Original articles

Idiopathic infantile hypercalcaemia—a continuing enigma

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SUMMARY Seventy six children with documented Fanconi-type idiopathic infantile hypercalcaemia were studied and compared with 41 with the Williams-Beuren syndrome. Clinical comparison showed, as expected, very close similarities but also considerable differences, particularly in the severity of feeding problems and the degree of failure to thrive. The estimated incidence of idiopathic infantile hypercalcaemia alone has remained constant for the past 20 years, at approximately 18 cases per year in the United Kingdom (1 per 47 000 total live births). Long term morbidity in these children is mainly due to mental handicap and arteriopathy, but hypertension (29%), kyphoscoliosis (19%), hyperacusis (75%), and obesity (50%) may be added complications. In one child, hypercalcaemia recurred during adolescence but this seems to be excessively rare. More detailed investigation before treatment is required to discover the aetiology of hypercalcaemia in this condition.

Idiopathic infantile hypercalcaemia is a rare but important cause of failure to thrive and in some cases is associated with mental handicap and long term morbidity. Since its description by Fanconi *et al*,¹ Lightwood,² and Payne³ in 1952, it has remained an enigma. The classic presentation is profuse vomiting, irritability, constipation, and poor weight gain, usually during the first year of life. Malnutrition and dehydration may be present on examination and hypotonia, if detected, is associated with hyperreflexia. Systemic hypertension is often found if the blood pressure is measured. Some patients have a persistent cardiac murmur, global developmental delay, and characteristic facies.⁴ The most prominent facial features include a retrousse nose with a flat nasal bridge, heavy orbital ridges, full cheeks, and a wide mouth ('elfin' facies, Fig. 2). In view of the mental handicap these infants have been classified as 'severe' in contrast with the 'mild' cases who lack these features and seem to have no long term morbidity.⁵ Whether this classification describes two ends of a continuum or two distinct entities has not yet been established. Objections have been raised to the use of the terms severe and mild and we prefer to refer to them as Fanconi-type idio-

pathic infantile hypercalcaemia and Lightwood-type idiopathic infantile hypercalcaemia respectively.

The cause of hypercalcaemia in this condition was soon established to be increased intestinal absorption of calcium, associated with increased urinary excretion.⁶ Since vitamin D intake did not seem to be excessive in most patients, Lightwood suggested that vitamin D sensitivity might exist.⁷ In the face of an apparent epidemic of idiopathic infantile hypercalcaemia in the United Kingdom during the 1950s, the British Paediatric Association recommended a general reduction in the level of vitamin D supplementation to infant foods.⁸ A subsequent survey did suggest that these measures had reduced the incidence of the condition.⁹ No precise distinction, however, was made in this survey between the Fanconi and Lightwood types of idiopathic infantile hypercalcaemia, and the exact link with vitamin D has never been defined.

In 1961, Williams *et al*¹⁰ described four children who had supraaortic stenosis, mental handicap, and peculiar facies. Beuren *et al*¹¹ expanded the syndrome to include dental abnormalities and peripheral pulmonary artery stenosis. In the following year, Black and Bonham Carter¹² noted that the

facies of children with the Williams-Beuren syndrome resembled the elfin facies of Fanconi-type idiopathic infantile hypercalcaemia and thus proposed that the cardiac murmurs associated with the latter condition might be related to stenotic lesions. Likewise that children with Williams-Beuren syndrome, who often seemed to have feeding problems during infancy, might have had a period of undiagnosed hypercalcaemia which had spontaneously resolved. This link was clearly established when Garcia *et al*¹³ described the coexistence of hypercalcaemia and supra-valvular aortic stenosis in one infant, and subsequently Black himself published post mortem data on an original case of Fanconi-type idiopathic infantile hypercalcaemia who was found to have supra-valvular aortic stenosis.¹⁴ It has since been generally assumed that Fanconi-type idiopathic infantile hypercalcaemia and Williams-Beuren syndrome are identical conditions.

In 1979 a parent support group called the Infantile Hypercalcaemia Foundation was formed with charitable status and up to 1983 some 400 cases have become affiliated. This offered a unique opportunity to study the link between Fanconi-type idiopathic infantile hypercalcaemia and Williams-Beuren syndrome and to define their long term complications.

