Fetal and Neonatal Development in Relation to Maternal Trace Element Nutrition: Manganese, Zinc, and Copper

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Certain elements are found in animal tissues and fluids in very small amounts. The body of an adult human man, for example, contains about 2 g zinc, 0.2 g copper, and 20 mg manganese (Table 1). Despite their minute quantities, essential trace elements have important roles in biological systems. Four major functions may be noted:

1. Trace elements may be structural components of macromolecules
2. They can be components of body fluids
3. They may be cofactors in enzymatic reactions or integral parts of metalloenzymes
4. They can serve to bind, transport, and release oxygen

Examples of the first function would be the presence of silicon as a component of the organic matrix of bone and the role of zinc as a part of the DNA molecule. Examples of enzymes in which trace elements are components or cofactors are cytochrome oxidase (Fe) and superoxide dismutase (Mn, Cu, and Zn). Fifteen trace elements have been reported to be essential for the growth and health of animals: arsenic, cobalt, copper, chromium, fluorine, iodine, iron, lead, manganese, molybdenum, nickel, selenium, vanadium, and copper. Although a deficiency of many of these elements has been demonstrated only under rigidly controlled laboratory conditions, deficiencies of copper, iodine, iron, manganese, selenium, and zinc have been reported to occur in domestic animals and humans under natural conditions (1).

SEVERE DEFICIENCIES OF MANGANESE, COPPER, AND ZINC

Manganese

Studies on the effects of severe deficiencies in nutritional factors have been very useful in elucidating the biological and metabolic role of nutrients.
The most dramatic effect of severe manganese deficiency during prenatal life is an irreversible congenital ataxia, characterized by incoordination, loss of equilibrium, and retraction of the head. The inability to swim can be an important indicator for this condition.

Animals with prenatal manganese deficiency resulting in congenital ataxia are unable to swim or to maintain their balance in water owing to abnormal development of the otoliths in the inner ear, which results in defective vestibular function (2,3). The condition is brought about by depressed activity of the glycosyl transferase enzymes, which require manganese as a cofactor and are necessary for the synthesis of glycosaminoglycans and glycoproteins. Depression of these enzymes also causes the abnormal skeletal development that is so characteristic of manganese deficiency. The same abnormal development also occurs in a certain genetic mutant of the mouse, the pallid mouse, which shows the typical inability to swim, retraction of the head, and abnormal development of the otoliths. In this case prevention of the congenital genetic defect can be achieved by feeding the pregnant female a diet containing high concentrations of manganese during the critical period of gestation (2).

**Copper**

Copper deficiency in prenatal life also causes a form of ataxia in newborn offspring. This condition has been observed in lambs under field conditions.
and in guinea pigs and other experimental animals in the laboratory. It results from abnormal development of the cerebral cortex and the central nervous system. A similar condition is seen in humans with the genetic disorder called Menkes' syndrome. These infants exhibit the neurological defects and other signs of copper deficiency that are seen in copper-deficient animals (4).

**Zinc**

The effects of severe zinc deficiency during pregnancy are very different from those of manganese or copper. When pregnant rats are given a diet that is severely deficient in zinc throughout pregnancy, embryonic and fetal mortality are very high. The fetuses that are alive at term are small in size, and almost all of them show gross congenital malformations. These defects can affect any of the organ systems of the body, and their incidence is high (2,5). In addition to the morphological abnormalities, biochemical functional abnormalities in the offspring also result from maternal zinc deficiency. These include defects of pancreatic function, lung metabolism, and immune competence (2,6). As with copper deficiency, there is a genetic disorder of zinc metabolism in humans. Acrodermatitis enteropathica produces in infants many of the same signs and defects seen in severely zinc-deficient animals. This disorder results in death if it is not treated, but oral zinc supplements can completely prevent all signs (7).

