112:2107-2110, 1939.
33. J.S. McLester: Borderline states of nutritive failure, J. Am. Med. Assoc. 112:2110-2114, 1939.
34. A. Hoffer, H. Osmond, M.J. Callbeck and I. Kahan: Treatment of schizophrenia withnicotinic acid and nicotinamide. J. Clin. Exper. Psychopath. 18:131-138, 1957.
35. J. Clancy, A. Hoffer, J. Lucy, H. Osmond, J. Smythies and B. Stefanivk, Design and planning in psychiatric research as illustrated by the

Weyburn chronic nucleotide project, Menninger Clin. Bull. 18:147-153, 1954.
36. H. Osmond: The background to the niacin treatment. Orthomolecular Psychiatry; Treatment of Schizophrenia, Eds. D. Hawkins and L. Pauling, W.H. Freeman & Co., 1973, pp 194-201.
37. A. Hoffer: Niacin Therapy in Psychiatry. Charles C. Thomas 1962.
38. J.R. Wittenborn: Premorbid adjustment and response

to nicotinic acid. Nutrition and Mental Functions, Ed. G. Serban, 1975, pp 213-224.
39. R.G. Green: Subclinical pellagra; its diagnosis and treatment. Schizophrenia 2:70-79, 1970.
40. R.G. Green: Personal communication, 1972.
41. A. Cott: Orthomolecular approach to the treat ment of learning disabilities. Schizophrenia 3:95-105, 1971.
42. T. Thiessen and L. Mills: The use of megavitamin treatment in children with learning disabilities. J. Orthomol. Psychiatry 4:228-296, 1975.
43. V.V. Dergachev, G.N. Pivovarova, T.G. Hamaganova, E.V. Saginjan, N.A. Krasnuskina, N.V. Kulinkova and V.B. Murkowski, Treatment with orotic and folic acids and vitamin Bi_2 of children with memory disorders. Sovet. Med. No. 7:78-82, 1970 (Russian).
44. H. Matthies, C. Fahse and W. Lietz: The effect of RNA-precursors on the maintenance of long-term memory. Psychopharmacologia (Berlin) 20:10-15, 1971.
45. T. Ott and H. Matthies: The influence of orotic acid on the retrograde amnesia caused by electroconvulsive shock. Psychopharmacologia (Berlin) 20:16-21, 1971.
46. Yu. M. Pratusevich and K.A. Lisitsyna: Distribution of amino acids, biogenic amines in the blood and the psychophysiological activity of children under the influence of dietary supplements. Pediatriya USSR No. 11:65-70, 1974.
47. K. Krnievic: Glutamate and gamma-aminobutyric acid in brain. Nature 228:119-124, 1970.
48. J.C. Price, H. Waelsch and T.J. Putman, dl-Glutamic acid hydrochloride in treatment of petit mal and psychomotor seizures. J. Am. Med. Assoc. 122:1153, 1943.
49. K.E. Albert, A. Hoch, H. Waelsch: Preliminary report of the effects of glutamic acid administration in mentally retarded subjects. J. Nerv, and Mental Dis. 104:263-274, 1946.
50. F.T. Zimmerman, B.B. Burgemeister and T.J. Putman: Effect of glutamic acid on mental functioning in children and in adolescents. Arch. Neur. & Psychiat. 56:489-506, 1946.
51. F.T. Zimmerman and S. Ross: Effect of glutamic acid and other amino acids in maze learning in white rats. Arch. Neur. & Psychiat. 51:446-451, 1944.
52. H.G. Windmuller and A.E. Spaeth: Intestinal metabolism of glutamine and glutamate from the lumen as compared to glutamine from blood. Arch, of Biochem. & Biophy. 171(2):662-672, 1975.
53. L.L. Rogers and R.B. Pelton: Effect of glutamine on IQ scores of mentally deficient children. Texas Reports on Biology and Medicine 15(l):84-90, 1957.
54. G. Watson: Differences in intermediary metabolism in mental illness. Psychol. Reports 17:563-582,1965.
55. C.C. Pfeiffer, V. Iliev and L. Goldstein: Blood histamine, basophil counts, and trace elements in the schizophrenias. Orthomolecular Psychiatry, Eds. D. Hawkins and L. Pauling, W.H. Freeman & Co., San Francisco, CA, 1973, pp 461-510 .
56. B. Rimland: High dosage levels of certain vitamins in the treatment of children with severe mental disorders, ibid, pp 513-539.
57. U.B. Blackwood: Can nutrients restore mental health? J. Orthomol. Psychiatry 4:132-141, 1975.
58. C.C. Pfeiffer: Mental and Elemental Nutrients. Keats Pub. Inc., New Canaan, Conn., 1975.
59. B.E. Leach, M. Cohen, R. Heath and S. Martens: Studies of the role of Ceruloplasmin and albumin in adrenaline metabolism. Arch. Neur. Psychiatry 76:635-642, 1956.
60. S. Akerfeldt: Oxidation of N.N-Dimethyl-p-phenylenediamine by serum from patients with mental disease, Sci. 125:117-118, 1957.
61. C.J. Rudolph, Jr.: Trace element patterning in degenerative diseases, J. Intern. Acad. Prev. Med. 4(1):9-31, 1977.
62. H. Scheinberg and I. Sternlieb: Copper metabolism. Pharmacological Reviews 12(3):355-381, 1960.
63. R.A. Jacob, L.M. Klevay and G.M. Logan, Jr.: Hair as a biopsy material. I. Hair metal as an index of hepatic metal in rats: copper and zinc. Am. J. Clin. Nutr. 31:477-480, 1978.
64. P.A. Shore, A. Burkhalter and V.H. Cohn, Jr.: A method for the fluorometric assay of histamine in tissues, J. Pharm. & Exp. Therap. 127:182-186, 1959.
65. J.A. Huff, V.E. Davis and H. Brown: A simplified technique for the estimation of histamine in blood and urine. J. Lab. Clin. Med. 67:1044-1047,1966.
66. R. Hakanson, A.-L. Ronnberg and K. Sjolund: Fluorometric determination of histamine with OPT: optimum reaction conditions and tests of identity. Analytical Biochem. 47:356-370, 1972.
67. J.B. Challergee, A.K. Majumder, B.K. Nandi and N. Subramanian: Synthesis and some major functions of vitamin C in animals. Annals N.Y. Acad. Sci. 258:24-47,1975.
68. S.A. Gunn, T.C. Gould and W.A.D. Anderson: Protective effect of thiol compounds against cadmium-induced vascular damage to testis. Proc. Soc. Exp. Biol. Med. 122:1036-39, 1966.
69. H.D. Baernstein and J.A. Grand: The relation of protein intake to lead poisoning in rats. J. Pharm. Exp. Therap. 74:18-24, 1942.
70. I. Gontzea, P. Sutzesco, D. Cocora and D. Lungu: Importance de l'appart de proteines sur la resistance de l'organisme a l'intoxication par le plomb. Arch. Sci. Physiol. (Paris) 18:211-224, 1964.
71. M.R.S. Fox: Protective effects of ascorbic acid against toxicity of heavy metals. Annals N.Y.

