94 Winder, C., Carmichael, N.G., and Lewis, P.D., Effects of chronic low level lead exposure on brain development and function. Trends Neurosci. *5* (1982) 207–209.
95 Zoback, M.D., and Zoback, M.L., State of stress and intraplate earthquakes in the United States. Science *213* (1981) 96–104.
96 Zoeger, J., Dunn, J.R., and Fuller, M., Magnetic material in the head of the common pacific dolphin. Science *213* (1981) 892–894.

0014-4754/87/010092-13$1.50 + 0.20/0

Soil and congenital malformations

by P.J. Aggett and S. Rose

Department of Child Health, Polwarth Buildings, Foresterhill, Aberdeen AB9 2ZD (Scotland)

Key words. Abnormalities; trace metals; soil; geology; geography.

Introduction

Congenital malformations are just one manifestation of reproductive failure which can be induced by environmental factors. The complete spectrum of effects includes sexual dysfunction, chromosomal abnormalities of the germ cells, sperm abnormalities, sub-fecundity, maternal illness during pregnancy, early and late fetal death, intrapartum and neonatal death, low birthweight, altered sex ratios, multiple births, congenital structural abnormalities, functional abnormalities, infant death, infant morbidity and, possibly, childhood malignancy[8, 24]. Although many countries have systems for reporting congenital abnormalities, these are not wholly effective for a number of reasons. Firstly there is the problem of diagnosing and defining lesions: with gross defects such as neural tube defects this is straightforward but with less distinctive abnormalities categorisation is more difficult. Moreover, associated or multiple abnormalities may not be completely recorded although, as in the case with neural tube defects, such information is important in epidemiological studies of possible associations[17, 20]. Another disadvantage with the recording of defects at birth is that many, such as those of the heart and cardiovascular system may in fact not be detected until later in childhood, and unless specific studies are made it is conceivable that many abnormalities of immune, neurological and intellectual, and endocrine function may be missed completely[20].

No stage of fetal development is protected from potential environmental insults and even the pre-implantation trophoblast has the capacity to metabolize some xenobiotics. After implantation considerable cellular differentiation and migration occurs as the fetus assumes the recognizable morphology of the adult. In man this stage of organogenesis occupies most of the first trimester and blends into the period of histogenesis during which extensive growth and functional maturation of the organs proceeds.

All of these developmental stages can be disrupted and the principles of teratology have been summarized in this manner: 1) susceptibility to a teratogen can be influenced by genetic background; 2) the teratogen or its metabolic sequelae must reach the fetus; 3) the effects of a teratogen are dose dependent and may cause fetal death; 4) the teratogen's effects depend also on the developmental stage of the conceptus; and 5) different teratogens may have different specific effects which nevertheless result in similar morphological and functional anomalies[21]. Additionally, in the broader context the possible ability of some environmental insults to induce genetic and chromosomal abnormalities should not be neglected[20].

Soil is, of course, an important source – through water, plants and animals – of many of the inorganic elements which are essential for life[10, 45]. In some areas, either as a result of anthropogenic activities (mining, smelting, reservoir construction, etc.) or of local geochemical anomalies, excessive quantities of both essential and non-essential elements may enter the food chain and influence human health[10]. Thus the effect of soil on human reproductive function may arise from both deficiencies or excesses in the abundance of inorganic elements; or, more specifically, it may be the relative amounts of these elements which could be important in influencing human health and reproductive function. The possible nature of the latter effects can best be assessed from experience derived from animal models and from the management of farm livestock.