It has been demonstrated that both zinc and copper are required specifically by the embryo and fetus and that metabolic lesions associated with deficiencies of these elements are caused at least in part by direct effects on the embryos rather than by indirect effects through changes in maternal metabolism (8). In these studies, young control rat embryos of 9.5 days gestational age were incubated with serum—either normal rat serum or serum deficient in zinc or copper taken from rats fed on diets deficient in these elements. After 48 hr of incubation the embryos were removed, measured for growth and abnormalities, and their protein content analyzed. Of 16 zinc-deficient serum samples, 12 gave rise to embryos that were abnormal; of 12 copper-deficient serum samples, 11 gave rise to abnormal embryos. When such serum samples were supplemented with the missing element, either zinc or copper, the embryos that developed were nearly normal (Table 2). Thus, zinc and copper are specific requirements for normal growth and development of mammalian embryos.

Utilization of the embryo culture system will permit further delineation of the metabolic lesions resulting from embryonic copper and zinc deficiency. In addition, this system may provide a valuable means of quickly screening drugs that are embryotoxic by virtue of their interference with embryonic mineral metabolism.
TABLE 2. Effects of zinc-copper deficiency on rat embryos in culture

| Deficient rat serum samples | Unsupplemented | | | | Supplemented | | |
|----------------------------|----------------|-----------------|----------------|-----------------|----------------|----------------|
|                             | Teratogenic samples | No. | % | Abnormal embryos | No. | % | Teratogenic samples | No. | % | Abnormal embryos | No. | % |
| Zinc                       | 8/8 100 | 11/16 69 | 1/8 13 | 1/16 6 |
| Copper                     | 7/7 100 | 8/14 57 | 0/7 0 | 0/14 0 |

*From Mieden et al. (8).

** Zinc acetate was added to culture medium.

*** Copper acetate was added to culture medium.

MARGINAL DEFICIENCIES

The effects of severe deficiencies of manganese, zinc, and copper are dramatic, but their occurrence in human populations under normal conditions is relatively rare. Manganese deficiency has not been reported in humans under normal conditions. Severe zinc deficiency has occurred not only in cases of acrodermatitis enteropathica, but also in infants and adults given total parenteral nutrition in which the solutions contained inadequate amounts of zinc (9). Copper deficiency also can occur under such conditions and is also reported in premature infants (10), but such cases of severe deficiencies are relatively rare. In a different category, however, is marginal deficiency, which can occur for long periods of time in large groups of people. Marginal deficiencies are therefore more relevant to the human condition than the severe deficiencies, which serve as such valuable tools in studying the roles of these nutritional factors.

Zinc: Monkey Model

For the last few years we have been engaged in a long-term study of the effects of marginal zinc deficiency during pregnancy in rhesus monkeys. In these experiments, the level of zinc given to the deficient group was such that nonpregnant females showed very little change in plasma zinc concentrations for a period of several months. Pregnant monkeys were given these purified diets containing either a control level of zinc or the marginally deficient level starting at the beginning of pregnancy. Plasma zinc concentration remained the same in both groups until about midway through the gestation period, and by the third trimester it was significantly lower in the deficient group than in the controls (11). A third group of monkeys served...
as controls for food intake; they were given the control diet in amounts equivalent to those eaten by the deficient animals on a pair-fed basis. At term, the deficient monkeys showed dermatitis and alopecia.

Some of the monkeys given the zinc-deficient diet were anorexic, whereas others were not, and their degree of weight loss was a function of the anorexia; that is, those that were anorexic showed some weight loss, while the others gained weight. An interesting observation was that the decline in plasma zinc was inversely related to the degree of anorexia. Anorexic monkeys showed a slower decline in plasma zinc concentration than those that were not anorexic. This observation is undoubtedly related to the effects of food intake on maternal catabolism. Studies with rats show that when the food intake of pregnant rats given a zinc-deficient diet is restricted, such animals will have a lower frequency of fetal death and fetal malformation than is seen in rats given a zinc-deficient diet ad libitum. The depression of food intake increases the rate of maternal tissue catabolism with a subsequent release of tissue zinc to the plasma; thus the higher level of circulating plasma zinc allows for more normal fetal development (12,13).

