Proc. Nutr. Soc. Aust. (1978) 3:13

TRACE ELEMENTS IN ANIMAL AND HUMAN NUTRITION: INTRODUCTION AND HISTORICAL BACKGROUND

R. M. SMITH*

It is no coincidence that Australia has often set the pace of progress in defining the role of trace elements in nutrition. A high proportion of our arable land is made up of very ancient soils, heavily weathered and leached and almost uniformly deficient in N and P. Many of these soils are also acutely deficient in one or more of the trace elements now known to be essential for the health and normal growth of plants and animals (Donald and Prescott 1975). In most cases these requirements for trace elements were first recognised as a result of the occurrence of specific diseases of animals or plants. These were eventually found to respond to treatment with minute quantities of one or other of the elements normally present in trace quantities in the tissues. Like the vitamins, the trace elements may be operationally defined as specific curative agents for diseases or disabilities associated with lowered concentrations of them in the tissues.

Our concern here is with trace elements in human and animal nutrition. In the historical context, both in Australia and elsewhere there have always been three discernible aspects to the management and prevention of specific nutritional diseases. These are their recognition and diagnosis, their treatment and prevention, and the scientific work and study that is aimed at their understanding. Each of these facets of knowledge and action bears on each of the others and advances in insight into any of them may be seen in retrospect to enhance the potential for knowledge and action in the others. Some examples may make this clear.

I. COBALT

Cobalt deficiency in sheep was identified in 1935 in both South Australia (Marston 1935; Lines 1935) and in Western Australia (Underwood and Filmer 1935). In both places the advance emerged from a deliberate attempt to resolve by scientific methods the nature of an economically important disease. The scientific understanding gained then was sufficient to classify the disease as a nutritional one and to identify the lacking nutrient as cobalt. In terms of the science of nutrition today, however, such knowledge was primitive. Further studies of the disease continued in both field and laboratory (Lee and Marston 1969; Smith and Marston 1970). A critical advance that took place in 1948 in both Great Britain (Lester Smith 1948) and the United States (Rickes et al. 1948) lay in the recognition that the newly isolated anti-pernicious anaemia factor, vitamin B_{12}, contained 4% by weight of cobalt. It soon became apparent (Smith, Koch and Turk 1951; Marston and Lee 1952) that the consequences of cobalt deficiency in sheep were entirely attributable to a lack of vitamin B_{12} and that cobalt was required only to permit synthesis of the vitamin by microorganisms in the rumen. Recognition of the role of the rumen microflora in the production of vitamin B_{12} from inorganic cobalt was a piece of fundamental knowledge that played a part in the invention of an entirely novel kind of preventative therapy, the heavy ruminal pellet. A dense pellet composed of cobalt oxide and iron filings was introduced into the rumen where it lodged more or less permanently and slowly released a minute but adequate supply of ionic

* CSIRO Division of Human Nutrition, Adelaide, South Australia 5000.

cobalt into the rumen fluid (Dewey, Lee and Marston 1958).

Study of the disease proceeded further. The predominant effect of the deficiency in sheep was a severe depression of appetite that eventually led to death by inanition. The extent to which appetite was depressed was found to be correlated with an observed impairment in the rate of clearance of propionate from the bloodstream (Marston, Allen and Smith 1972). This block in the metabolism of propionic acid, one of the major sources of energy in the ruminant, finally allowed the identification of a critical function of vitamin B_{12} at the biochemical level (Smith and Monty 1959; Marston, Allen and Smith 1961). It was shown that vitamin B_{12} in an appropriate form was an essential cofactor for one of the enzymic steps in the conversion of propionate into glucose in the sheep's liver.

A lowered activity of this enzyme in the liver of the cobalt deficient animal led to accumulation of propionate in the bloodstream. This in turn inhibited the metabolism of acetate and was accompanied by the observed depression of appetite (Underwood 1977).

It is now possible to ascribe almost all of the observable consequences of cobalt-deficiency in sheep to a lowering of activity of one or other of two vitamin B_{12}-dependent enzymes (Smith and Gawthorne 1975). One of these, mentioned above, is involved in the metabolism of propionate. The other is concerned with the metabolism of methionine, an essential amino acid that in addition to its role in the synthesis of proteins is also closely involved in the retention by the liver of folic acid. There is evidence to suggest that both of these reactions may be significant in the aetiology of human pernicious anaemia, but this remains to be established.