Effects of elemental deficiencies

The range of defects which has been observed with deficiencies of essential elements are summarized in table 1[15, 29, 47]. Probably the most important problems in practical terms arise from inadequate supply of copper, selenium, iodine and zinc. Geographical regions in which these deficiencies are known to affect livestock would be appropriate target areas in which to seek possible and analogous effects on human reproduction. The effect of copper deficiency on the fetus is particularly apparent in ruminants. Affected regions include Western Australia, Southern Africa and many sites in the South American plains as well as focal sites throughout the world. Calves, lambs and kids manifest the neurological lesions most obviously but often have associated defects in their hair, haematopoiesis, myocardial function and skeleton. It is apparent that the underlying copper deficiency arises from a relative excess of available molybdenum in the soil and forage which in turn can arise from a relative alkalinity of the soil, and poor drainage; molybdenum interacts with copper and sulphur to form insoluble precipitates

Table 1. Teratogenic effects of maternal deficiency of some elements

Zinc	Infertility, chromosomal abnormalities, failure of implantation, fetal death, micro and anophthalmia, syndactyly, neural tube defects, diaphragmatic and ventral herniae, skeletal abnormalities, impaired immune and intellectual function, neonatal respiratory distress, growth retardation, anaemia
Copper	Infertility, fetal death. spastic paralysis, incoordination, thin brittle bones, cardiac failure, aneurysms, defective connective tissue, skin and hair abnormalities, blindness, anaemia, impaired immune function, low birthweight
Manganese	Chondrodystrophy, bowed long bones, domed skull, absent otolittis, ataxia, increased convulsibility
Iron	Infertility, fetal death, reduced birthweight, functional depts of immunity and of intellect
Iodine	Infertility, psychomotor retardation, deaf-mutism, spastic paralysis, goitre growth retardation
Selenium	Fetal death

which prevent the intestinal absorption of copper[10]. This problem principally affects ruminants – hence the high prevelance of abnormalities in calves, sheep and goats – but some similar anomalies may occur in foals. Effects on the human fetus have not been reported.

Apart from the morphological depredations on the mammalian fetus[15], some other clues as to the potential importance of zinc deficiency in human teratogenesis emerge from animal models. One is the synergistic reaction between zinc deficiency and the effects of known teratogens such as thalidomide, 6-mercaptopurine, ethylenediamino tetra-acetate (EDTA), and vitamin A deficiency[15]. The latter effect is interesting because of claims that nutritional deficiencies of vitamins, such as vitamin A and folic acid, contribute to aetiology of human neural tube defects[38,39], cleft lips and cleft palates[44]. Another intriguing feature is that marginal zinc deficiency in pregnant rhesus monkeys produces intrauterine growth retardation of the fetus; male offspring are affected more frequently that females[11], thus combined analyses of the sex ratios of abortuses, and of infants with congenital malformations may provide an insight into the possible involvement of zinc deprivation or some similar insult in teratogenesis. Lastly the observed range of effects of zinc deficiency in laboratory models indicates that no stage of fetal development from conception to delivery is immune from its effects. Even transitory maternal restriction of the metal can induce subtle morphological and functional defects in the young[15].

The extensive areas of the Peoples Republic of China where a selenium responsive cardiomyopathy has been recognized are associated with low selenium content of the local soil and in locally produced grains and forage[3]. Since selenium deficiency is not associated with gross congenital deformities but rather with fetal death it would be valuable to know if an analogous problem confronts the human population in these areas. It would be equally interesting to know how extensive selenium responsive cardiac problems may be in a newborn, and also, since selenium responsive defects in immune function have been described in a relatively less selenium deficient region of Finland[1], whether or not such a problem compromises the well-being of the neonate in China.

Perhaps the best documented impact of soil on the human fetus is that which occurs in the areas of endemic goitre and cretinism[7]. This tragic relationship presents an enormous socio-economic burden. Affected regions include the Himalayas, Central Africa, the Andes, South East Asia and Oceania and the Alps. Two types of congenital cretinism have been described as the neurological and the myxedematous types[7]. The former occurs in most regions but the latter predominates in Central Africa and whereas their precise aetiologies probably differ, they represent the overt extremes of the clinical problem. Neurological cretinism is manifested by variable associations of mental retardation, deafness, mutism, blindness, strabismus, spastic diplegia and growth retardation. The insult to the central neurological system can be averted by the systemic administration of iodized oil to the mother before conception. Since later administration of iodine is less effective it would seem that iodine deficiency during organogenesis is of pathogenic importance in neurological cretinism[32]. Marginal iodine deficiency in utero with no obvious clinical features may also impair subsequent neurological development[4]. – In Northern Zaire up to 70% of the population is goitrous, but the incidence of cretinism is low (2–6%)[46]. In this region ingestion of goitrogens derived from cyanogenic compounds in detoxified cassava is thought to interact with a marginal iodine supply in inducing myxedematous cretinism. Levels of thiocyanate in cord blood are high at birth and fall progressively until mixed feeding starts. This implies that thiocyanate or a related goitrogen crosses the placenta and could affect the fetal thyroid[46].