Acad. Sci. 258:144-150, 1975.
72. V. Banta: Tests for the evaluation of early childhood education: the Cincinnati autonomy test battery (CATB). Cognitive Studies 1, Ed. J. Hellmuth, Special Child Publications, Seattle, Wash., 1968.
73. M. Schleifer and V. Douglas: Moral judgements, behavior and cognitive style in young children. Canad. J. Behav. Sci. 5(2): 1939,1973.
74. C.K. Conners: Symptom pattern in hyperkinetic, neurotic, and normal children. Child Development

11:667-682, 1970.
75. C.K. Conners: A teacher rating scale for use in drug studies with children. Am. J. Psychiatry 126:884-888, 1969.
76. CJ. Levy, M.E. Carroll, J.C. Smith and K.G. Hofer: Antihistamines block radiation-induced taste aversions. Sci. 186:1044-1046, 1974.
77. J. Wallach: Interpretation of Diagnostic Tests. Little, Brown & Co., Boston, Mass., 1978, pp 4,5.
78. L. Kopito, R.K. Byers and H. Schwachman: Lead in hair of children with chronic lead poisoning. N. Eng. J. Med. 276(17):949-953, 1967.
79. W.H. Strain, L.T. Steadman, CA. Lankau, Jr., W.P. Berliner and W.J. Pories: Analysis of zinc levels in hair for the diagnosis of zinc deficiency in man. J. Lab. Clin. Med. 68(2):244-249, 1966.
80. LH. Tipton and M.J. Cook: Trace elements in human tissue. Part II. Adult subjects from the United States. Health Phys. 9:103-145, 1963.
81. M.R.S. Fox: Nutritional considerations in designing animal models of metal toxicity in man. Environ. Health Perspec. 25:137-140,1978.
82. R.O. Pihl and M. Parkes: Hair element content in learning disabled children. Sci. 198:204-206,1977.
83. G. Winneke, A. Brockhaus and R. Baltisson: Neurobehavioral and systemic effects of longterm blood lead elevation in rats. I. Discrimination learning and open field-behavior. Arch. Toxicol. 37:247-263, 1977.
84. A.S. Prasad, A. Miale, Z. Farid, A. Schulert and H.H. Sandstead. Zinc metabolism in normals and patients with the syndrome of iron deficiency anemia, hypogonadism and dwarfism. J. Lab. Clin. Med. 61:537-549, 1963.
85. K.M. Hambidge, C Hambidge, M. Jacobs and J.D. Baum: Low levels of zinc in hair, anorexia, poor growth and hypogeusia in children. Pediat. Res. 6:868-874, 1972.
86. L.E. Kopito and H. Shwachman: Lead in human scalp hair: some factors affecting its variability. J. Invest. Derm. 64:342-348, 1975.
87. M.R.S. Fox, R.M. Jacobs, A.O.L. Jones, B.E. Fry, Jr. and C.L. Stone: Effects of vitamin C and iron on cadmium metabolism. Ann. N.Y. Acad. Sci. 355:249-261, 1980.
88. M.R.S. Fox, R.M. Jacobs, A.O.L. Jones and B.E. Fry, Jr.: Effects of nutritional factors on metabolism of dietary cadmium at levels similar to those of man. Environ. Health Perspectives 28:107-114, 1979.
89. H.G. Petering: The influence of dietary zinc and copper on the biologic effects of orally ingested lead in the rat. Ann. N.Y. Acad. Sci. 355:298-308, 1980.
90. K.R. Mahaffey and J.I. Rader: Metabolic interactions: lead, calcium, and iron. Ann. N.Y. Acad. Sci. 355:285-297, 1980.
91. H.A. Pearson: Pathophysiology of thalassemias. Ann. N.Y. Acad. Sci. 241:274-279, 1974.
92. T.G. Randolph: The enzymatic, acid, hypoxia, endocrine concept of allergic inflammation. Clin. Ecology, Ed. L. Dickey, Charles Thomas Pub., Springfield, IL, 1976, pp 577-596.