Vitamin A metabolism is also affected by marginal zinc deficiency. By the third trimester, plasma vitamin A was lower in the zinc-deficient monkeys than in the controls, and the ratio of retinol-binding protein (RBP) to vitamin A was higher (14). Plasma RBP was directly related to plasma zinc in the zinc-deficient monkeys but not in the controls, and the correlation of plasma zinc to plasma vitamin A indicated that there is a threshold level of plasma zinc below which the plasma vitamin A is directly correlated. Above this threshold level, plasma zinc and plasma vitamin A are not related. In studies with pregnant rats, feeding a higher than normal level of vitamin A with a zinc-deficient diet did not ameliorate the deleterious effect of zinc deficiency on vitamin A metabolism (15).

A consistent finding in the monkey studies was a depression of immune function in the marginally zinc-deficient animals. The mitogen responsiveness of leukocytes was significantly lower throughout pregnancy in the zinc-deprived pregnant females than in the controls (11).

Pregnancy outcome was significantly worse in the ad libitum-fed zinc-deficient animals and the pair-fed controls than in the ad libitum-fed controls, and the deficient group also had more complications of pregnancy than the controls (16). Birthweight of male newborn infants was significantly lower than in either of the control groups. There was thus a specific effect of the zinc deficiency on the birthweight of male offspring that was not seen in the pair-fed controls. The crown-rump and femur length of male newborns were also significantly less than those of controls. Female newborn infants did not show any differences in birthweight or length among the three groups.

When birthweight was correlated with the plasma zinc concentration of the mothers during the last trimester, there was a different relationship in the controls and in the zinc deficient groups. In the controls there was a
direct relationship between maternal plasma zinc concentration and infant birthweight. In the deficient animals, however, the relationship was inverse; the higher the maternal plasma zinc, the lower was the infant birthweight. Statistical analysis also revealed that in control animals, both food intake and maternal plasma zinc had a direct positive influence on birthweight. In zinc-deficient animals, however, only maternal plasma zinc had a direct effect on birthweight, whereas the influence of food intake was indirect, mediated by its effect on plasma zinc. These observations may be related to the effects of anorexia on plasma zinc concentration and the concomitant effect on maternal catabolism.

It is also of interest that studies of the relationship of infant birthweight to maternal plasma zinc at term in human pregnancies have been variable; that is, some studies indicate a direct correlation, whereas others find an inverse correlation (17–22). Perhaps our results indicate that in cases of human studies in which an inverse relationship has been observed, a significant proportion of the subjects were marginally deficient in zinc. A study of the effects of vomiting in human pregnancy has indicated that there was a correlation between the frequency of vomiting and higher infant birthweight (23). Again, this observation is consistent with our findings relating to anorexia, plasma zinc, and birthweight.

In addition to the low birthweight of the male newborn rhesus monkeys from zinc-deprived mothers, these neonates also showed lower than normal plasma zinc and plasma vitamin A concentrations. As in humans and other animals, the plasma zinc level of all the neonates was significantly higher than that of the mothers (16).

Another important observation in these newborn monkeys was abnormal skeletal development. The skeleton showed osteoporotic effects with wide epiphyses similar to those seen in rickets. There was also delay in appearance of ossification sites and some fractures. Supplementation with zinc brought about recovery (24).

Although the male infants were smaller than the controls at birth, by 1 month of age their bodyweight had caught up to that of the controls, and in both the males and the females, bodyweight remained at the control level until 9 months of age. At this time growth began to slow, and by 1 year of age it was significantly lower than in the control group. Throughout the first year of life there was abnormal immune function in zinc-deprived offspring. Mitogen stimulation of lymphocytes was lower than in the controls. Behavioral defects of various types were also apparent (25,26).

