INFANTILE HYPERCALCAEMIA AND CARDIOVASCULAR LESIONS

EVIDENCE, HYPOTHESIS, AND SPECULATION

BY

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Since the recognition of the benign and severe forms of infantile hypercalcaemia (Lightwood, 1952; Fanconi, Girardet, Schlesinger, Butler, and Black, 1952), circumstantial evidence has assigned a causal role to vitamin D ingested by infants peculiarly sensitive to that substance. The disease failed to disappear, though its incidence declined, after the vitamin D₂ content of infant foods and vitamin concentrates had been reduced (Stewart, Mitchell, Morgan, Lowe, and Thomson, 1964; British Paediatric Association Report, 1964). It accounted for the admission of 39 infants to the Royal Hospital for Sick Children, Glasgow, during 1956-57 at the height of its incidence, but of only 13 during 1962-63. All but one of these 13 patients lived outside the city (10) or on its periphery (2), a situation contrasting with the recent incidence of infantile rickets in the area (Arneil and Crosbie, 1963), which has been largely confined to the central districts of the city.

Children poisoned with a massive dose of vitamin D may sustain damage to the cardiovascular system (Hjelt, Tähkä, and Hallman, 1956), and it is quite logical to expect similar effects in a disease acknowledged as qualitatively identical. Cardiovascular lesions have indeed been reported in infantile hypercalcaemia, and while their inconstancy and variety are notable they represent a serious aspect of the disease deserving close attention.

Electrocardiographic and Clinical Findings

An abnormal contour of the ST-T complex in the bipolar limb leads was reported in 14 of 24 patients suffering from infantile hypercalcaemia (Coleman, 1959), but further experience and the use of praecordial leads have shown the incidence to be higher. Indeed 12 of the 13 patients admitted to hospital during 1962-63 demonstrated the abnormality; no electrocardiographic examination was made of the

remaining patient. The abnormal pattern bears little resemblance to that usually attributed to hypercalcaemia and may persist longer than the elevation of serum calcium. Instead of the Q-T interval (QT_c) being short and reflecting a short S-T interval, it is of average duration because the shortened S-T interval is masked by a broad T wave; this has a flattened or notched summit and is usually tall. The abnormal T wave is typically present not only in bipolar leads I and II, but also in unipolar leads from V4 to V6 (Fig. 1). Furthermore even in bipolar leads with apparently normal T wave summits the waves can be shown to be of significantly greater length than in healthy infants (Coleman, 1961).

Of the 13 patients with infantile hypercalcaemia during 1962-63, 4 gave transient electrocardiographic evidence of left ventricular hypertrophy. Three

FIG. 1.—Infantile hypercalcaemia. Broad plateau T waves in leads I, II, V4, and V6.

FIG. 2.—Infantile hypercalcaemia and pulmonary stenosis. V4 and V6 recorded at half-standard amplitude. Right ventricular hypertrophy and abnormal T waves (II and V6).

others had systemic hypertension which was most pronounced in the single patient who suffered from the disease in its severe form. This patient, from his first attendance when 5 months old, had a systolic murmur at the pulmonary area and by 18 months physical signs characteristic of pulmonary valve stenosis, with electrocardiographic evidence of right ventricular hypertrophy (Fig. 2). Cardiac catheterization confirmed the diagnosis; the right ventricular

pressure was 45/0 mm. Hg, but the systolic pressure gradient of 30 mm. Hg over the pulmonary valve was regarded as insufficient to justify surgical treatment. None of these patients died.

Experimental Findings

Because the electrocardiographic changes were so specific and might result from a myocardial lesion, the possibility of a specific lesion caused by vitamin D was examined after its administration in large doses to young rabbits.

Vitamin D₃ in arachis oil was given by mouth to 9 rabbits, vitamin D₂ in arachis oil was given to 9 rabbits, and there were 9 controls. The rabbits belonged to 6 litters, and the administration of vitamin D was carried out within 10 days and completed by the age of 6 weeks. The dosage per g. body weight was from 100 to 770 international units of vitamin D₃ and from 40 to 420 units of vitamin D₂. Where possible they were allowed to survive to 4, 8, or 40 weeks after the beginning of the experiment, but 7 that had received vitamin D died, and another had to be killed earlier than planned.

