

## Copper metabolism in children

How important is copper in the metabolism of children? It was recognized as early as 1928 that copper deficiency in animals gave rise to an anaemia. The essential nature of copper was established when it was shown to be a major component of caeruloplasmin, an  $\alpha_2$ -globulin. However, it is extremely difficult to produce copper deficiency in a normal infant, and Scheinberg and Sternlieb (1969) have concluded that copper deficiency in man rarely, if ever, occurs. There is exciting new evidence to show that this conclusion was mistaken. Infants with marasmus and kwashiorkor who were treated with skimmed-milk diets developed a hypochromic anaemia, neutropenia, and osteoporosis, responsive only to copper therapy (Cordano, Baertl, and Graham, 1964). Neonates maintained on unusual diets or fed intravenously, for periods as short as 6 weeks, developed copper deficiency presenting with a variable anaemia, profound neutropenia, and vascular and bone changes which were reversed by oral copper therapy (Karpel and Peden, 1972). In this situation the young red cells in the marrow showed vacuolation and deposition of ferritin granules (Ashkenazi *et al.*, 1973). Supplementing the infant on intravenous feeds with trace metals by a twice-weekly infusion of plasma was totally inadequate as it supplied only 6  $\mu\text{g}/\text{day}$  (Shaw, 1973), and it has been shown that an infant's requirements are between 200 and 500  $\mu\text{g}/\text{day}$  (Alexander, Clayton, and Delves, 1974).

The extreme effects of copper deficiency are to be seen in the X-linked, recessively inherited, degenerative brain disease described by Menkes *et al.* (1962). Changes in the hair ('kinky' or 'steely' hair), arterial wall, and bones, and a substantial part of the cerebral disorganization can be accounted for by a lack of ionic copper, and serum copper and caeruloplasmin levels may be extremely low (Danks *et al.*, 1972a). Radioactive copper studies have suggested that the defect is a failure of absorption of copper from the upper small intestine (Danks *et al.*, 1972b). Recently Danks *et al.* (1973) have shown a very high (3 times normal) copper content of cells in the duodenal mucosa of patients with this disease and suggested that the defect in absorption

lay in the failure of transport of copper within the cell or through its serosal surface. One feature of kinky hair disease which is at the moment totally unexplained is the normal level of copper found in the red cells in the blood, and patients do not usually suffer the anaemia or neutropenia seen in children with nutritional copper deficiency. Treatment with intramuscular copper raises the serum copper and caeruloplasmin levels but appears to make little difference to the progression of the cerebral disorder.

Plasma levels of copper and caeruloplasmin vary widely in different disease states (Klein and Haddow, 1968). They are accountably low in situations involving protein loss, or defective production, such as cystic fibrosis, nephrosis, starvation, and severe liver disease. However, the levels are raised in such unconnected conditions as pregnancy, leukaemia, acute myocardial infarction, and the collagen vascular diseases. Curiously, the plasma copper concentration is invariably in inverse proportion to that of zinc. In acute lymphoblastic leukaemia, for example, before treatment plasma copper concentration is high but zinc is lower than normal; both these values return to normal levels once the child is in remission (Delves, Alexander, and Lay, 1973). This inverse relation may be a manifestation of competition for binding sites or it may be the result of an interaction between carrier globulins.

Most of our knowledge of copper metabolism in children has come from dynamic studies with radioactive copper in patients with Wilson's disease. An excellent resumé of the presentation and treatment of this condition has been given by Walshe (1970). From these studies we know that 40% of an oral dose of copper is absorbed principally from the upper small gut. Copper enters the blood and becomes loosely bound to albumin, is rapidly taken up by the liver and incorporated into caeruloplasmin. At the cellular level the copper is bound to an enzyme, superoxide dismutase, and a metallothionein-like protein of low molecular weight.

Two questions concerning Wilson's disease have remained unanswered until recently. What is the basic defect? Is the accumulation of copper in the

body due to an increased absorption of copper, a decreased excretion in the bile, or both of these mechanisms?

Evans, Dubois, and Hambidge (1973) have shown that the metallothionein in the liver cells of patients with Wilson's disease has four times the copper binding capacity of normal metallothionein. This avidity would upset the normal copper equilibrium and prevent its incorporation into caeruloplasmin. The liver cell becomes saturated with copper which allows free copper to enter the circulation in large amounts. Whether it is the free copper in the blood or the presence of an abnormal protein in other tissues which gives rise to extrahepatic copper deposition is not yet known.