Study design

The parents of 183 children were sent a questionnaire; they were asked if they wished their child to be included in the nationwide survey and if so whether they would give consent for access to medical records. Subsequently all paediatricians involved with the child's management were informed of the study and invited to withhold permission for the child to participate if for any reason they felt it would be inadvisable. Visits were then made to interview the parents, examine the children, and view hospital records. In addition, a control group of parents completed the same questionnaire. This group was selected by asking parents of index cases to find one of their friends to complete the questionnaire. Data was analysed by the χ^2 or Student's *t* tests, as appropriate.

Patients

It became apparent that paediatricians vary in what they regard as necessary or sufficient evidence to make a diagnosis of Fanconi-type hypercalcaemia or Williams-Beuren syndrome. Therefore, having assessed a variety of clinical parameters, we chose certain criteria to select our cases. These criteria are shown in Table 1. A total of 153 of the 183 (83%)

Table 1 Patient selection criteria

<i>Fanconi-type idiopathic infantile hypercalcaemia</i> (group 1)			
(1)	Mental handicap/global developmental delay AND		
(2)	Blood calcium ≥ 3.0 mmol/l OR		
	Blood calcium 2.70 to 2.99 mmol/l IF		
	'Elfin facies' OR		
	Radiological osteosclerosis OR		
	Evidence of SVAS or PPAS OR		
	Positive calcium load test.		
<i>Williams-Beuren syndrome</i> (group 2)			
(1)	Mental handicap/global developmental delay AND		
(2)	Evidence of SVAS or PPAS AND		
(3)	'Elfin facies'		
SVAS=supra-valvular aortic stenosis; PPAS=peripheral pulmonary artery stenosis.			

questionnaires distributed were returned completed and the subjects were subsequently examined. Seventy six cases of Fanconi-type hypercalcaemia were fully documented: these form group 1 in this study. Sixty three children had blood calcium concentrations greater than or equal to 3.0 mmol/l when diagnosed. In only five were mental handicap, abnormal facies, and raised calcium concentrations the only criteria present. Twelve children had blood calcium concentrations of 2.70 to 2.99 mmol/l and 11 had either radiological osteosclerosis, clinical evidence of arteriopathy, or a positive calcium load test in addition to mental handicap and elfin facies.¹⁵ One child whose initial plasma calcium concentration was normal was included as he was mentally handicapped and had elfin facies, a cardiac murmur, and a positive calcium load test. Forty one cases of Williams-Beuren syndrome were identified (group 2). Twenty one cases had data from cardiac catheterisation or echocardiography to confirm the diagnosis. The other 20 children all had characteristic facies, cardiac murmurs, and were mentally handicapped. Details of these two study groups and of the control group are given in Table 2. Twelve children were excluded as no evidence to justify the original diagnosis was found. Nine were excluded

Table 2 Study population

	Group 1	Group 2	Control group
No	76	41	59
Sex (% boys:girls)	47:53	46:54	44:56
Age (yrs). Mean (SD)	12.1 (7.3)	11.9 (6.0)	10.2 (5.9)
Maternal age at conception (yrs). Mean (SD)	27.9 (5.7)	26.2 (4.5)	26.9 (4.3)
Paternal age at conception (yrs). Mean (SD)	30.5 (6.1)	28.5 (5.3)	29.6 (10.2)

Group 1—Fanconi-type idiopathic infantile hypercalcaemia; group 2 Williams-Beuren syndrome.

because the hospital records were unobtainable or inadequate to substantiate the likely diagnosis. Although 10 cases were suggestive of Fanconi-type hypercalcaemia in that they had similar facies, feeding problems, and mental handicap, they were excluded as there was no documented evidence of hypercalcaemia or a cardiac murmur. Five cases of Lightwood-type hypercalcaemia without mental handicap were also excluded from the study.

