TRACE ELEMENT RESEARCH IN PEDIATRIC PRACTICE

B. Sharda

Research on trace element, hitherto considered "research for the West", is now well accepted in our country. Everyday, preparations containing variable amounts of zinc and other traces are pouring into the market. Changes in knowledge and understanding about trace elements during childhood and pregnancy can be compared to a revolution and the subject has been the full topic of several workshops and monographs.

An important development in this field has been the development of accurate and simple methodology using atomic absorption spectrophotometry to measure the element in tissues and body fluids with reproducibility. Despite their minute quantity, essential trace elements (iron, iodine, zinc, copper, cobalt, fluorine, manganese, chromium, and selenium) have important roles in biological functions as integral parts of enzymes or cofactors in reactions, components of body cells, and associated with oxygen transport. This article provides an insight in the role of trace elements throughout childhood, beginning from the antenatal period, to help the pediatrician suspect, diagnose, and treat trace element deficiencies at an early stage. Better known elements like iron, iodine, calcium, *etc.* are omitted, while special reference is provided about malnutrition, central nervous system disorders and infections.

From the Department of Pediatrics, R.N.T. Medical College, Udaipur 313 001.

Reprint requests: Dr. B. Sharda, Government Bungalow No. 105, A Road, Bhupalpura, Udaipur 313 001.

A. Trace Elements in Antenatal, Neonatal Period and in Infancy

Human and animal studies clearly show that inadequate prenatal nutrition can result in postnatal risk for the offspring and that some of these effects can persist through several generations. Maternal nutritional status is considered to be one of the most important environmental factors influencing the course and outcome of pregnancy. Many studies have clearly shown that the human fetus is vulnerable to nutritional deprivation in pregnancy ending up as a small-for-date infant, with increased neonatal morbidity and mortality, poor postnatal growth, and increased susceptibility to infection(1). Infants, especially those born prematurely, are susceptible to zinc deficiency(2). Friel *et al.*(3) examined nutrient intakes and growth in preterm and term infants, and observed that zinc intake played an important role in determining the height at 3 months and weight at 12 months than did any other measured variable. Walravens *et al.*(4) found that infants aged 6-24 months with failure to thrive of primarily nutritional origin, benefitted from a daily 5 mg zinc supplement in terms of achieving weight-for-age and height-for-age. Intrauterine growth retardation has been linked to low

polymorphonuclear (PMN) zinc concentration; 85% of mothers having small-for-gestational-age infants had low maternal zinc in PMN or smoking during pregnancy or both(5). When nutrient intake during the last trimester of pregnancy was assessed in mothers shortly after, low zinc intake was significantly associated with intrauterine growth retardation(6). Zinc levels were analyzed in placentas from 100 women who had obstetrically normal births and it was found that placental zinc concentrations were positively correlated with birth weight and head circumference over the lower end of the normal range(7). Oral zinc supplementation (20 mg/day from the 12th week onwards) reduces the overall complication rate for both the mother and fetus(8). By 12 weeks the development of most of the fetal tissues and organs is complete and subsequent zinc deprivation has adverse effects on fetal growth rather than a teratogenic effect.

Copper deficiency is seen mainly in preterms but in contrast to zinc, breast milk is a good source of copper even in preterm babies.

There is a high incidence of selenium deficiency in young formula fed infants when compared with breast fed infants; zinc and selenium deficiencies result from the lower content of these elements in the milk(9).

Magnesium in preterm milk is also possibly inadequate.

Nutrition of preterm infants, especially those weighing less than 2500 g at birth, is critical for their growth, survival, and ultimate outcome. Despite the benefits of human milk, its nutritional adequacy for preterm infants has been questioned. The rapidly growing preterm infant fed formula or pooled banked milk is at a risk of copper, zinc and iron inadequacies. Controversy exists over the precise requirement of trace elements in preterm and low birth weight infants, and a great deal of research is still needed in order to improve our understanding in this area.

