Idiopathic Hypercalcaemia*

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In their earnest desire to cure or prevent certain diseases paediatricians are apt to become over-enthusiastic in their treatment, and actually produce other disorders. Retrolental fibroplasia from too much oxygen in premature babies and kernicterus from an overdose of Vitamin K are good examples, and idiopathic hypercalcaemia may well be another. There is good reason to believe that this last condition is the result of hypersensitivity to Vitamin D. The disease only seems to have have been discovered in England since the war and it was about this time that Vitamin D was added to all varieties of dried milk. This is the almost universal method of feeding in my country if lactation fails, and nutritional rickets has therefore virtually disappeared. Mothers are now so vitamin-conscious that they usually supplement the milk with cod liver oil or some other equivalent preparation. In this way the dose of Vitamin D may well rise above the normal requirements, which can however still be easily tolerated by the average infant, but may produce serious or even disastrous results when the child happens to be hypersnsitive.

The condition was first recognised in 1952 (Lightwood, 1952; Payne, 1952; Fanconi, G., Girardet, P., Schlesinger, B., Butler, N. and Black, J., 1952), and since then cases have been described in various parts of England and other countries. Reports have come from Finland, Sweden, Norway, Switzerland, Portugal, France, Germany and the United States, and there are no doubt other accounts which I have missed. My last case was sent to me from Rhodesia.

Clinical Picture.

There are two varieties of the disease, a simple and a severe form, and some cases are undoubtedly intermediate. During the first year of life, even a few weeks after birth but usually at about four months, the infant fails to thrive, ceases to gain weight, is hypotonic and suffers from anorexia, vomiting and constipation. The characteristic biochemical picture is a rise in the level of serum calcium and blood urea. These are the main changes in the benign form, which has a good prognosis.

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In the severe type *renal impairment*, which invariably accompanies the hypercalcemia, is apt be more severe. *Hypertension* may result and prove fatal, but in survivors kidney function ultimately improves. A *systolic murmur* is audible in most cases, widely conducted and of sufficient intensity to suggest an organic lesion. But the most striking features are a characteristic *facies*, *dwarfism*, *mental retardation* and *osteosclerosis* of the skeleton. We have studied these changes in some detail and have come to the following conclusions:

Facies: The curious apperance of all these children is the same and not found in any other condition. They look rather like pixies, reminiscent of our childhood fairy tales, with prominent epicanthic folds, an overhanging lip, a snub nose and an underdeveloped mandible. The ears are relatively large and set low on the side the face. A squint is usually present and occasionally a transient facial paresis. The cause of these peculiar features is not known, although abnormal growth of the basi- sphenoid and premature fusion of the spheno-occipital suture have been suggested as contributory factors.

Physical and Mental Development: Physical growth is retarded during the acute stage, whereas bone age, measured by the degree of calcification in the epiphyses, is generally normal. In children who survive, physical development accelerates soon after blood calcium levels return to normal,so that eventually they reach a standard weight, but still remain somewhat stunted. Reduction in skull circumference is always present, which persists even when height and weight begin to increase. *Craniostenosis* may occasionally develop to such a degree as to cause papilloedema, and then surgical reconstruction of the skull is required to save sight. The curious aspect with mental retardation has led to these infants being mistaken for cretins, but their extraordinary degree of liveliness, with ill-directed purposeless movements, is quite inconsistent with this diagnosis. In spite of marked hypotonia, the tendon reflexes are brisk and the hyperkinetic reaction of the children, especially when frightened, is quite unlike that observed in hypothyroidism.

Mental retardation unfortunately persists, although some slight improvement may result from early treatment. Nevertheless it is very unlikely that the I. Q. will ever be far above about 60%. Its cause has never been satisfactorily explained. Hypercalcaemia has been known to cause mental symptoms in adults and by inference could be expected to have a deleterious effect on the infant's brain at a stage when development is at its height. On the other hand equally high blood calcium levels may be present in the

benign form of the disease, and here the intelligence is not affected. There are also other disorders associated with hypercalcaemia—hypophosphatasia for instance—where mental development is always normal. Sinclair (1956) has propounded an ingenious theory, that lack of essential fatty acids in the diet may lead to imperfect formation of phospholipid in the brain and thus interfere with its normal growth, but this has never been confirmed.

Skeletal Changes : Osteosclerosis can be demonstrated radiologically in the vault and at the base of the skull and in the orbits, giving that region the X-ray appearance of wearing motor goggles. Similar areas of over-calcification can be made out in the metaphyses and epiphyses of the long bones, the vertebral bodies,ribs and iliac crests.The changes in the long bones consist of dense transverse bands, particularly noticeable at the lower end of the femur and upper end of the tibia. These are irregularly placed at various levels in the shaft, probably corresponding to periods of cessation of growth, when the excess calcium is laid down in the greatest concentration. Similar bands are present in many instances in the ends of the metacarpals and metatarsals and in the vertebral bodies and iliac crests. The epiphyses may show alternate rings of dense and normal bone, indicating presumably exacerbations and remissions in the course of the disease.