Results

Clinical presentation and feeding behaviour. (Data from questionnaires—parental recall). Relevant data are listed in Tables 2 and 3. The control group was matched for age, sex ratio, and class distribution. Both study groups had an equal sex ratio. No significant difference was found, either between study groups or with controls, in parental age at conception, duration of pregnancy, or mode of delivery. Nor was there any difference in the parental recall of vitamin D or drug ingestion during pregnancy or history of maternal infection during the first trimester. No significant seasonal variation was found in the month of birth. Birthweights of groups 1 and 2 were significantly lower than controls ($P<0.005$). Ten per cent of all babies were found to have a congenital abnormality at birth—in most cases a cardiac murmur. Six infants were noted to be cyanosed in the perinatal period. Thirty per cent of

babies were admitted to special care units because of low birthweight or problems with resuscitation. Significantly more parents of group 1 babies stated that they felt their baby's face had looked abnormal at birth than parents of group 2 babies ($P<0.01$). Phrases such as 'wide mouthed', 'monkey faced', or 'very dark' were frequently used to describe their appearance.

Parental recall of symptoms during infancy were qualitatively similar between study groups but differed significantly for some symptoms, particularly the degree of vomiting and lack of weight gain. Profuse vomiting, often described as projectile, was described in 74% of group 1 compared with 44% of group 2 babies ($P<0.01$). Correspondingly, 88% of group 1 infants were reported to have failed to gain weight compared with 49% of group 2 ($P<0.001$). Symptoms of feed refusal, profound constipation, swallowing difficulties, and noticeable floppiness were commonly recalled by both groups of parents.

The mean onset of these problems was between 2 and 3 months of age in each group, ranging from birth to 15 months in group 1. The mean age of diagnosis for group 1 children was 12 months, ranging from 4 to 26 months. One was diagnosed at 48 months when a positive calcium load test was obtained despite the presence of normocalcaemia. At least 52% of mothers of babies in group 1 who started to breast feed stated that these problems began before the introduction of fortified milk feeds, which is supported by the fact that on average they stopped breast feeding earlier than control mothers ($P<0.001$).

Treatment of hypercalcaemia. All but two children from group 1 had been treated with a low calcium and vitamin D restricted diet. Only 54% used distilled water at any stage, although many boiled the water supply instead. Twenty five per cent had had a course of corticosteroids usually for one to four weeks. The duration of the diet was in some cases difficult to determine but ranged from 1 to 132 months with a mean of 27 months. Adverse effects were few, but 7 cases of iatrogenic rickets were documented radiologically and biochemically after treatment lasting 10 to 29 months with a mean of 20 months. In 16 children hypocalcaemia was documented—6 in association with rickets (range 1.75 to 2.10 mmol/l). No case was symptomatic and hypocalcaemia was detected after treatment lasting 2 to 128 months. No other ill effects were clearly documented.

Growth. Fig. 1 shows the heights of each child at the time of examination. Before puberty all the children were at or below the 50th centile, however only two

Table 3 Clinical presentation/feeding problems (parental recall of events) in children with Fanconi-type idiopathic infantile hypercalcaemia (group 1) and Williams-Beuren syndrome (group 2) and in a control group

	Group 1	Group 2	Control group
Birthweight (kgs). Mean (SD)	2.77 (0.49) ¹	2.68 (0.46) ²	3.34 (0.55)
Gestation (wks). Mean (SD)	40.5 (1.9)	40.4 (1.8)	39.8 (2.2)
Abnormal facies at birth (%)	45 ¹ ‡	17 ²	2
Admitted to special care unit (%)	26	34	14
Breast fed (%)	65	59	66
Stopped breast feeds (mths). Mean (SD)	2.1 (1.9) ²	2.8 (2.7)	4.6 (4.1)
Frequently refused feeds (%)	84 ¹	68 ²	3
Frequently vomited (%)	80 ¹	66 ²	17
Vomited 'large' amounts (%)	74 ¹ ‡	44 ²	7
'Extremely' constipated (%)	22 ¹	10 ²	0
Had difficulty swallowing (%)	82 ¹	66 ²	2
Failed to gain weight (%)	88 ¹ §	49 ²	0
Felt 'floppy' (%)	55 ¹	34 ²	2
Onset of problems (mths). Mean (SD)	2.7 (2.7)	2.3 (4.5)	—
Condition diagnosed (mths). Mean (SD)	12.0 (6.7) [§]	61.9 (44.9)	—

¹Groups 1 and 2—controls, $P<0.01$; ²groups 1 and 2—controls $P<0.005$.

³Group 1—group 2 $P<0.01$; ⁴Group 1—group 2 $P<0.005$.