In studies currently underway, adult female breeder monkeys were given a control diet or a diet marginally deficient in zinc for 1 year prior to mating. During this time, the plasma zinc concentration of the females remained quite stable, although after 1 year of age it was significantly lower in the deficient group. Several immune parameters, including serum IgM and IgG levels and polymorphonuclear leukocyte function, were depressed in the
zinc-deprived group (27). At midgestation, fetal growth was evaluated by ultrasonography. These measurements showed that fetal growth in the zinc-deficient females was significantly lower than normal, even as early as midgestation.

Discriminant analysis revealed that maternal lymphocyte response to concanavalin-A, maternal fibrinogen, serum IgM, amniotic fluid iron level, and fetal abdominal circumference were discriminators for the diet group, all lower in zinc-deficient monkeys than in controls. Maternal plasma zinc concentration was positively correlated with fetal abdominal circumference and abdominal area and with maternal concanavalin-A response and serum uric acid level. Maternal red blood cell concentration was positively correlated with fetal abdominal circumference and fetal abdominal area and with response of maternal lymphocytes to phytohemagglutinin. These observations suggest that immune function is a strong discriminator of marginal zinc deprivation in rhesus monkeys (28).

**Zinc Deficiency in Human Pregnancy: The Rat Model**

There is some evidence that zinc deficiency is a teratogenic agent in humans (Table 3). Sever and Emanuel (29) first called attention to the high frequency of neural tube defects in regions of the world where zinc deficiency was prevalent. Two years later, Hambidge et al. (30) summarized the literature of pregnancy outcome in women with acrodermatitis enteropathica (AE). At this time, 1975, some women with AE had survived to maturity, but in the absence of knowledge that the disease was a disorder of zinc metabolism, the treatment available at the time did not bring their plasma levels to normal. The frequency of fetal death and malformed infants in these patients was extremely high. In a prospective study, Jameson (17) in Sweden

<table>
<thead>
<tr>
<th>Observation</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>Neural tube defects in regions of zinc deficiency</td>
<td>29</td>
</tr>
<tr>
<td>Fetal death and malformation in acrodermatitis enteropathica</td>
<td>30</td>
</tr>
<tr>
<td>Low maternal blood zinc and malformations in infants</td>
<td></td>
</tr>
<tr>
<td>in Sweden</td>
<td>17</td>
</tr>
<tr>
<td>in Turkey</td>
<td>31</td>
</tr>
<tr>
<td>in Ireland</td>
<td>32</td>
</tr>
<tr>
<td>Low maternal zinc and low birthweight</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>34</td>
</tr>
<tr>
<td>Zinc supplementation in prevention of low birthweight and pregnancy</td>
<td>35</td>
</tr>
<tr>
<td>complications</td>
<td></td>
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TABLE 4. Zinc supplementation and pregnancy complications*

<table>
<thead>
<tr>
<th>Complication</th>
<th>Controls (N = 358) (%)</th>
<th>Zinc supplemented (N = 179) (%)</th>
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</thead>
<tbody>
<tr>
<td>Fetal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotrophy (SFD)*</td>
<td>3.4</td>
<td>1.7*</td>
</tr>
<tr>
<td>Suspect CTG*</td>
<td>21.8</td>
<td>11.7*</td>
</tr>
<tr>
<td>Maternal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premature rupture of membrane</td>
<td>26.0</td>
<td>24.0</td>
</tr>
<tr>
<td>Preterm labor</td>
<td>2.8</td>
<td>0.6*</td>
</tr>
<tr>
<td>Green amniotic fluid</td>
<td>11.5</td>
<td>11.7</td>
</tr>
<tr>
<td>Premature separation of placenta</td>
<td>4.8</td>
<td>1.7</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6.2</td>
<td>3.9</td>
</tr>
<tr>
<td>Toxemia</td>
<td>3.4</td>
<td>1.7</td>
</tr>
<tr>
<td>Vaginal bleeding in labor</td>
<td>5.6</td>
<td>2.2*</td>
</tr>
</tbody>
</table>

* From Kynast and Saling (35).