B. Trace Elements in Human and Animal Milk and in Infant Formulas

With the exception of the rate *in utero*, growth during infancy far exceeds that experienced at any other time, therefore, nutrient requirements during this period are also very high. Infants also receive for most of this time a simple species-specific food and hence the composition of this food assumes paramount importance. The concentration of trace elements in human milk are usually 1/10th the levels encountered in most biological materials. *Table I* shows the trace element composition of human and animal milk and of various infant formulas.

It is well documented that exclusive breast feeding provides sufficient iron for at least the first 4 to 6 mo of life due to the high bioavailability of iron from human (retention is reported to vary between 20 and 100%).

The mean concentration of human milk zinc decreases from approximately 10 mg/L in colostrum to 2 mg/L in mature milk(10). The highest zinc concentration is found in formulas intended for preterm infants who are at greatest risk of deficiency. The high bioavailability of human milk zinc is well known compared with cow milk based or soy based formula.

The mean concentration of copper is highest in colostrum and then falls rapidly to levels typical of mature milk (approximately) 100 to 600 μg/L(10). Cow milk is low in copper; the highest amount of copper is in formulas designed for preterm

TABLE I—*Trace Elements Concentrations in Different Milks and Various Infant Formulas*

Milk	Copper (mg/L)	Zinc (mg/L)	Magnesium (mg/L)	Cadmium (μg/L)	Manganese (μg/L)	Selenium (μg/L)
Human						
Colostrom	0.72 ± 0.23	9.32 ± 1.63	46.22 ± 15.7	20.0 ± 7.1	—	40-80
Mature	0.35 ± 0.15	1.03 ± 0.42	39.1 ± 10.6	11.8 ± 6.4	1.9-27.5	11-53
Cow	0.22 ± 0.10	2.98 ± 0.90	111.6 ± 19.4	33.8 ± 11.3	35	—
Goat	0.20 ± 0.13	2.87 ± 0.39	122.0 ± 12.8	41.0 ± 9.7	30	—
Buffalo	0.31 ± 0.13	3.01 ± 0.21	139.1 ± 18.0	41.9 ± 12.3	32	—
Dairy	0.57 ± 0.21	4.95 ± 1.19	168.6 ± 16.7	43.6 ± 12.3	40	—
Lactogen I*	0.3	3.7	41	—	35	5
Lactogen TI*	0.3	3.4	61	—	32	5
Soya-formula*	—	3.0	40	—	—	—

*Values are per 100 g of powder instead of per litre.
Values are mean ± SD and range.

infants. The bioavailability of copper from various milks is still not known precisely.

The quantity of manganese in cow milk is about 35 mg/L while formulas provide 40-60 μg/L. Differences among human, bovine milk, and infant formulas in number and type of manganese ligands which may affect bioavailability have been reported(11).

Selenium is high in colostrum (40-80 μg/L), but levels fall to those in mature milk (11-35 μg/L) by 2 weeks of lactation. The bioavailability of selenium from human milk and formulas is not precisely known(12).

Trace Elements in Preterm Milk

The exact requirements of preterm and LBW infants for various trace elements are not known. When rapidly growing preterm infants are fed formula or pooled banked breast milk they are likely to develop copper, zinc, and iron deficiencies. Preterm milk is higher in these minerals than term milk(13).

Recently, an attempt has been made by the infant formula manufacturers to produce specially adapted preterm milk formulas having a higher content of certain trace elements, *e.g.*, zinc (12 mg/L), copper (2 mg/L), iron (3 mg/L), as well as higher sodium and protein content and calcium/phosphorus ratio(14). Nutritional management of preterm infants to achieve growth similar to a fetus *in utero* requires the infant's own mother's milk, which may be further supplemented with some micronutrients. Addition of commercial fortifiers (minerals and vitamins) to human milk appears to be a promising approach to correct these shortcomings.

C. Trace Elements in Malnutrition

Many trace elements have been studied in malnutrition; levels of some were observed to be subnormal and to further decline during recovery. The fundamental question is whether inadequate intake of trace elements is playing any role in the genesis of malnutrition or whether these

observed changes are secondary to malnutrition. Zinc and copper have been widely studied in the recovery phase of malnutrition with supplementation(15-21).