Fig. 1 Heights of girls and boys at the time of study plotted on a centile chart.

* Case with second episode of hypocalcaemia.

were less than 3 SD below the mean. As reported by their parents, the age of menarche was mean (SD), 11.2 (1.3) years and pubic hair developed in the boys at mean (SD), 12.3 (1.6) years. The adult height (at 19 years) for 6 boys was mean (SD), 159 (9) cm, with a corrected parental height of 172 (6) cm. The adult height of 8 girls was mean (SD) 147 (5) cm, with a mean corrected parental height of 162 (3) cm. In 7 of 14 adult cases their weight was more than 2 SD above their height centile, indicating substantial obesity. Occipitofrontal head circumferences were similarly distributed below or close to the 50th centile and in only 6 cases were less than 3 SD below the mean. Mean adult head circumferences for girls and boys were 54.8 cm and 52.8 cm respectively. No case of craniosynostosis was identified.

Mental development. No formal assessment of intelligence quotient (IQ) was possible in this study but all available data from psychological testing were analysed. Where more than one identical test was performed the individual mean was calculated and this value used to calculate the group means. No difference was seen between groups 1 and 2 and so a joint analysis was performed.

The Griffith scales were performed on 26 patients at a mean chronological age of 42 months. The development quotient (DQ) was mean (SD), 60 (9), with individual subscale means ranging from 55 to 65. The score for personal and social behaviour (mean (SD), 65 (8)) was not significantly greater than the score for eye and hand coordination (mean (SD), 55 (12)). The Stanford-Binet intelligence test was performed on 10 children at a mean age of 63 months and the IQ was found to be mean (SD) 66 (4). The Weschler intelligence scale for children was performed on 11 children with a mean age of 115 months and the IQ was mean (SD), 56 (14).

Major motor milestones were determined by questionnaire and the ages of smiling, sitting, and walking solo were reported to be mean (SD) 3.8 (1.8), 12.4 (3.8), and 26.9 (7.6) months respectively in group 1. The corresponding values for the group 2 children were mean (SD), 3.3 (2.5), 10.5 (2.5), and 23.4 (6.9) months. Solo walking was significantly slower in the group 1 children ($P < 0.01$).

All children had special schooling, although 19% initially attended normal primary schools. Seventy per cent of children over 10 years of age were literate and 65% could write their own name. After leaving school most attended local authority adult training centres. Four out of 26 school leavers were in remunerative employment and a further three attended job training schemes.

Cardiovascular system. Seventy four per cent of the

group 1 children had a pathological cardiac murmur on examination by one of us (NM). A further 14% were reported to have had a murmur in the past (but this had resolved) and 12% had at no time any clinical evidence of a cardiovascular abnormality. Of the 54 cases with a cardiac murmur only 12 (21%) had undergone cardiac catheterisation and only three had required cardiac surgery. In comparison 19 (49%) of group 2 cases had been catheterised and 10 of these had undergone surgery. The cardiovascular findings at catheterisation are listed in Table 4. There was no significant difference in the site of the major stenoses between the groups and evidence of widespread arteriopathy was found in 52%, although full angiography was not always attempted. Stenotic lesions that were found, in addition to supravalvular aortic stenosis and peripheral pulmonary artery stenosis affected the following arteries; innominate (2), left common carotid (2), left subclavian (4), right coronary (2), superior mesenteric (1), and left renal (1). Structural anomalies of the renal tract were found in three patients. Eleven of the 13 who required cardiac surgery were boys and only 2 were girls. Two boys developed profound hypertension after operation.

Blood pressure measurements were taken where possible (65%) from both upper limbs, and if raised were rechecked. Where both the systolic and diastolic blood pressures were greater than the 95th centile for the individual's age, values were regarded as hypertensive.¹⁶ No significant difference was found between the two groups and 29% of all cases were hypertensive. Analysed by age, 40% of cases over 12 years and 63% of cases over 18 years were hypertensive. Six of the 16 hypertensive patients were hypertensive in the right arm but normotensive in the left arm. In one the femoral pulses were felt to be reduced and one was on antihypertensive treatment.