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reported on a large number of pregnant women and showed that those who gave birth to malformed infants had significantly low blood zinc levels. Similar observations were made by Cavdar et al. (31) in Turkey and Soltan and Jenkins (32) in Ireland. Additional evidence suggesting a relationship between zinc deficiency in humans and the outcome of pregnancy was provided by Meadows et al. (33) and Simmer and Thompson (34), who found low maternal zinc to be correlated with low birthweight. Kynast and Saling (35) carried out a prospective study in which pregnant women supplemented with zinc showed a lower frequency of pregnancy complications and low birthweight than unsupplemented women (Table 4).

Some indirect evidence with regard to marginal zinc deficiency in human pregnancy comes from studies of diabetic pregnancy. Despite improvements in prenatal care, the frequency of congenital anomalies in humans is considerably higher in the pregnancies of diabetic women than in those of non-diabetic women (36). Anomalies of the central nervous system, cardiac, skeletal, renal, gastrointestinal, and pulmonary systems are all encountered. Data have been accumulating, which, taken together, support the idea that the increased risk of birth defects is in part due to factors other than disturbances in maternal and fetal fuel metabolism. Specifically, there is increasing evidence that diabetes-induced alterations in essential trace element metabolism may underlie some of the birth defects observed.

Using the nonpregnant streptozotocin (STZ) and alloxan-diabetic rat as models, investigators have shown that the diabetic condition results in elevated liver and kidney concentrations of zinc and copper, in addition to elevated liver concentrations of manganese (37–39). The higher amounts of
zinc and copper in the soluble fraction of the tissues are associated primarily with metallothionein (MT), whereas the higher manganese levels are associated with arginase (39). In addition to the accumulation of these trace elements in liver and kidney, their increased urinary excretion is a characteristic of poorly controlled diabetic patients (40–42), and hyperzincuria has also been shown in diabetic animal models (39,43,44).

These observations, as well as the similarities of the anomalies of diabetic pregnancy to those produced by zinc deficiency led to studies using the diabetic rat model (45). In these experiments, rats were made diabetic by injections of streptozotocin. The diabetic state was confirmed by measurement of blood glucose levels, and 27 days after the injection of the drug, the rats were mated. Blood glucose was determined on day 13, and the fetuses were delivered by cesarean section on day 20 of gestation.

The number of live pups per litter was smaller in the diabetic group than in the controls. Fetal length, fetal weight, and placental weight were all less in the diabetics than in the controls, whereas the resorption frequency was higher. The fetuses of diabetic mothers also showed a higher incidence of skeletal abnormalities than the controls. The skeletal abnormalities noted were similar to those observed with zinc deficiency. Analyses of trace elements demonstrated that metabolism of copper and zinc was abnormal in the diabetic animals. The diabetic dams at term had high concentrations of copper in kidney and liver. The zinc concentrations of the maternal kidney and liver were also higher than normal in the diabetic group, but fetal liver was significantly lower in zinc in the fetuses of diabetic mothers than in the controls (Table 5).

Studies have found that in the pregnant diabetic rat, similar to the non-pregnant rat, the increased zinc in the soluble fraction of the liver is asso-

<table>
<thead>
<tr>
<th>Trace element</th>
<th>Control (µg/g wet wt)</th>
<th>Diabetic (µg/g wet wt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal liver</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zinc</td>
<td>27.7 ± 1.4</td>
<td>33.6 ± 1.1*</td>
</tr>
<tr>
<td>Copper</td>
<td>4.7 ± 0.3</td>
<td>8.9 ± 1.6*</td>
</tr>
<tr>
<td>Iron</td>
<td>126 ± 11</td>
<td>133 ± 15</td>
</tr>
<tr>
<td>Manganese</td>
<td>2.7 ± 0.1</td>
<td>3.7 ± 0.1*</td>
</tr>
<tr>
<td>Fetal liver</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zinc</td>
<td>78.1 ± 3.3</td>
<td>51.0 ± 2*</td>
</tr>
<tr>
<td>Copper</td>
<td>13.0 ± 0.6</td>
<td>13.5 ± 0.8</td>
</tr>
<tr>
<td>Iron</td>
<td>174 ± 11</td>
<td>244 ± 9*</td>
</tr>
<tr>
<td>Manganese</td>
<td>0.3 ± 0.0</td>
<td>0.5 ± 0.1*</td>
</tr>
</tbody>
</table>