Only about 10% of human iodine intake is derived from water, the rest comes from the diet. It has been proposed that an imbalance between soil Co, Mn, Sr, Cu, Ca, Mo and Zn, and I limits its uptake by plants from soil[2]. Additionally high soil pH, high organic content and iron and aluminium oxides reduce the uptake of iodine by crops[48,49]. Thus these factors, as well as the production by some plants (eg. *Brassicae* spp) of goitrogenic factors may contribute to some of the variable endemicity of cretinism.

Effects of elemental excess

Experience derived from laboratory studies and animal husbandry provide insight to the possible effects of exposure to excessive amounts of metals. These effects are summarized in table 2[29,47]. Lithium, aluminum, manganese, zinc, arsenic, selenium, cadmium, mercury and lead can all be embryocidal but the exposure required is seldom achieved in human experience other than in industrial environments. Similarly, poisoning of the human fetus with organic mercury has been encountered when, as in Minimata Bay, Japan, alkylated mercury is consumed as a result of potential foodstuffs metabolizing or becoming contaminated with industrial effluent[12], or when seed-grain treated with a mercurial pesticide is eaten rather than sown[29]. In contrast, whereas the use of sewage sludge to treat pastures does not as yet affect man, this practice may cause cadmium and lead toxicity and consequent reproduction failure in animals grazing the pastures.

Selenium toxicity occurs extensively throughout the world; in the central plains of North America, in Ireland,

Israel, USSR, Southern Africa and Australia. Most livestock are susceptible. Some of the effects on the fetus are similar to those in adults; the newborn may have limb and hoof abnormalities[45]. Additionally, selenium toxicity can cause cleft palate and a variety of congenital ophthalmic defects including cystic changes, microphthalmia, colobomata, cataracts, and abnormalities of the cornea and iris. Growth retardations and hypoplasia of the reproductive organs also occur. In one study 75% of malformed lambs died at birth and another 10% died within five months of birth[34]; there is no record, however, of similar human problems which can be related to selenium toxicity. Cowgill[5] calculated neonatal death rates/1000 live births for high, medium and low selenium regions in the USA and found only a marginal and insignificant increase in the rate for possibly high selenium areas. Another brief report found no correlation in Venezuela, a seleniferous zone, between the selenium burdens of populations as assessed by their urinary selenium excretion and their mortality rate due to congenital malformations[16]. Seleniferous areas have been described in China[50]; in these areas of Enshi province mobilization of selenium from coal leads to symptomatic selenium toxicosis in adult humans and to congenital abnormalities and neonatal deaths in swine and poultry. As with those areas where soils predispose to a selenium responsive cardiomyopathy, this would seem an important area in which to explore the impact of a local soil selenium anomaly on fetal and neonatal health.

Molybdenum toxicity has been referred to in respect to its ability to affect copper metabolism. An association in Armenia between altered metabolism of copper and purine, and a high molybdenum content of local soil has not been re-examined, but it offers an area in which human reproductive efficiency could be assessed in relation to the geochemical anomaly[22]. Similar imbalances occur in Southern and Eastern Africa, and in India. Adults in these areas are afflicted with skeletal abnormalities which have been related to imbalances between the available calcium, molybdenum and fluoride from the soil; there appears to be no published data on possible effects of these on the conceptus.

