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SEVERE TYPE OF INFANTILE HYPERCALCAEMIA

BY

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Infantile hypercalcaemia has only recently been recognized (Lightwood, 1952a ; Payne, 1952), but it is clear that there are two varieties of the disease. In the simple or benign form, described by Lightwood and Payne, the prognosis is good. A more severe type with a definite mortality can be recognized by a characteristic facies, present from an early age. All survivors so far followed have been mentally retarded. Physical growth is also affected at the height of the disease ; it becomes accelerated as the condition improves, though the skull remains small and craniostenosis may be a complication. The renal impairment which invariably accompanies the hypercalcaemia is apt to be more severe than in the simple type. Though hypertension can result and prove fatal, kidney function may improve in survivors. Hypercholesterolaemia is often present. A systolic murmur is audible in most cases. Increased radiological density of the skeleton appears at some stage, involving principally the base of the skull, the epiphyses, and the growing ends of the long bones. This may be severe enough to be confused with Albers-Schönberg's disease or so slight as to escape recognition, unless radiological examination has been possible from the onset.

A report of a case fulfilling these criteria was made by one of us (Butler, 1951), and a similar case was published by Fanconi (1951). These were more fully discussed in a joint paper (Fanconi *et al.*, 1952). Since then others have discovered five further examples of the disorder (Creery, 1953 ; Lowe *et al.*, 1954 ; Dawson *et al.*, 1954 ; Russell and Young, 1954). A child described earlier by Lightwood (1932) showed many features characteristic of this condition. She was a girl with a squint and facial palsy, who was mentally retarded and dwarfed. Intermittent vomiting from birth was the chief symptom, and at about 2 years of age she died of renal failure. The *x*-ray picture showed increased density of the skull and long bones ; this was confirmed at necropsy, which also revealed widespread calcification in the kidneys, viscera, and cardiovascular system. The serum calcium level originally reported was 11 mg. per 100 ml. Unfortunately, no note was made of the facies.

We have already summarized our ideas on this disorder (Schlesinger *et al.*, 1954). In the present paper we review seven cases previously recorded and report three more (Table I). The severity of the disease is well illustrated, as four of the ten patients died. Two of these cases have already been published (Lowe *et al.*, 1954 ; Dawson *et al.*, 1954), and two other cases examined *post mortem* are described here.

Case 3

A female infant was born on September 2, 1949, birth weight 7 lb. 7 oz. (3,370 g.), after a normal pregnancy and labour, the third child of healthy parents. *X*-ray films of the long bones of her two elder siblings were normal at 5 and 7 years, but the mother's skull was reported as showing some thickening of the outer table with partial obliteration of the diploic space ; the cortex of the long bones also appeared to be unusually thick. The mother's detailed history is not available. The baby progressed well on the breast for the first month, but was weaned on to dried milk because of vomiting. Anorexia, vomiting, and constipation continued thereafter throughout her life with only short remissions. Vitamin D was never given in excess of normal supplement dosage and was withheld for long periods on account of vomiting. She was late in all her milestones, only achieving head control at 10 months and sitting up three months later, when she spoke her first word. As she was still backward at 18 months and was noticed to have an odd facies suggestive of cretinism, thyroid extract was given in small doses without result over the next few months. A transient right facial weakness was noted during this time.

On admission to hospital at 27 months she was still puny, miserable, and backward. Her weight was 17 lb. 2 oz. (7,768 g.) and she was extremely hypotonic. The skull measured only 17 in. (43 cm.) in circumference and there was early bilateral papilloedema. No cardiac murmur was detected and electrocardiography was normal. The main biochemical findings are summarized in Fig. 1. The serum calcium, blood inorganic phosphorus, and alkaline phosphatase levels were normal. Hypercholesterolaemia was present. *X*-ray films of the skull showed greatly increased density in both base and vault, with thickening of the frontal bones and obliteration of the diploic space (Fig. 2). The vertebral bodies appeared denser in the centre and the periphery, with an intermediate normal zone. There was thickening of the cortex of some of the long bones, with dense transverse lines at the metaphyses. The epiphyses at the lower end of the femur and upper end of the tibia contained an outer ring of increased density surrounding a normal core. The ribs were also dense. Bone age was about six months advanced. A provisional diagnosis of Albers-Schönberg's disease was made on the radiological appearance.

Three months later she was admitted to the Children's Hospital at Birmingham, where further investigations showed the serum calcium to be raised, the blood inorganic phosphorus and alkaline phosphatase levels still being normal (Fig. 1). Papilloedema had disappeared. The blood pressure was 110/70, and the urine was normal on routine examination and by chromatography. Radiologically the epiphyses now contained an outer concentric area of normal ossification, signifying that normal bone growth had probably recommenced. Subsequently there was some clinical improvement with cessation of vomiting and gain in weight, corresponding to a temporary return of the serum calcium and blood cholesterol levels to normal. Three months later, however, after an acute upper respiratory infection, vomiting recurred and her physical condition again deteriorated, with a rise in serum calcium to 12 mg. per 100 ml.

On her final admission to hospital at 35 months she was febrile and severely dehydrated after four days of vomiting.