II. SELENIUM

In 1957 Schwarz and Foltz identified selenium as an integral part of Factor 3, a hepatoprotective factor in rats fed certain necrogenic diets. Work in the United States (Muth *et al.* 1958) and in New Zealand (McLean *et al.* 1959) showed that selenium was also important in ruminant nutrition. In the New Zealand work unthriftiness in lambs, infertility in ewes and white muscle disease in lambs and hoggets were all associated with low dietary intakes of selenium. In Australia both field studies of similar selenium responsive conditions (Godwin *et al.* 1970) and experimental approaches aimed at an understanding of the nature of white muscle disease (Godwin *et al.* 1974) have been carried out. The latter work has focussed on the abnormalities of calcium metabolism in dystrophic muscle. These well established pathological consequences are now known to be the result of progressive changes that commence very early in the history of the disease and that may involve the muscle mitochondria (Godwin *et al.* 1975).

Perhaps the most significant recent advance in understanding the role of selenium in nutrition has been the demonstration that the enzyme glutathione peroxidase is a selenoprotein (Rotruck *et al.* 1973). Effective in the destruction of hydrogen peroxide, the enzyme is also active with a wide range of hydroperoxides including those of the steroids (Little 1972). The enzyme forms part of the protective mechanism of biological membranes against the deleterious actions of peroxides and its depleted activity in tissues of selenium deficient animals provides a rational basis on which to explain the consequences of deficiency (Ganther *et al.* 1976).

The importance of selenium in human nutrition may be inferred from the fact that glutathione peroxidase from human erythrocytes is a

selenoprotein (Awasthi et al. 1975). A low selenium status of Guatamalan children suffering from kwashiorkor has been reported (Burk et al. 1967) and blood selenium levels in the New Zealand population are reported to be low in comparison with other European communities (Watkinson 1974). It has yet to be established that selenium deficiency constitutes a human disease.

III. IODINE

Although iodine was one of the earliest of the essential trace elements to be identified, a deficiency of iodine still remains a major nutritional problem in many of the underdeveloped nations. Kelly and Sneddon (1960) in a report to the World Health Organization placed the number of affected individuals at two hundred millions. Published maps of the geographical distribution of goitre show that iodine deficiency occurs to some extent in all of the major land masses. Presumably because of leaching of iodine from sparse mountain topsoils the severity of the disease is generally greatest in highland areas. One such region recently defined lies in the highlands of New Guinea (Hetzel 1970, 1974).

A consequence of severe iodine deficiency in man that is of particular concern is the condition known as endemic cretinism. This disease differs from the simple thyroxine-responsive sporadic cretinism of early infancy in that the associated abnormalities of the central nervous system are more deep-seated and severe and they do not respond to treatment with thyroid hormone. It is also established that the condition need not be accompanied by symptoms of hypothyroidism (Ingbar et al. 1965; Stanbury 1971).

Controversy as to the aetiology of endemic cretinism has now been resolved as a result of a controlled clinical trial in the New Guinea highlands in which the efficacy of a single injection of iodised oil as a long-term prophylactic was studied. It transpired that effective prevention of endemic cretinism in children in affected regions was achieved only if the mother had received iodised oil either before pregnancy or during its very early stages (Pharaoh et al. 1971).

These experiments provide a classic example of the interplay of the three basic modes of progress in the management of nutritional disease. First, endemic cretinism was positively identified as a consequence of iodine deficiency. Secondly, a highly effective and suitable preventative treatment was devised and tested, and finally a substantial advance was made in understanding the fundamental nature of the disease. The latter consequence emerged from the observation that iodine was needed before the foetal thyroid gland appeared. Since maternal thyroid hormones seem not to cross the placental barrier, this suggests that iodine in some form other than thyroid hormone may be required for the early development of the central nervous system. The nature of this involvement remains to be established.

IV. TRACE ELEMENT NUTRITION IN MAN

For many reasons the techniques and strategies in the study of nutritional diseases in animals are not directly applicable to studies with man. In human populations the experimental approach is severely limited by logistical as well as ethical considerations. Deficiency states in experimental animals rarely provide adequate models of the human case. Treatments, even when adequately established, may not find ready acceptance. Nonetheless, the principle of parallel and interactive development in the fields of detection, prevention and the acquisition of

fundamental knowledge remains valid and new strategies to achieve these ends have emerged. The techniques of epidemiology, the study of the geographical and life-style correlates of disease may be applied here to the identification of inadequacies of trace element nutrition. In the area of treatment and prevention the emphasis must change from the provision of salt licks and heavy pellets to the fields of education, persuasion and to new and improved methods of food technology.

REFERENCES

AWASTHI, Y.C., BEUTLER, E. and SRIVASTAWA, S.K. (1975). J. Biol. Chem. 250: 5144.