An international survey of congenital malformations demonstrated a striking geographical variation of the prevalence at birth of neural tube defects[40]. This study included infants born after 28 weeks gestation and may, therefore, have underestimated the true prevalence of such defects; another drawback is that the participating centres were in urban areas and therefore may not have reflected any peculiarities in the local soils. Nevertheless, particularly high rates were noted in Belfast and in Alexandria, Egypt; high rates have also been described in Cairo and in Iran[36]. In North America neural tube defects are more common in the eastern than in the western section of the continent; this gradient is only evident in whites and not in blacks. These observations and studies in regions where there is a low incidence of neural tube defects support an ethnic and genetic contribution to the aetiology of the defect[19,27,37]. Interacting with this background, there may be numerous environmental insults. In these circumstances females are involved more than male infants. It has been proposed that the prevalence of neural tube defects correlated negatively with water hardness[23,31,42]. Negative correlations have been reported with the copper content[26] and, in a case control study, with the zinc content[41] of local water supplies, but the authors have been justifiably cautious in attributing any causal relationship in these cases. These studies are matched by an extensive Canadian investigation[9] which corrected its data for maternal birthplace, legitimacy of the infant, maternal age, season and year of birth, previous number of live and still births and child death as well as adjusting for longitude. Thus it was shown that, although mothers delivering infants with neural tube defects tended to live in areas with high concentrations of chromium, selenium and silver in their water, there was no correlation between these factors nor with the domestic water content of calcium, magnesium, zinc, copper, nickel, lead, mercury, cobalt, molybdenum and cadmium. This was a retrospective study and it did not measure the actual mineral intake of the mothers. Nevertheless it is an interesting and valuable contribution which illustrates well the inherent difficulties of epidemiological assessment of the interactions between environment and birth defects.

A South Australian survey found a significant association of neural tube defects, cleft palate and neuromuscular abnormalities with the nitrate content of the domestic water supply; when compared with mothers using rainwater, other women had a 2.6-fold increased risk of such fetal abnormalities if their water contained 5–15 ppm nitrate. With water supplies containing more than 15 ppm the risk was increased by a factor of 4.1[6]. In the area concerned near Mount Gambier most surface water drains rapidly to an underground limestone aquifer or to a local lake and the investigators point out that, in this association, nitrate may be no more than a marker for other pollutants which could have accumulated in the soil and then have been leached out by the water.

The high rate of neural tube defects in the Middle East, the occurrence of an endemic malnutrition syndrome in which zinc deprivation is a component, and the teratogenic effect of maternal zinc deficiency has generated the hypothesis of a causal association in man[35]. This has yet to be explored systematically, but much interest has been shown in the problem in some areas of Turkey. An intriguing practice in this area is geophagia or clay eating. In temperate climates grazing animals may derive 3–5% of their mineral intake from soil, in arid zones this may be as much as 50%. The availability of minerals from ingested

Table 2. Effects of elemental excess on reproductive function

Cu	Embryocidal
Zn	Embryocidal, perinatal deaths
Mn	Embryocidal
Pb	Sterility, placental necrosis, abortions, perinatal and neonatal death, growth retardation, neurobehavioural abnormalities
Cd	Chromosomal abnormalities, embryotoxic, facial and neural tube malformations, skeletal changes
Hg	Inorganic: relatively low toxicity; organic (e.g. methyl Hg): neurotoxicity
As	Neural tube defects, micrognathia, genito-urinary and skeletal abnormalities, growth retardation
Se	Embryotoxic, skeletal and limb malformations, growth retardation, ophthalmic defects
Li	Reduced fertility, cleft palate, eye and ear malformations, liver damage
Fe	Neurobehavioural effects, impaired immune function

soils is not known but molybdenum rich soils in these circumstances can interfere with the absorption of copper and cobalt in ruminants[10]. Studies on Turkish clays show that they can limit the solubility of zinc and iron, and that they can interfere significantly with the intestinal absorption of both these metals[25]. A distinctive geophagic or clay eating syndrome has been recognized in Turkey and among its reported features are growth retardation and delayed puberty. Thus this would be another region with a distinctive geochemistry, feeding practices, and a stable population living on local produce which could lend itself to a systematic study of the impact of soil on the prevalence of birth defects and related evidence of reproductive failure.