The radiological appearance has a resemblance to Albers-Schönberg's but in hypercalcaemia there is no 'clubbing' of the ends of the bone through lack of distal modelling. These osteosclerotic changes clear up shortly after the acute stage of hypercalcaemia and the bones eventually return to normal.

Metastatic Calcification : As in Vitamin D intoxication, calcium may be deposited in various tissues, the most significant being in the kidneys and resulting in seriously impaired function. Irreversible damage may follow which eventually leads to chronic uraemia, hypertension, cardio-vascular changes and death. Nephrocalcinosis can sometimes be demonstrated radiologically during life and is always present post mortem. The systolic murmur may be directly attributable to the hypertension, which can be considerable, but the presence of calcified plaques, occasionally found in the valves at autopsy, is another possible cause. Subcutaneous calcium deposits have also been demonstrated radiologically in pseudo-sclerematous areas (Clay, 1956), and corneal bands, probably made up of crystalline calcium deposits, are very occasionally found (Lang and Eiardt, 1957).

Biochemistry.

Both in the benign and severe forms the serum *calcium* is raised

during the acute stage, reaching levels as high as 19 mg. /100 ml. In untreated cases high levels may persist for one or two years, during which symptoms are constantly present. Death may then occur, but in the less severe form the serum calcium gradually falls to normal as the child recovers. Treatment will hasten this process. High blood *urea* levels invariably accompany the hypercalcaemia, and impaired renal function can be demonstrated by the usual tests. A trace of albumin, with a few white and red blood cells and the occasional granular cast, also reflect renal disturbance, and urinary infection can readily become superimposed. The urea level tends to remain raised for many months even after hypercalcaemia has disappeared, and correspondingly some degree of renal impairment persists. Blood *cholesterol* figures are also found to be above normal in the majority of severe cases, tending to run parallel with the hypercalcaemia, but there are exceptions to this. Probably this is in some way connected with the renal damage, although, as we shall see, there are other theories. In this connection high cholesterol levels with a normal blood urea is common in nephrosis. It has also been noted in hypercalcaemia due to an excessive Vitamin D intake or in sarcoidosis.

Other biochemical findings are an occasional high blood inorganic phosphorus reading, particularly when the blood urea is raised in a late stage of the illness. There is also an increase in alpha - 2 and gamma globulin. On the other hand alkaline phosphatase tends to be low. Balance studies usually show an excessive retention of calcium despite an increased urinary output, as could be expected from overactivity of Vitamin D. One other interesting finding is a raised plasma level of Vitamin A in the absence of an extra high intake. A similar disordered metabolism of Vitamin A has been described in the nephrotic syndrome and chronic nephritis. It is therefore not an unexpected finding in hypercalcaemia and is again a reflection of the renal damage.

Post Mortem Studies.

Several necropsy reports are now available, which all show the same changes in varying degree. In the *kidneys* there is extensive destruction of the cortex and medulla. Ischaemic necrosis with endothelial proliferation is found in the glomeruli or hyalinization with fibrosis. Widespread destruction occurs in the tubules, with intercanalicular or interstitial calcinosis. In the *blood vessels* focal degeneration and fragmentaion of the internal elastic lamina is seen and some medial hypertrophy in the smaller arteries, with occasional calcification. Left ventricular hypertophy is present in the *heart* and calcification

may be seen in the valves and myocardium. Histological examination of the *bones* reveals a normal architecture in the sclerotic areas, suggesting excessive deposition of calcium rather than a primary bone affection, although endochondral ossification may be abnormal with persistence of cartilaginous areas. *Metastatic calcification* may be widely spread throughout the tissues and, apart from the renal tubules, has been found in the lungs, the glands at the cardiac end of the stomach, the heart and rarely the meninges, mostly areas which produce acid secretions. No pathological changes have ever been demonstrated in the *parathyroid glands.*

Aetiology.