An aortic lesion was present in every rabbit given vitamin D, but in none of the controls. In most the lesions were widespread, but the thoracic aorta was most severely affected (Fig. 3). The inner half of the media was affected and in some instances there was intimal thickening. The least severe lesions were the most cellular, with many fibroblasts and macrophages. The elastic fibres were distorted or even disrupted and between the elastic laminae

FIG. 3.—Rabbit thoracic aorta. Longitudinal sections. (H. and E. $\times 150$.) (a) Early lesion. Thickened intima. Elastic laminae straightened, thickened, and disrupted. Fibroblast proliferation. (b) Severe lesion showing in addition cartilage formation and proliferation of fibroblasts and macrophages.

FIG. 4.—Rabbit left atrial wall. (a) Subendocardial fibrous tissue proliferation; collagenous layer and deeper fibroelastic layer. (Verhoeff-van Gieson. $\times 67$.) (b) Another example. Fibrous tissue proliferation overlying normal muscle. (H. and E. $\times 275$.)

muscle cells were destroyed. Here calcium deposition was often suggested by staining reactions; cartilage had formed in 2 instances and bone in one instance.

Two died in congestive heart failure (D_2 347 units/g.; D_3 103 units/g.); histology of the heart revealed no focal lesion but hypertrophy of muscle fibres and severe aortic wall lesions. Four others (D_2 230 units/g., 40 units/g.; D_3 770 units/g., 660 units/g.) had focal myocardial lesions which in 3 consisted of periarterial muscle fibre necrosis with staining reactions suggesting the presence of calcium, and, in relation to dead muscle fibres, a cellular reaction consisting of macrophages, fibroblasts, and multinucleate giant cells. In the fourth rabbit (D_2 40 units/g.) focal lesions were present at some distance from the arterial branches and consisted of a patchy loss of muscle fibres with replacement by granulation tissue in which were macrophages, eosinophils, and occasional giant cells, but without evidence of calcium deposition. The rabbit that became ill and had to be killed 6 weeks after the administration of vitamin D (D_2 40 units/g.) was the only one in which coronary artery lesions were detected; there was distortion and disruption of the internal elastic lamina, thickening of the intima, and narrowing of the media.

In 10 rabbits that had received vitamin D there were lesions immediately subjacent to the mural endocardium of the left ventricle, left atrium, or right ventricle (D_2 40-420 units/g.; D_3 100-770 units/g.). Immediately beneath the endocardium there was a collagenous layer containing only a few fibroblasts; in some there was a deeper and substantially thicker

layer of fibroelastic tissue which sometimes surrounded islands of muscle cells (Fig. 4).

Serum calcium levels in excess of those of the control animals (10-11.5 mg./100 ml.) were found as long as 32-38 weeks after the administration of vitamin D_2 or D_3 had ceased (12.9-14.1 mg./100 ml.).

Discussion

The wide but inconstant array of cardiovascular lesions reported in a relatively few cases of infantile hypercalcaemia has included left ventricular or biventricular myocardial hypertrophy, myocardial fibrosis, or calcification, valvular endocardial lesions including fibrosis and calcification, lesions of the intima and inner media of arteries including the coronaries, and peripheral systemic and pulmonary arterial stenosis (Schlesinger, Butler, and Black, 1956; Joseph and Parrott, 1958; Lamy, Nezelof, Fauré, Jammet, and Aussannaire, 1958; Rashkind, Golinko, and Arcasoy, 1961; Bonham Carter and Sutcliffe, 1964).

Aortic Lesions. Black and Bonham Carter (1963) have described aortic supra-valvar stenosis in a child thought to have suffered from severe infantile hypercalcaemia. Histological features in the aorta were thickening of the media with fibrosis and some deficiency of both muscle and elastic tissue, a circular ridge of fibrous tissue, and, distal to this stricture, intimal thickening with atheromatous change. There was fibrous thickening of the aortic valve.