Conclusions

On several occasions we have made reference to functional abnormalities, and evaluation of these would seem as valuable as seeking structural anomalies when infants are surveyed. These may be of particular relevance in attempting to discern the effects of possible exposure to lead, cadmium or mercury in contaminated soils, and behavioural teratology is, indeed, an expanding discipline as is that of studying environmentally induced immunological and haematopoietic dysfunction; especially since these defects may predispose to infection or to malignancy in later childhood. The fetal brain and thymus (and the thyroid gland) are organs which are privileged to receive first the oxygenated and nutrient enriched blood returning from the placenta. Thus they may also be the most vulnerable to any potential toxicities or deficiencies of agents.

We have not elaborated on the mechanisms and interactions which affect the entry of elements from the soil into plants and animals. These are legion and have been well summarized elsewhere[10, 33, 43]. Some plants have specific abilities to accumulate metals, legumes accumulate copper, iron, molybdenum, zinc, calcium and magnesium more so than do grasses. There is a seasonal variation in the mineral content of these plants, and this is reflected in a similar variation in their toxicity. Specific accumulator plants for selenium or copper can induce toxicities but teratogenesis has only been associated with the former element[45]. Lupinosis, a teratogenic problem in cattle, is not ameliorated by mineral supplements although the plant is a copper accumulator and is well adapted to growth on copper-poor soil such as those in Western Australia[21]. Some forage crops can take up and concentrate nitrate and nitrite from sewage sludge treated pastures. This is enhanced when warm weather enables nitrifying bacteria to proliferate in the soils and severe nitrate toxicity and abortions have occurred in cattle grazing such crops[18,28]. The teratogenicity of plants producing goitrogens has been outlined above, and provides more evidence that soil-plant interaction with man can influence fetal health.

Soil may additionally have other indirect effects on the fetus. Not only the soil's elemental content, but also its chemical form, drainage and redox potential will influence the growth of pathogens, parasites, and fungi as well as potentially poisonous or accumulator plants[14]. All such factors could influence human maternal health but their influence and that of mycotoxins on the fetus is an underexplored area.

Although there is little quantitative data about the impact of soil on human health, or on congenital malformations in particular, there is no doubt that it could have a significant impact especially in stable nonitinerant populations who consume their own local produce. Communities affected by local geochemical anomalies have been identified and these would be ideal areas to seek an effect of soil on the fetus. However, the prevalence at birth of congenital defects is probably an unsatisfactory end point and as much evidence as is possible of the entire range of human reproductive failure, and of abnormalities of the conceptus should be sought; additionally functional deficits should be sought systematically in the young; field experience with overt cretinism and subclinical intellectual impairment in the same community emphasize this. Furthermore, such studies should consider the variables which are known to influence the passage of elements along the food chain to man. Experience with laboratory and farm animals have revealed numerous element interactions which should be taken into account. The tenets of epidemiology have been enumerated as strength of association, consistency, specificity, temperality, biological gradient, plausibility, coherence, experiment and analogy[13]. These provide a standard which should be met when studying any effect of soil on human reproduction and serve to emphasize that, even when we can draw upon animal data to justify considering a problem, a retrospective approach would be particularly difficult to achieve and that well-planned prospective projects would be the most rewarding means of trying to study it.

1 Arvilommi, H., Poikonen, K., Jokinen, L., Muukkonen, O., Rasanen, L., Foreman, J., and Huttunen, J.K. Selenium and immune functions in humans. Infect. Immun. *41* (1983) 185–189.

2 Blokhina, R.I., Geochemical ecology of endemic goitre, in: Trace Element Metabolism in Animals, pp. 426–432. Ed. C F Mills. E & S Livingstone, Edinburgh/London 1970.

3 Chen, X., Yang, G., Chen, J., Chen, X., Wen, Z., and Ge, K., Studies on the relations of selenium and Keshan Disease. Biol. Trace Elem. Res. *2* (1980) 91–107.

4 Connolly, K.J., Pharoah, P.O.D., and Hetzel, B.S., Fetal iodine deficiency and motor performance during childhood. Lancet *1* (1979) 1149–1151.

5 Cowgill, U.M., Selenium and neonatal death. Lancet *2* (1976) 816–817.

6 Dorsch, M.M., Scragg, R.K.R., McMichael, A.J., Baghurst, P.A., and Dyer, K.F., Congenital malformations and maternal drinking water supply in rural South Australia: a caste control study. Am. J. Epidem. *119* (1984) 473–486.