Some indication has already been given of how closely the clinical, chemical and pathological changes just described resemble those found in Vitamin D intoxication (Schubert and Kleint, 1957). No case of hypercalcaemia has as yet been reported in an entirely breast-fed child and yet we have encountered a number in whom the Vitamin D intake has not been excessive. To explain this an *individual hypersensitivity* to this vitamin has been suggested (Stapleton, Macdonald and Lightwood, 1957). In favour of this theory we have recently seen two infants born in succesion to a mother, who during her pregnancies had continued to receive large doses of Vitamin D on account of osteomalacia. Immediately after birth the calcium level in the cord blood of both infants was found to be raised. A little later this fell to normal in the blood serum, but subsequently rose again despite the fact that the diet contained no excessive amount of Vitamin D. In addition one of the infants developed the typical clinical picture of the mild type of hypercalcaemia just described, but with suitable treatment both ultimately recovered (Smellie, personal communication). It would appear that these infants had been rendered hypersensitive to Vitamin D through their mother during foetal life and soon after birth reacted unfavourably to amounts of this vitamin in their diet which normally would have been well tolerated. There is also another account of twin brothers both of whom received massive injections of calciferol because they were not thriving. One died with the typical pathological picture of severe hypercalcaemia and the other escaped unharmed, suggesting again an individual idiosyncrasy to Vitamin D (Lars Hjelt et al., 1956).

Some authorities believe that *infection* also plays a part in the pathogenesis (Creery and Neill, 1956) by causing a temporary arrest of bone growth. This might well interfere with the normal calcium requirement for ossification, so that any superfluous calcium absorbed

would be deposited to form osteosclerotic areas. Experiences during an epidemic of interstitial plasma cell pneumonia in Finland have often been quoted (Hjelt et al., 1956). Forty children died from this infection, and the post mortem appearance of the kidneys and cardiovascular system was identical to that found in severe hypercalcaemia. These changes were particularyly noticeable in children who had suffered long-standing asphyxia and who had received large doses of Vitamin D. But there were others where this treatment had not been given and serum calcium levels during life had been normal. Though Vitamin D therapy was obviously highly significant in contributing to renal damage in these cases, there were probably other contributory factors, such as renal anoxia and disturbance in acid base equilibrium from asphyxia, particularly as many of the children were newly born and had not come under the influence of excessive Vitamin D administration.

To explain some of the discrepancies in the theory of hypervitaminosis just propounded, a disturbance in cholesterol metabolism has been suggested, with the production of some derivative (toxisterol) which may have a hypercalcaemic and toxic effect (Forfar et al., 1956). Sinclair (1958) argues along similar lines, believing that the main fault is a lack of essential fatty acid in the diet. He bases his evidence on animal experiment and the fact that much of the essential fatty acid is lost in dried milk and even more on storage. A rise in serum cholesterol and in unesterified Vitamin D results, which is said to have an especially strong hypercalcaemic action. Ingenious though this theory may be, it has not received much support (James et al., 1958) and earlier in this accont I have mentioned that the high blood cholesterol in hypercalcaemia is much more likely to be connected with the nephrocalcinosis.

Hyperparathyroidism can be confidently excluded. No pathological changes have been found in these glands in fatal cases, and the usual normal plasma phosphorus level, the low alkaline phosphatase and the action of cortisone in increasing calcium excretion all run contrary to what occurs in hyperparathyroidism.

Treatment.

Leaving the aetiology not finally settled, we are on less debatable ground in considering treatment. Here everyone is agreed that by some means the high calcium level must be reduced and maintained at a normal level until the child is able to achieve this himself.

The most effective method is by giving a low calcium diet and at first no Vitamin D. A special dried milk (Locasol) made up with distilled water, and semolina as a cereal (Farola) are now available

in England. With these there is a rapid fall in the serum calcium and symptomatic improvement. The child's appetite returns, the weight goes up, the raised blood pressure falls and cardiac murmurs disappear (Russell and Young, 1954; Ferguson and McGowan, 1954; Bonham Carter et al., 1955; Stapleton et al., 1956). Cortisone has also been used as a preliminary step, if a more rapid effect is desired, (Creery and Neill, 1954; Macdonald and Stapleton, 1955), but is not usually necessary. Obviously this treatment must be instituted as soon as the diagnosis is made, and no satisfactory response can be expected if the child is already suffering from the severe form of the disease when seen by the doctor and the kidneys are irreversibly damaged. In those in whom the treatment is proving successful a time will come when a limited amount of Vitamin D will have to be carefully reintroduced into the diet so as to avoid rickets. After a while in most cases the low calcium diet need no longer be continued, as the child's hypersensitivity to Vitamin D seems to disappear and he becomes normally tolerant to ordinary food.

I have brought to your notice a disorder which is certainly uncommon and may in fact not exist in Turkey. Nevertheless it was becoming quite a problem in my country and in one city in Scotland, Dundee, it came high on the list of medical diseases requiring hospital admission. Recently the Ministry of Health made new regulations, reducing to a safer level an infant's intake of Vitamin D in the milk and as supplements. This then is the story of one more iatrogenic disease which by reasonable precautions may be prevented in the future.

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