The lesions in rabbits reported here indicate the susceptibility of the aortic media and intima in one

mammalian species to damage by vitamin D. Extensive examination of the controls failed to reveal any vestige of the spontaneous aortic lesion known to occur in some laboratory rabbits (Kesten, 1935). The histological pattern of the experimental lesion seems to resemble that of the human lesion described by Black and Bonham Carter (1963), and therefore lends support to the concept of a causal relation between infantile hypercalcaemia and aortic supra-valvar stenosis on the assumption that the former disease is causally linked with vitamin D activity.

Endocardial Lesions. The experimental lesion immediately subjacent to the mural endocardium has no exact counterpart in infantile hypercalcaemia. The only endocardial lesion detected during 1962-63 in the hospital in association with infantile hypercalcaemia was pulmonary stenosis confirmed by cardiac catheterization. The same association occurred in a male infant of 6 months who died of the severe type of infantile hypercalcaemia in 1954. In addition to advanced renal medullary calcinosis necropsy revealed pale, thickened, rigid, but discrete, pulmonary valve cusps in a valve ring of average size, these appearances being due to the presence of oedematous fibrillary collagen within the cusps (Fig. 5).

This pulmonary valve lesion may have its parallel in the aortic valve lesion mentioned by Black and Bonham Carter (1963).

The fibroelastic form of the experimental lesion is reminiscent of congenital endocardial fibroelastosis, and like that disease affects principally the left heart chambers. Endocardial fibroelastosis remains of uncertain aetiology. It has no recognized connexion with infantile hypercalcaemia or vitamin D, but its

known association with congenital cardiovascular malformations is so inconstant (Forfar, Miller, Bain, and Macleod, 1964) that other or additional causal factors are likely. The experimental lesion indicates decisively that a form of endocardial fibroelastosis may be caused by a toxic substance, but since the human disease usually presents in the earliest weeks of life (Forfar *et al.*, 1964) its occurrence then seems to require the transplacental passage of the toxic substance. Not only has transmission through the placenta been claimed for vitamin D (Decio and Alamanni, 1956), but the early appearance of the striking clinical features of severe infantile hypercalcaemia suggests the likelihood of prenatal intoxication in some instances. The lesion of congenital endocardial fibroelastosis may not be confined to the endocardium, but may, as in the case of infantile hypercalcaemia, occasionally include myocardial fibrosis or calcification and coronary artery lesions (Blumberg and Lyon, 1952; Thomas, Lee, McGavran, and Rabin, 1956). Curiously, the hospital incidence of endocardial fibroelastosis proven at necropsy, as of infantile hypercalcaemia diagnosed clinically, has declined since 1958 when measures had been taken and the reasons publicized for reducing the vitamin D₂ intake of infants (Table).

TABLE
NUMBER OF CASES DURING FIRST YEAR OF LIFE

Disease	1954-58	1959-63
Infantile hypercalcaemia	61	24
Endocardial fibroelastosis	19	10

Outside the cardiovascular system, however, severe infantile hypercalcaemia and endocardial

FIG. 5.—Infantile hypercalcaemia and pulmonary stenosis. (a) Irregular bulbous enlargement of free extremity of pulmonary valve cusp. (H. and E. $\times 22.5$.) (b) This enlargement caused by proliferation of oedematous fibrillary collagen. (H. and E. $\times 183$.)

fibroelastosis are quite dissimilar, and an attempt to reconcile these as effects of a single intrauterine toxic agent relies on the concept that the quality of teratogenic effect depends on the dose of the agent and the timing of its application during embryogenesis.

Myocardial Lesions. The infrequency of myocardial and coronary artery lesions in the experimental material would not suggest the probability of a high incidence in infantile hypercalcaemia, though in that disease similar lesions have been found at necropsy (Rashkind *et al.*, 1961). It is evident, however, that no conclusion is possible as to the relative amounts of vitamin D required in different species to produce similar lesions and especially in relation to a disease dependent for its existence on hypersensitivity.