Miscellaneous disorders. A variety of abnormalities were found equally in groups 1 and 2. These include

Table 4 Cardiovascular pathology at catheterisation in 12 children with Fanconi-type idiopathic infantile hypercalcaemia (group 1) and in 19 with Williams-Beuren Syndrome (group 2)

	Group 1	Group 2
Supravalvular aortic stenosis	10 (83%)	16 (84%)
Peripheral pulmonary aortic stenosis	7 (58%)	11 (58%)
Pulmonary stenosis	1	1
Right ventricular outflow obstruction	0	2
Bicuspid aortic valve	0	1
Hypertrophic obstructive cardiomyopathy	0	1
Atrial septal defect	1	1
Ventricular septal defect	1	3
Coarctation of aorta	1	1

concomitant strabismus (50%), inguinal herniae (31%), rectal prolapse (12%) and umbilical herniae (11%). Musculoskeletal abnormalities were frequently detected. Kyphosis or scoliosis was detected in 19% but in only one girl had it become progressive requiring surgical stabilisation. Eleven (55%) of the other cases had minor structural curvatures and the remainder had postural curvatures. The parents of the older patients frequently complained that their child had 'poor' posture. Other skeletal abnormalities detected were radio-ulnar synostosis (5), dislocatable patellae (3), and unstable knee joints (2).

Hyperacusis, particularly in early childhood, was reported in 94% of cases compared with 9% of controls ($P<0.001$). This was severe enough in many to make it impossible to travel in town, or to perform household chores in the presence of the child. In 75%, hyperacusis was still reported at the time of the study. No auditory abnormalities have as yet been detected to explain these findings which seem to become less obvious with time and may develop a degree of supratentorial overlay (Dr D N Brooks—personal communication).

Facies. Standard photographs were taken of all cases and where possible photographs taken soon after birth were viewed. It was apparent that the classic 'elfin' facies was not obvious at birth, was most recognisable during early childhood, and became less specific during adolescence and adulthood. Fig. 2 shows this progression in three cases. The facies from both groups did seem to be indistinguishable.

Chromosomal analysis. Routine chromosome analysis had been performed in 25 cases, although G-banding was rarely performed. One girl displayed an aberration with satellites of the G group chromosomes while one boy showed a translocation of the long arms of 9+17.

Biochemistry and radiology. Biochemical data at the time of diagnosis, before treatment, and in almost all cases from the same blood sample were analysed. The total blood calcium of the group 1 infants was mean (SD), 3.31 (0.37) mmol/l, the maximum value being 4.0 mmol/l. Values for phosphate were generally normal (mean (SD), 1.64 (0.38)) and alkaline phosphatase concentrations were depressed (mean (SD), 113 (73) IU/l). Calcium concentrations correlated significantly with plasma urea ($r=0.29$; $P<0.01$), creatinine ($r=0.63$; $P<0.005$), total protein ($r=0.31$; $P<0.05$), and alkaline phosphatase ($r=-0.45$; $P<0.001$). There was also a weak positive correlation with total cholesterol ($r=0.31$;

Fig. 2 Facies of three children with Fanconi-type idiopathic infantile hypercalcaemia. Infant photographs taken around the time of diagnosis; second portrait taken at the time of study.

$P=0.05$), but samples were not necessarily fasting samples.

Two cases were initially normocalcaemic when supraaortic stenosis or peripheral pulmonary aortic stenosis was found at 3 and 9 months of age. On subsequent follow up, four and 12 months later, the calcium concentrations were found to be

raised and a therapeutic response obtained to a low calcium diet. In one case the plasma calcium seemed to rise after the introduction of vitamin supplements (400 IU/day).

One case, one of the most severely handicapped in the series who also had extremely short stature (Fig. 1), had had a recurrence of the hypercalcaemia at 15 years of age. After a period of ill health, his plasma calcium concentration was found to be raised to above 3.0 mmol/l on several occasions and investigations showed normal concentrations of 25 hydroxyvitamin D and undetectable parathormone by radioimmunoassay. He again became normocalcaemic on starting a low calcium diet, although little change in his clinical condition was evident.

Of 25 cases diagnosed in the last 8 years since parathormone and vitamin D metabolite assays have been readily available, in only three had any attempt been made to measure these parameters.