* From Uriu-Hare et al. (45).

* *p < 0.05.
associated with the putative zinc storage protein metallothionein. Conversely, the lower liver zinc in the diabetic fetus is reflected by a reduction in the amount of zinc normally found associated with this protein (Uriu-Hare, unpublished data). Thus, it is possible that the diabetic state in the mother results in stimulation of the synthesis of maternal liver metallothionein. Such an increase could cause a redistribution of maternal zinc pools, in turn resulting in maternal hypozincemia, and embryonic and/or fetal zinc deficiency. Since the concentration of zinc in the heptocyte is thought to be one of the regulators of metallothionein synthesis, this could explain our finding of low liver metallothionein in the diabetic fetus.

If this overall hypothesis is correct, maternal zinc supplementation during pregnancy may result in a reduction in the teratogenicity associated with diabetes. A second observation that can be made from these studies is that infants born to diabetic mothers may be at risk of postnatal zinc deficiency due to a reduction in accumulation of this element during the prenatal period. Physicians should be alert to this possibility.

In contrast to zinc, iron was significantly higher in the livers of fetuses from the diabetic females than in controls, so that these fetuses had low zinc combined with high iron concentrations in the liver (45). This is a combination that we have seen many times in zinc deficiency; we think that the high iron concentration may exacerbate the deleterious effects of the zinc deficiency by its peroxidant properties (5). Thus, diabetes altered the trace element metabolism of the pregnant rat and also affected the trace element metabolism of her fetuses. Abnormal trace element metabolism may be one of the mechanisms of the teratogenicity of the diabetic state.

**Zinc: Mouse Model**

Prenatal and neonatal mice are especially sensitive to zinc deficiency, even marginal deficiency. Mice fed by females given diets inadequate in zinc from the time of birth showed striking retardation of growth and development. Especially affected was the immune system. Thymus glands and spleens were very much smaller proportionally than other parts of the body, and immune function was also impaired (46,47). Even more dramatic is the effect of marginal zinc deficiency during gestation. When pregnant mice were given a diet marginally deficient in zinc for the last two-thirds of pregnancy, their offspring showed low levels of IgM that continued up to at least 6 months of age, even though they received diets adequate in zinc from birth. These effects persisted through at least three generations, although the detrimental influence of prenatal zinc deficiency was attenuated with each generation (48). Similar intergenerational persistence was also observed in postnatal mortality (49). These multigenerational effects on immune function imply a potential public health problem for zinc-deficient populations.
The mechanisms responsible for the persistent effect of prenatal marginal zinc deficiency on postnatal life have been investigated. We have studied the effect of zinc deficiency during gestation on the expression of metallothionein (MT), a class of proteins that have a high binding capacity for divalent metals. MTs probably serve as storage proteins for zinc and copper. In the mouse, as well as the human, there is a rapid increase during the latter part of gestation in the synthesis of MT in fetal liver, which may be induced by the fetal accumulation of zinc and copper during this period (50). In this study, pregnant mice were fed the control diet or the diet marginally deficient in zinc from day 7 of gestation to parturition (51). A third group of mice was fed the control diet in amounts equal to those eaten by the deficient group. At parturition, the mice were all fed the control diet for the rest of the experiment.