7 Editorial, Endemic goitre and cretinism. Lancet *2* (1979) 1165–1166.

8 Edmonds, L., Hatch, M., Holmes, L., Kline, J., Letz, G., Levin, B., Miller, R., Shrout, P., Stein, Z., Warburton, D., Weinstock, M., Whorton, R.D., and Wyrobek, A., Guidelines for reproductive studies in exposed human populations, in: Guidelines for studies of human populations exposed to mutagenic and reproductive hazards, pp. 37–100. March of Dines Birth Defects Foundation, White Plains. A.D. Bloom, New York 1981.

9 Elwood, J.M., and Coldman, A.J., Water composition in the etiology of anencephalus. Am. J. Epidem. *113* (1981) 681–690.

10 Environmental goechemistry and health. Eds S.H.U. Bowie and I. Thornton. D. Reidel, Publishing Company, Boston/Lancaster 1985.

11 Golub, M.S., Gershwin, M.E., Hurley, L.S., Baly, D.L., and Hendrickx, A.G., Studies of marginal zinc deprivation in rhesus monkeys. II. Pregnancy outcome. Am. J. clin. Nutr. *39* (1984) 879–887.

12 Harad, M., Congenital Minamata disease: intrauterine methylmercury poisoning. Teratology *18* (1978) 285–288.

13 Hill, A. B., The environment and disease: association or causation. Proc. r. Soc. Med. *58* (1965) 295–301.
14 Horvath, D. J., and Reid, R. L., Indirect effects of soil and water on animal health. Sci. tot. Envir. *34* (1984) 143–156.
15 Hurley, L. S., Teratogenic aspects of manganese, zinc and copper nutrition. Physiol. Rev. *61* (1981) 249–295.
16 Jaffe, W. G., and Velez, B., Selenium intake and congenital malformations in humans. Archs latinoam. Nutr. *23* (1973) 515–517.
17 Janerich, D. T., and Polednak, A. P., Epidemiology of birth defects. Epidem. Rev. *5* (1983) 16–37.
18 Jones, T. O., and Jones, D. R., Nitrate/nitrite poisoning of cattle from graze crops. Vet. Rec. *101* (1977) 266–267.
19 Jorde, L. B., Fineman, R. M., and Martin, R. A., Epidemiology of neural tube defects in Utah 1940–1979. Am. J. Epidem. *119* (1984) 487–495.
20 Kalter, H., and Warkany, J., Congenital malformations: etiologic factors and their role in prevention. New Engl. J. Med. *308* (1983) 424–431; 491–497.
21 Keeler, R. F., Teratogens in plants. J. Anim. Sci. *58* (1984) 1029–1039.
22 Kovalsky, V. V., Jarovaja, G. A., and Smavonjan, D. M., Changes in purine metabolism in man and animals in various molybdenum rich biogeochemical provinces. 2. Obsc. Biol. *22* (1961) 179–189.
23 Lowe, C. R., Roberts, C. L., and Lloyd, S., Malformations of the central nervous system and softness of local water supplies. Br. med. J. *2* (1971) 357–361.
24 Miller, R. K., Perinatal toxicology: its recognition and fundamentals. Am. J. ind. Med. *4* (1983) 205–244.
25 Minnich, V., Okcuoglu, A., Tarcon, Y., Arcasoy, A., Cin, S., Yorukoglu, O., Renda, F., and Denirag, T. S., Pica in Turkey II. Effect of clay on iron absorption. Am. J. clin. Nutr. *21* (1968) 78–86.
26 Morton, M. S., Elwood, P. C., and Abernethy, M., Trace elements in water and congenital malformations of the central nervous system in South Wales. Br. J. prev. soc. Med. *30* (1976) 36–39.
27 Naggan, L., and McMahon, B., Ethnic differences in the prevalence of anencephaly and spina bifida in Boston, Massachusetts. N. Engl. J. Med. *277* (1967) 1119–1123.
28 O'Hara, P. J., and Fraser, A. J., Nitrate poisoning in cattle grazing crops. N. Z. vet. J. *23* (1975) 45–53.