Radiological increase in bone density was documented in 51% of group 1 cases. No radiological evidence of nephrocalcinosis was found but nephrocalcinosis was shown by ultrasound in one case where no radiological calcification could be seen. Renal calculi were found in two cases, both from group 2.

Discussion

After the efforts of the Infantile Hypercalcaemia Foundation to publicise the condition, it has become apparent that Fanconi-type idiopathic infantile hypercalcaemia is perhaps not as rare as sometimes suggested,¹⁷ nor can we detect any major change in its incidence over the past 20 years. Assuming, at a conservative estimate, that half of all cases in the UK have been identified, then 18 cases per year are born in the UK (1 per 47 000 total live births). It is probable that at least an equal if not a greater number of children with Williams-Beuren syndrome are recognised each year. Therefore, taken as a group they are not an insignificant cause of childhood morbidity.

One object of this survey was to study the link between Fanconi-type idiopathic infantile hypercalcaemia and Williams-Beuren syndrome. Certainly their facial morphology seems indistinguishable and the pattern of system involvement identical. We have, however, discovered significant differences in the parental recall of infant feeding problems and in the degree of delay in motor development. There was a consistent trend towards greater feeding problems in group 1 infants with significantly greater recall of profuse vomiting and poor weight gain. The latter is born out by the fact that the characteristic pattern of failure to thrive followed by definite

weight loss between 6 and 12 months of age was only, but not always, seen in the presence of documented hypercalcaemia. Related to this, the group 1 infants were on average significantly slower in walking than group 2 infants. Therefore, if a common aetiology does exist, there must be heterogeneity of expression. Hence in 12% of group 1 cases no cardiovascular pathology had ever been identified. Similarly recognition of Williams-Beuren syndrome during infancy, without evidence of hypercalcaemia, is not unusual. However, the two cases reported where hypercalcaemia was documented suggest, at a later date that the calcium metabolism should be investigated more fully at the time of diagnosis and perhaps prospectively. In essence, until we can discover the cause of the hypercalcaemia the exact relation between Fanconi-type idiopathic infantile hypercalcaemia and Williams-Beuren syndrome will remain uncertain and the terms will continue to be used synonymously.

The symptoms of hypercalcaemia are unfortunately non-specific, which may explain the delay in diagnosis. This has not changed since Forfar reviewed the subject in 1959.¹⁸ Although there is no conclusive evidence that this delay alters the long term prognosis, in particular with respect to mental handicap, it cannot be optimal management and might be improved upon if a plasma calcium estimation were included more frequently in the assessment of an infant with profuse vomiting, especially in association with a cardiac murmur. Where hypercalcaemia is borderline, a calcium load test and documentation of hypercalcaemia are necessary if long term, potentially harmful, treatment is contemplated.

Dietary treatment in many cases in group 1 was not followed by a dramatic improvement in health. More often there was some lessening of the vomiting with a slow increase in weight, but considerable problems with feeding continued. The infants were often fed solely on puréed foods for several years because of difficulties with chewing and swallowing. It is important that dietary advice is readily available over this stressful period. Restriction of calcium and perhaps also of vitamin D led to iatrogenic rickets in 9% of cases and episodes of asymptomatic hypocalcaemia in 21%. Some may feel this indicates effective treatment of the hypercalcaemia but when the risks to the childhood dentition of neonatal hypocalcaemia¹⁹ and infantile rickets²⁰ are well established, it is logical to assume that iatrogenic rickets and hypocalcaemia should be avoided if possible. It seems, from the data available, that less prolonged calcium restriction may be safer and equally effective. Therefore, we would recommend

the introduction of a normal diet after perhaps 6 to 12 months. If such a policy were adopted, the use of either the calcium load test or urinary calcium: creatinine ratio²¹ to predict calcium tolerance, should be considered.

The prognosis and incidence of complications associated with Fanconi-type idiopathic infantile hypercalcaemia have not been systematically studied since 1959²² and parents found that advice was inevitably guarded and incomplete. Where the diagnosis is clearly established, the findings from this series may allow more specific advice to be given. Thus, on average the children will walk at around 2 to 2.5 years of age and will require special schooling, although an appreciable minority may manage for a while in normal primary schools. Most will learn to read and write, although a substantial minority will be more severely handicapped. They may have special learning difficulties, which have been the subject of a recent study,²³ and their 'psychological profile' has attracted much comment but little systematic study.^{23 24}

Most group 1 children did not have severe large artery disease, although a cardiac murmur persisted in 60% of cases into adult life. Since one episode of subacute bacterial endocarditis was recorded in this series and other cases have been documented, it is advisable that antibiotic prophylaxis be given for dental extractions.