Newborn mice from dams in the low-zinc group had significantly lower concentrations of both zinc and MT in liver than did either of the control groups. At 8 weeks of age, the mice from dams in the low-zinc group had IgM levels that were only about 25% of control levels, thus confirming the earlier report of postnatal impairment of immune function in prenatally zinc deficient mice. At 10 weeks of age, however, in response to zinc injections, the offspring of dams given the zinc-deficient diet during the last two-thirds of pregnancy had liver MT levels that were very much higher than those of controls (Fig. 1). Thus, amplification of MT synthesis apparently occurred in the mice subjected to zinc deficiency during prenatal life. It therefore appears that prenatal zinc deficiency can alter the adult expression of some proteins involved in zinc metabolism. There also appears to be at least some degree of specificity to this effect on MT, since kidney MT was not affected, nor were concentrations of liver copper or iron.

Copper: Human Infants

Examples of marginal copper deficiency are indirect. Copper deficiency occurs clinically in premature human infants, in whom the condition is caused primarily by insufficient gestational time (10,52). Copper is accumulated in the fetus mainly at the end of the gestational period; in infants born prematurely, the copper concentration of the liver is abnormally low, and unless the postnatal nutrition of the infant is especially rich in copper, the infant is at risk for the development of copper deficiency (53). Even infants who do not show signs of frank copper deficiency will be susceptible to copper deficiency anemia if their copper stores are low and if their iron stores and intakes are also marginal. These effects may be exacerbated in infants of women whose copper intake during pregnancy is inadequate. Copper deficiency has also been reported in children receiving continuous ambulatory peritoneal dialysis (54).
In addition to simple dietary copper deficiency, copper-deficiency syndrome can also be induced by excess supplementation of zinc. Because of their similar physicochemical properties, excess zinc in the diet can inhibit the absorption of copper (55). In adults, zinc-induced copper deficiency has been reported in individuals taking zinc supplements ranging from 50 to 150 mg/day (56–58). Although zinc-induced copper deficiency has not been reported in either pregnant women or infants, it is clear that if zinc supplements are to be used during either pregnancy or infancy, caution must be exercised to ensure that copper-deficiency syndrome is not precipitated.

Manganese

Although severe dietary manganese deficiency in humans has not been reported, there are suggestions that manganese nutriture may not always be optimal. Poor manganese status, defined as low manganese concentrations
in hair, plasma, and/or blood, has been reported to be a possible complication in children suffering from the inborn errors of metabolism maple syrup urine disease and phenylketonuria, even though the dietary intake of manganese by these children is similar to that of control children (59). Soft tissue (liver and heart) manganese concentrations have also been reported to be lower than normal in children suffering from protein-calorie malnutrition (60). Manganese deficiency may also be a complication of some forms of epilepsy in both adults (61,62) and children (63). Finally, during the last 5 years, manganese deficiency in adults has been reported to be associated with congenital prolidase deficiency (64), hip dysplasia (65), and osteoporosis (66).

In addition to the potential risk of simple dietary manganese deficiency, there is the possibility that excess dietary iron can result in a conditioned manganese deficiency. At high levels of dietary iron intake there can be a reduction in manganese absorption, which can be reflected by low tissue manganese concentrations (67). Therefore, iron supplementation during infancy may have a negative effect on the infant’s ability to absorb manganese from the diet. This may be a particular problem for infants who are breast fed, since human milk is very low in manganese content (68). Thus it is evident that the manganese status of pregnant women and their offspring requires further investigation.

CONCLUSIONS

The studies we have summarized of both animal experiments and human investigations clearly show that inadequate prenatal nutrition can result in postnatal risk for the offspring and, indeed, that some of these effects can persist through several generations. These considerations point to the need for prospective studies in both animals and humans on pregnancy outcome in relation to certain critical nutrients. In addition, methods should be established for assessing the trace element status of newborn infants, especially those at high risk. Such infants should also be reassessed at 2 to 3 months of age, when deficits in liver stores of these essential trace elements may become apparent.

REFERENCES