BURK, R.F., PEARSON, W.N., WOOD, R.P. and VITERI, F. (1967). Am. J. Clin. Nut. 20: 723.

DEWEY, D.W., LEE, H.J. and MARSTON, H.R. (1958). Nature (Lond.) 181, 1367.

DONALD, C.M. and PRESCOTT, J.A. (1975) in Trace elements in Soil-Plant-Animal Systems. Eds. Nicholas, D.J.D. and Egan, A.R. (Academic Press: New York).

GANTHER, H.E., HAFEMAN, D.G., LAWRENCE, R.A., SERFASS, R.E. and HOEKSTRA, W.G. (1976) in Trace Elements in Human Health and Disease, Vol. II. Eds. Prasad, A.S. and Oberleas, D. (Academic Press: New York).

GODWIN, K.O., EDWARDLY, J. and FUSS, C.N. (1975). Aust. J. Biol. Sci. 28, 457.

GODWIN, K.O., KUCHEL, R.E. and BUCKLEY, R.A. (1970). Aust. J. Exp. Agric. Anim. Husb. 10, 672.

GODWIN, K.O., KUCHEL, R.E. and FUSS, C.N. (1974). Aust. J. Biol. Sci. 27, 633.

HETZEL, B.S. (1970). Med. J. Aust. 2, 615.

HETZEL, B.S. (1974). N.Z. Med. J. 80, 482.

INGBAR, S.H., BRAVERMAN, L.E., DAWBER, N.A. and LEE, G.Y. (1965). J. Clin. Invest. 44, 1679.

KELLY, F.C. and SNEDDON, W.W. (1960). W.H.O. Monog. Ser. 44, 27.

LEE, H.J. and MARSTON, H.R. (1969). Aust. J. Agric. Res. 20, 905 and 1109.

LINES, E.W.L. (1935). J. Counc. Sci. Indust. Res. (Aust.) 8, 117.

LITTLE, C. (1972). Biochim. Biophys. Acta 284, 375.

McLEAN, J.W., THOMSON, G.G. and CLAXTON, J.H. (1959). N.Z. Vet. J. 7, 47.

MARSTON, H.R. (1935). J. Counc. Sci. Indust. Res. (Aust.) 8, 111

MARSTON, H.R., ALLEN, S.H. and SMITH, R.M. (1961). Nature (Lond.) 190, 1085.

MARSTON, H.R., ALLEN, S.H. and SMITH, R.M. (1972). Br. J. Nutr. 27, 147.

MARSTON, H.R. and LEE, H.J. (1952). Nature (Lond.) 170, 791.

MUTH, O.H., OLDFIELD, J.E., REMMERT, L.F. and SCHUBERT, J.R. (1958). Science 128, 1090.

PHAROAH, P.O.D., BUTTFIELD, I.H. and HETZEL, B.S. (1971). Lancet, 1. 308.

RICKES, E.L., BRINK, N.G., KONIUSZY, F.R., WOOD, T.R. and FOLKERS, K. (1948). Science 108, 134.

ROTRUCK, J.T., POPE, A.L., GANTHER, H.E., SWANSON, A.B., HAFEMAN, D.G. and HOEKSTRA, W.G. (1973). Science 179, 588.

SCHWARZ, K. and FOLTZ, C.M. (1957). J. Am. Chem. Soc. 79, 3292.

SMITH, E.L. (1948). Nature (Lond.) 162, 144.

SMITH, R.M. and GAWTHORNE, J.M. (1975). in Trace Elements in Soil-Plant-Animal Systems. Eds. Nicholas, D.J.D. and Egan, A.R. (Academic Press: New York)

SMITH, R.M. and MARSTON, H.R. (1970). Br. J. Nutr. 24, 857 and 879.

SMITH, R.M. and MONTY, K.J. (1959). Biochem. Biophys. Res. Commun. 1, 105.

SMITH, S.E., KOCH, B.A., and TURK, K.L. (1951). J. Nutr. 44, 455.

STANBURY, J.B. (1971). in Endemic Cretinism. Eds. Hetzel, B.A. and Pharoah, P.O.D. (Surrey Beatty & Sons: Chipping Norton, N.S.W.)

UNDERWOOD, E.J. (1977). Trace Elements in Human and Animal Nutrition. (Academic Press: New York).

UNDERWOOD, E.J. and FILMER, J.F. (1935). Aust. Vet. J. 11, 84.

WATKINSON, J.H. (1974). N.Z. Med. J. 80, 202.