Cardiac surgery was only undertaken in 13 cases from both study groups (11 cases for correction or bypass of supra-avalvular aortic stenosis and two cases for closure of atrial septal defect or resection of coarctation of the aorta). Correction of supra-avalvular aortic stenosis was performed on average at 11 years of age and the boy:girl ratio was 9:2 compared with the same sex ratio at catheterisation of 2:1. We can find no reference to a similar disparity in the published reports. The discrepancy may reflect patient selection but a preponderance of boys in other forms of congenital heart disease is recognised, notably aortic valve stenosis.²⁵

Hypertension in association with Fanconi-type idiopathic infantile hypercalcaemia is well recognised but the fact that it may be manifest later in life is not well documented.²⁶ The high incidence in this series may be due to several factors. Firstly, the children are in general anxious personalities and blood pressure measurements were only taken on one occasion. Moreover, in 6 of 16 cases the raised blood pressure was due to supra-avalvular aortic stenosis as the blood pressure measured in the left arm was normal. Further investigation of this association is necessary as antihypertensive treatment may be inappropriate in many, but not all, cases and undiagnosed aortic coarctation or renal

artery stenosis are, at least potentially, surgically treatable.

Hyperacusis does seem to be a real association with the condition, although very difficult to quantify in the mentally handicapped. The clinical problem generally becomes less troublesome later in childhood and shows considerable variability in relation to the source and nature of the sound indicating that supratentorial factors are important.

The aetiologies of Fanconi-type idiopathic infantile hypercalcaemia and Williams-Beuren syndrome are unknown. There can be little doubt that they are congenital anomalies since the birthweights of each group are significantly less than normal and cardiac murmurs are often noted at birth. In this series the condition was sporadic (apart from one pair of identical twins) and no siblings were affected. Previous reports of 'Familial Williams Syndrome'²⁷ were less exact in diagnostic criteria and it would seem that the risks of recurrence are very low and less than occasionally stated.²⁸ Chromosomal aberrations have been reported^{29 30} but no consistent pattern emerges. The incidence of 8% in this series is more than one might expect from other populations of mentally handicapped children and further prospective study is necessary.

The role of vitamin D remains controversial. Metabolic balance studies have shown consistently that the infants absorbed calcium more avidly than matched controls but clinical studies, including our own, have usually failed to find evidence of excessive vitamin D intake during infancy or of increased maternal intake during pregnancy. Studies of vitamin D teratogenicity in rabbits performed by Friedman *et al*^{31 32} and in part confirmed by Chan *et al*³³ used doses of vitamin D equivalent to at least 35 000 IU/week throughout a human pregnancy. To account for these facts and to support the theory of vitamin D teratogenicity in humans, vitamin D sensitivity has been proposed. This theory, however, would not explain adequately some of the clinical observations in this study. Firstly, of the mothers who breast fed, 52% stated that the feeding problems began before fortified milk feeds were introduced. Secondly, iatrogenic rickets may be produced in a significant minority of cases even when sunlight, the primary physiological source of vitamin D, is not restricted. Thirdly, the sporadic and transient nature of the hypercalcaemia militates against an inborn error of vitamin D metabolism.

Therefore, other factors require investigation. Forbes *et al*³⁴ have shown that calcium homeostasis may be defective, and postulated a deficient response of calcitonin to hypercalcaemia. This would not in itself, however, explain the findings of increased calcium absorption. From our own study,

in at least two of three cases where parathormone assays were performed before dietary treatment was begun, immunoreactive parathormone was detectable despite the presence of hypercalcaemia. This suggests inadequate parathormone suppression by plasma calcium during hypercalcaemia. There are many possible aetiologies for idiopathic infantile hypercalcaemia and we suggest that it is time to evaluate new cases more thoroughly, using newer techniques of examining calcium and vitamin D metabolism, before embarking upon treatment.

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