Zinc

Plasma, hair, and urine zinc is reported to be low in malnourished children (kwashiorkor) and this deficiency may complicate severe malnutrition. Zinc deficiency in malnutrition may occur much more frequently, however, as a mild deficiency that limits growth and can be corrected by zinc supplementation. Recent studies indicate that zinc supplementation hastens the improvement in clinical signs and symptoms during treatment of malnutrition and recommend that zinc should be supplemented (2 mg/kg daily as elemental zinc) for optimal recovery(15-21).

Copper

Castillo-Duran *et al.*(19) reported that deficiency of copper during recovery from malnutrition in infants impairs growth, whereas Sharda *et al.*(16) did not observe any difference in serum copper in Grade III-IV malnourished cases because milk was boiled and stored in brass vessels. Other trace elements, like magnesium, cadmium, selenium, molybdenum, chromium, vanadium, and manganese have been studied in malnutrition but what do these measurements mean? No clinical observations in malnutrition could be ascribed to abnormalities in levels of these elements, which would point to their possible role.

D. Trace Elements and Central Nervous System (CNS)

Deficiency as well as excess of some trace elements can have a deleterious effect on the development of CNS and its functions. This includes deficiency of zinc, iodine, cobalt, iron and possibly chromium and molybdenum; excess of mercury, lead, and aluminium; and both (deficiency and excess) of copper and manganese. There is little doubt that copper and zinc play very important roles in CNS functions, *e.g.,* copper is a co-factor of dopamine-b-hydroxylase; zinc is also a cofactor of many enzymes in the brain including nucleotide phosphohydrolase.

Studies of mineral concentrations in hair have found that children with impaired learning and with behavioral disorders tend to have higher levels of toxic metals, especially copper, lead and cadmium(22). There is evidence of an association with dyslexia; low concentrations of zinc in sweat and high concentrations of copper, lead, and cadmium in hair from dyslexic children compared with controls(22). Lower zinc and higher cadmium and lead concentrations in placental tissue from obstetrically normal births were related to reduced head circumference in neonates. Zinc deficiency in parents before conception may possibly contribute to familial dyslexia. Prospective studies of zinc concentrations and the effect of supplementation before conception, during pregnancy, and in childhood are urgently required.

E. Pediatric Exposure to Toxic Elements

Mercury, lead, arsenic and cadmium are nonessential toxic metals. These may be detected in variable amounts in the environment (air, water and food) and there are chances of their contamination in amounts which are detrimental to human health.

Lead

Lead has been mined, smelted and refined throughout recorded history. Exposure to lead may be from dust (air), diet and drinking water. Foods and beverages can be seriously contaminated through storage in improperly lead glazed ceramic ware, by boiling in electric kettles in which the heating element in contact with water is soldered with lead, and cooking of foods in opened old leadsoldered cans. In general, acidic substances, *e.g.,* fruits, fruit juices, cola drinks, alcoholic beverages and tomatoes cause much greater leaching of lead than neutral or alkaline foodstuffs. The concentration of lead in human milk obtained from mothers with normal lead exposure is quite low(23). Automotive exhausts are also important contaminants of lead in ambient air. Lead paint pigments are important source of lead toxicity in children. Although direct inhalation of lead-bearing air may be responsible for increased lead absorption in children, recent studies indicate that the major route of entry of lead in young children is through hand-to-mouth activity, the hands being contaminated with lead bearing dust(24). Drinking water passing through old lead pipes may also be a source of lead. Lead toxicity in children leads to neurobehavioral disturbances.

Arsenic

With the exception of sea-foods, the arsenic content of food is low and therefore toxicity is uncommon other than in areas of high thermal activity (volcanoes and hot springs), or naturally high arsenic content in ground water. Exposure to airborne arsenic may cause toxicity in adults, particularly smelter workers. Arsenic toxicity causes dermatological, CVS, and CNS effects.