93. R.B. Clark, S.R. Stephens and F.E. Greifenstein: Fetal and maternal effects of bicarbonate administration during labor. Anesthesics & Analgesics 50:713-718, 1971.
94. C. Weiler and B.R. Boylan: How to Live With Hypoglycemia, Award Books, New York, NY, 1970.
95. N.P. Sherwood: Immunology, CV. Mosley Co., St. Louis, MO, 1935, pp 89-91.
96. R.E. Faith, M.I. Luster and CA. Kimmel: Effect of chronic developmental lead exposure on cell-mediated immune functions. Clin. Exp. Immunol. 35:413-420, 1979.
97. S. Muller, K.E. Gillert, C Krause, G. Jautzko, U. Gross and T. Diamantstein: Effects of cadmium on the immune system of mice. Experimentia 35:909-910,1979.
98. R. A. Good, G. Fernandes and A. West: Nutrition, immunity, and cancer — a review. Part I; influence of protein or protein-calorie malnutrition and zinc deficiency on immunity. Clinical Bulletin 9(1):3-12, 1979.
99. B.F. Argyris: Role of macrophages in the immune response. Developments in Lymphoid Cell Biology, Ed. A.A. Gottlieb, CRC Press, Inc., Cleveland, OH, 1974, pp 27-50.
100. F.H. Nielson: Studies on the essentiality of nickel. Newer Trace Elements in Nutrition, Eds. W. Mertz and W.E. Cornatzer, Marcel Dekker, Inc., New York, NY, 1971, pp 215-253.
101. H. Beck-Nielsen: Insulin receptors in man. The monocyte as model for insulin receptor studies. DMB, Dan. Med. Bull. 24(4): 173-185, 1980.
102. S.J. Bhathena, J. Louie, G.P. Schechter, R.S. Redman, L. Wohl and L. Recant: Identification of human mononuclear leukocytes bearing receptors for somatostatin and glucagon. Diabetes 30(2):127-131, 1981.
103. K. Krogballe, H. Beck-Nielsen, O. Pederson, J. Ellegaard and N.S. Soerensen: Monocyte-mediated antibody-dependent cytotoxicity. Modulation by glycolysis and insulin. Scand. J. Haematology 26(2): 137-144, 1981.
104. H.S. Jones and B. A. Fowler: Biological interaction of cadmium with calcium. Ann. N.Y. Acad. Sci. 355:309-316, 1980.
105. R.O. Pihl, H. Drake and F. Vrana: Hair analysis in learning and behavior problems. Hair, Trace Elements and Human Illness (Human Hair Symposium), Eds. A.C Brown and R.G. Crounse, Praeger Pub., New York, NY, 1980, pp 128-143.
106. C.R. Calcutt: The role of histamine in the brain. General Pharmacology 7:15-25, 1976.
107. M.C Gerald and R.P. Maickel: Studies on the possible role of histamine in behavior. Brit. J.

Pharmac. 44:462-471, 1972.
108. R.E. Rocklin, D.K. Greineder and K.L. Melmon: Histamine-induced suppressor factor (HSF): further studies on the nature of the stimulus and the cell which produces it, Cellular Immunology 44:404-415, 1979.
109. C.A.B. Clemetson: Histamine and ascorbic acid in human blood. J. Nutrition 110(4):662-668,1980.
110. G.M. Tomkins and K.L. Yielding: Regulation of the enzymic activity of glutamic dehydrogenase mediated by changes in its structure, Cold Spring

Harbor Symposia on Quantitative Biology, XXVI: 331-337, 1961.

111. H. Selye: The Stress of Life, McGraw-Hill Book Co., New York, NY, 1956.

112. G. Lynch and M. Baudry: The biochemistry of memory a new and specific hypothesis. Sci. 224(4653): 1057-1063, 1984.