29 Oehme, F. W., (Ed.), Toxicity of heavy metals in the environment. M. Dekker, New York 1978.
30 Patterson, S. P., and Sweasey, D., Hypocupraemia in experimental border disease. Vet. Rec. *93* (1973) 484–485.
31 Penrose, L. S., Genetics of anencephaly. J. ment. Defic. Res. *1* (1957) 4–15.
32 Pharoah, P. O. D., Buttfield, I. H., and Hetzel, B. S., Neurological damage to the fetus resulting from severe iodine deficiency during pregnancy. Lancet *1* (1971) 308–310.
33 Reid, R. L., and Horvath, D. J., Soil chemistry and mineral problems in farm livestock. A review. Anim. Feed Sci. Technol. *5* (1980) 95–167.
34 Rosenfeld, I., and Beath, O. A., Congenital malformations of eyes of sheep. J. agric. Res. *75* (1947) 93–103.
35 Sever, L. E., Zinc and human development. Hum. Ecol. *3* (1975) 43–57.
36 Sever, L., Central nervous system malformations and maternal zinc deficiency in Turkey. Am. J. clin. Nutr. *34* (1981) 967.
37 Sever, L. E., An epidemiologic study of neural tube defects in Los Angeles County II. Etiologic factors in an area with low prevalence at birth. Teratology *25* (1984) 323–324.
38 Smithells, R. W., Seller, M. J., and Harris, R., Further experience of vitamin supplementation for prevention of neural tube recurrences. Lancet *1* (1983) 1027–1031.
39 Smithells, R. W., Sheppard, S., Schorah, C. J., Seller, M. I., Nevin, N. C., Harris, R., Read, A. P., and Fielding, D. W., Possible prevention of neural tube defects by periconceptional vitamin supplementation. Lancet *1* (1980) 339–340.
40 Stevenson, A. C., Johnston, H. A., Stewart, M. I. P., and Golding, D. R., Congenital malformations: a report of a study of series of consecutive births in 24 centres. Bull. Wld Hlth Org., suppl. *34* (1966).
41 St. Leger, A. S., Elwood, P. C., and Morton, M. S., Neural tube malformations and trace elements in water. J. Epidem. Comm. Hlth *34* (1980) 186–187.
42 Stocks, P., Incidence of congenital malformations in the regions of England and Wales. Br. J. prev. soc. Med. *24* (1970) 67–77.
43 Thornton, I., and Alloway, B. J., Geochemical aspects of the soil-plant-animal relationship in the development of trace element deficiency and excess. Proc. Nutr. Soc. *33* (1974) 257–266.
44 Tolarova, M., Periconceptional supplementation with vitamins and folic acid to prevent recurrence of cleft lip. Lancet *2* (1982) 217.
45 Underwood, E. J., Trace elements in human and animal nutrition, 4th edn. Academic Press, New York/London 1977.
46 Vandarpas, J., Bourdoux, P., Lagasse, R., Rivera, M., Dramaix, M., Lody, D., Nelson, G., Delange, F., Ermans, A. M., and Thilly, C. H., Endemic infantile hypothyroidism in a severe endemic goitre area of central Africa. Clin. Endocr. *20* (1984) 327–340.
47 Vanugopal, B., and Luckey, T. D. (Eds.), Metal Toxicity in Mammals. 2 volumes. Plenum Press, New York/London 1978.
48 Whitehead, D. C., The sorption of iodide by soil as influenced by equilibrium conditions and soil properties. J. Sci. Food Agric. *24* (1973) 547–556.
49 Whitehead, D. C., Uptake by perennial ryegrass of iodide, elemental iodine and iodate added to soil as influenced by various amendments. J. Sci. Food Agric. *26* (1975) 361–367.
50 Yang, G., Wang, S., Zhou, R., and Sun, S., Endemic selenium intoxication of humans in China. Am. J. clin. Nutr. *37* (1983) 872–881.

0014-4754/87/010104-05$1.50 + 0.20/0