Other radioactive copper studies by Strickland and his co-workers (1972) have shown conclusively that copper uptake in Wilson's disease is normal and that the accumulation of copper is due to a significantly reduced excretion in the faeces via the bile.

None of these recent studies have cast any further light on the role of caeruloplasmin. Its oxidase activity towards the ferrous ion is well documented (Frieden, 1970), and in this capacity it may be involved in the release of iron from the reticulo-endothelial system to be incorporated as haemoglobin in the red cell. This may account for the vacuolation and granules of ferritin seen in red cell precursors in nutritional copper deficiency, but does not explain the normal levels of haemoglobin, and of red cell copper in kinky hair disease. Finally, there still remains no explanation for the fact that certain patients with clinically severe Wilson's disease have normal or near normal caeruloplasmin levels, nor for the reverse situation where certain heterozygotes for Wilson's disease have a profound deficiency of caeruloplasmin but never develop the

hepatic and neurological symptoms. Clearly there is much work still to be done.

#### REFERENCES

- Alexander, F. W., Clayton, B. E., and Delves, H. T. (1974). Mineral and trace metal balances on children receiving normal and synthetic diets. *Quarterly Journal of Medicine*, **43**, 89.
- Ashkenazi, A., Levin, S., Djaldehi, M., Fishel, E., and Benvenisti, D. (1973). The syndrome of neonatal copper deficiency. *Pediatrics*, **52**, 525.
- Cordano, A., Baertl, J. M., and Graham, G. G. (1964). Copper deficiency in infancy. *Pediatrics*, **34**, 324.
- Danks, D. M., Campbell, P. E., Stevens, B. J., Mayne, V., and Cartwright, E. (1972a). Menkes' kinky hair syndrome. *Pediatrics*, **50**, 188.
- Danks, D. M., Cartwright, E., Stevens, B. J., and Townley, R. R. W. (1973). Menkes' kinky hair disease. Further definition of the defect in copper transport. *Science*, **179**, 1140.
- Danks, D. M., Stevens, B. J., Campbell, P. E., Gillespie, J. M., Walker-Smith, J., Blomfield, J., and Turner, B. (1972b). Menkes' kinky-hair syndrome. *Lancet*, **1**, 1100.
- Delves, H. T., Alexander, F. W., and Lay, H. (1973). Copper and zinc concentration in the plasma of leukaemic children. *British Journal of Haematology*, **24**, 525.
- Evans, G. W., Dubois, R. S., and Hambidge, K. M. (1973). Wilson's disease: identification of an abnormal copper binding protein. *Science*, **181**, 1175.
- Frieden, E. (1970). Caeruloplasmin: a link between copper and iron metabolism. *Nutrition Reviews*, **28**, 87.
- Karpel, J. T., and Peden, V. H. (1972). Copper deficiency in long-term parental nutrition. *Journal of Pediatrics*, **80**, 32.
- Klein, R., and Haddow, J. E. (1968). Trace elements in health and disease. *Practitioner*, **201**, 314.
- Menkes, J. H., Alter, M., Steigleder, G. K., Weakley, D. R., and Sung, J. H. (1962). A sex-linked recessive disorder, with retardation of growth, peculiar hair, and focal cerebral and cerebellar degeneration. *Pediatrics*, **29**, 764.
- Shaw, J. C. L. (1973). Parenteral nutrition in the management of sick and low birthweight infants. *Pediatric Clinics of North America*, **20**, 333.
- Scheinberg, I. H., and Sternlieb, I. (1969). *Duncan's Diseases of Metabolism*, 6th ed. Vol. 2, p. 1321. Ed. by P. K. Bondy. Saunders, Philadelphia.
- Strickland, G. T., Beckner, W. M., Mei-Ling, L., and O'Reilly, S. (1972). Turnover studies of copper in homozygotes and heterozygotes for Wilson's disease and controls. *Clinical Science*, **43**, 605.
- Walshe, J. M. (1970). Wilson's disease. *British Journal of Hospital Medicine*, **4**, 91.

FRASER W. ALEXANDER

Newcastle General Hospital, Westgate Road,  
Newcastle upon Tyne NE4 6BE.