Cadmium

Cadmium has a very long half-life and therefore is of greater concern from the public health viewpoint. Exposure to cadmium fumes is a major industrial hazard. The risk of acute poisoning is likely when ice or acidic beverages are placed in cadmium plated pots and pans. Similar episodes may result from the storage of foods and beverages in cadmium containing glazes or from release from silver solder in water containers. The critical organ for cadmium toxicity is the renal cortex.

Mercury

In some fishes mercury accumulates in large quantities, leading to toxicity in fish eaters (Minimata disease). Mercury toxicity has also been caused by the consumption of methyl mercury treated wheat. Surviving infants and fetuses shows permanent CNS injury.

F. Trace Elements and Immune Responses

It is axiomatic that childhood mortality rates increases progressively with worsening nutritional status, mainly due to infections; that duration and severity of infections are greater among the malnourished; that opportunistic infections are more likely in malnourished children; that nutritional deficiency results in lymphoid dysfunction; and that decreased intake of trace elements results in impaired immunity. Important elements closely involved in this phase of trace-element-immune responses-infection are mentioned here.

Zinc

Zinc deficiency affects the immune system as follows: (*i*) Reversible atrophy of lymphoid tissues; (*ii*) Cell-mediated immunity is impaired; (*iii*) Depression of IgG levels; and (*iv*) Impaired chemotaxis. Supplementation of zinc and correction of its deficiency leads to normalcy of these functions and reduction in the incidence of infections.

Copper

Direct evidence about the effect of copper deficiency on immunity in humans is limited, but it is known that patients with Menkes Kinky-Hair disease (an inherited disease with low serum copper) have increased incidence of infection. In experimental animals, copper deficiency leads to impaired antibody response.

Selenium, Magnesium and Cobalt

There is inconclusive evidence of the role of these elements in immune responses. Recently, it has been observed that children with infantile tremor syndrome (ITS) succumb to infections, particularly of respiratory system, which are difficult to treat even with parenteral antibiotics. These children have low blood zinc levels which predisposes them to infections, so a therapeutic trial of zinc supplementation is urgently required.

G. Trace Elements in Various Body Tissues and Fluids

Levels of some important trace elements in various body tissues and fluids are mentioned in *Table II*.

Accumulation of copper in the liver from milk boiled and stored in brass vessels is now well known to cause hepatic injury resulting in Indian Childhood Cirrhosis (ICC). Once this practice was changed by health education, the incidence of ICC has declined significantly.

REFERENCES

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TABLE II--*Values of Some Elements in Human Tissues and Body Fluids*

Specimen	Copper	Zinc	Selenium	Manganese	Cobalt	Cadmium
Plasma (μg/dl)	0.97 ± 0.11	94.7 ± 22.4	< 0.005 (μg/ml)	0.3 ± 0.1	0.3 ± 0.1	9.3 ± 2.4 (μg/L)
Urine (μg/24 h)	28.2 ± 6.7	0.51 ± 0.12	< 0.005 (μg/dl)	0.6 ± 0.3	1.2 ± 0.4	10.6 ± 3.2
Liver (μg/g dry wt)	27.2 ± 11.3	84.13 ± 5.36 (wet wt)	0.033 ± 0.003	0.20 ± 0.10	0.08 ± 0.03 (wet wt)	0.7 ± 0.2
Hair (μg/g)	27.2 ± 11.3	180.0 ± 50.0	0.5 ± 0.06	1.6 ± 1.1	0.07 ± 0.05	1.8 ± 0.2
Nails (μg/g)	22.2 ± 10.1	139.0 ± 48.0	0.7 ± 0.5	0.8 ± 0.3	0.14 ± 0.04	1.4 ± 0.3

Values are mean ± SD.

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NOTES AND NEWS

INTERNATIONAL CONFERENCE ON SLEEP WAKEFULNESS

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Dr. V. Mohan Kumar,
Organizing Secretary,
International Conference on Sleep-Wakefulness,
Department of Physiology,
All India Institute of Medical Sciences,
New Delhi-110 029.
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