The electrocardiographic features of infantile hypercalcaemia, which are of such constancy as to be of diagnostic value, are caused neither by hypercalcaemia nor by any generalized electrolyte disturbance. Quinidine intoxication may temporarily produce prominent and broad T waves, and a lengthened Q-T interval (Sagall, Horn, and Riseman, 1943), indicating the increased refractory period of the ventricular myocardium. In infantile hypercalcaemia the abnormal shape of the ST-T complex in leads I, II, and V4 to V6 outlasts the hypercalcaemic phase of the disease, and it is tempting to suggest that it signifies left ventricular myocardial damage. In children poisoned with massive doses of vitamin D₂ a closely similar ST-T pattern has been described (Jelke, 1946; Skatvedt, 1947; Hjelt *et al.*, 1956), and the possibility exists that a specific toxic effect is exerted on myocardial metabolism by vitamin D or some related toxic sterol, or that a specific pattern of myocardial damage is caused by such a substance. Correlation of electrocardiographic pattern with myocardial pathology was reported in one child who died of classical vitamin D poisoning; the T waves had been tall and broad and the myocardium showed periarterial necrosis and fibrosis (Hjelt *et al.*, 1956).

The search for left ventricular lesions of a type that could cause electrocardiographic signs such as these included the myocardial fibrosis of uncertain pathogenesis found as a rare accompaniment of fibrocystic disease of the pancreas (Kintzen, 1950; Feer, 1952; Powell, Newman, and Hooker, 1957; Nezelof and Lancet, 1959), for McGiven (1962) described a child in whose published electrocardiogram the ST-T complexes of lead I, V4, and V5 were closely similar if not identical with those described here. In the only other reported electrocardiogram (Nezelof and Lancet, 1959) the T waves were also

abnormal. The characteristic lesion affects principally the left ventricular myocardium and consists of muscle fibre degeneration, and replacement by fibrous tissue. Endocardial fibroelastosis has been twice reported (McGiven, 1962; Nezelof and Lancet, 1959). Nezelof and Lancet (1959) did not mention diet or medication but vitamin D had been given in all other instances. Nephrocalcinosis was present in both patients whose renal histology has been reported; this would, according to Shanks and MacDonald (1959), argue the occurrence at some time of hypercalcaemia. Rickets is virtually unknown in fibrocystic disease of the pancreas but extra vitamin D is customarily added to the diet as it is in coeliac disease. It seems possible that there could exist in fibrocystic disease a compensatory mechanism for the conservation of vitamin D and accordingly that toxic effects of overdosage might readily occur.

In regard to the absence of calcification in this cardiac lesion and other lesions ascribed to vitamin D, it is evident from animal feeding experiments (Gillman and Gilbert, 1956), as from some cardiac lesions in infantile hypercalcaemia (Rashkind *et al.*, 1961), and from the natural history of nephrocalcinosis associated with infantile hypercalcaemia (Shanks and MacDonald, 1959), that calcification is neither a primary nor an invariable feature of these lesions.

Prognosis. Spontaneous healing and complete repair have been reported by Gillman and Gilbert (1956) in relation to a wide range of cardiovascular lesions induced in the rat with vitamin D₂. There is no reason to suppose that human cardiovascular lesions similarly produced would behave differently, provided that the toxic stimulus were removed. No conclusion is possible from the present experimental material, because of the apparent long persistence of vitamin D effect as judged from serum calcium levels.

Summary and Conclusions

In infantile hypercalcaemia (infantile hypersensitivity to vitamin D) the high incidence of transient changes in the ST-T complex of the left praecordial electrocardiogram suggests a high incidence of transient damage to the left ventricular myocardium.

Vitamin D given in high dosage to young rabbits causes lesions of the aortic wall, of the mural endocardium (fibroelastosis), and occasionally of the myocardium.

The possibility exists that congenital endocardial fibroelastosis and the myocardial lesion of fibrocystic disease of the pancreas are related to vitamin D.

The persistence of infantile hypercalcaemia and

the possibility of residual cardiovascular lesions is disquieting. Where infantile rickets and infantile hypercalcaemia coexist in different parts of the same community as they do in south western Scotland, it may prove impracticable to eliminate one without increasing the incidence of the other, and in such circumstances it is impossible to evade making a responsible inquiry into the nature of residual effects and their relative importance.

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