TABLE I.—*Principal Findings in 10 Cases of Severe Infantile Hypercalcaemia*

Case No.	Sex	Birth Weight			Hypercalcaemia				Highest Recorded Level (mg./100 ml.)		Max. Recorded B.P.	Systolic Murmur	Other Features
					Initial Symptoms	Age in Months		Highest Level (mg./100 ml.)	Bldod Urea	Blood Cholesterol			
		lb.	oz.	g.		First Symptoms	Hypercalcaemia First Discovered						
1	M	6	4	2,835	Vomiting	5	20	14·2	104	265	270/250	Loud	Squint
2	F	6	6	2,890	Anorexia	Birth	22	14·2	70	306	110/80	,,	Squint. Facial paresis. Craniostenosis. Radiological nephrocalcinosis
3	F	7	7	3,370	Vomiting	1	30	13·3	76 (N.P.N.)	290	150/95	Nil	Facial paresis. Died, 35 months
4	M	4	12	2,155	,,	Birth	7	14·3	87	162	130/80	Loud	
5	M	5	8	2,495	,,	4	17	14·5	108	105	95/50	Soft	
6	M	5	15	2,695	,,	4	15	15·0	270	350	110/70	,,	Died, 3 years
7	M	6	11	3,030	Anorexia, constipation	Birth	7	17·6	140	117	90/65	Nil	
8	M	6	14	3,120	Vomiting ,,	5 3	14	14·0	133	320	—	Soft	
9	F	6	8	2,950	Constipation Vomiting	Birth 11	16	18·7	170	235	120/80	Loud	Craniostenosis. Radiological nephrocalcinosis. Died, 26 months
10	M	5	14	2,665	,,	5	7	16·4	110	350	150/60	,,	Died, 11 months

Note.—All cases had radiological osteosclerosis of the skull base, some of them in other bones, and they were severely retarded in development.

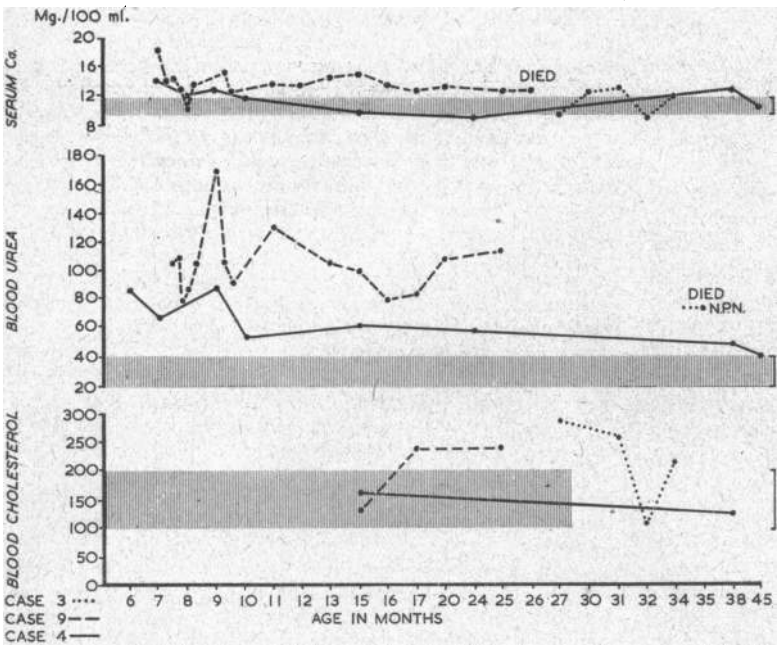

FIG. 1.—Blood chemistry in Cases 3, 4, and 9. The shaded areas represent the normal ranges.

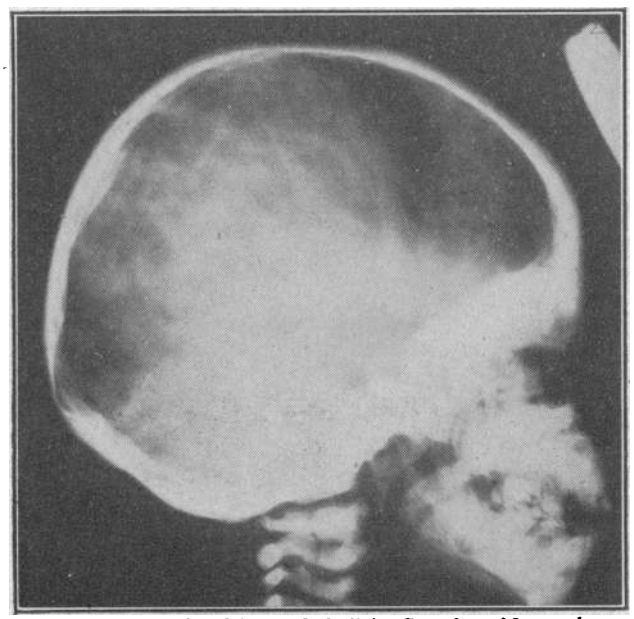

FIG. 2.—Sclerosis of base of skull in Case 3 at 35 months.

Pallor (Hb 40%), dyspnoea, hypertension (150/95), and triple rhythm were the main clinical features. There was marked albuminuria, with a raised level of non-protein nitrogen in the blood. She died the day after admission, from pneumonia and cardiac failure.

Post-mortem Examination

At post-mortem examination (Dr. H. S. Baar) the body was very wasted, with generalized oedema.

Kidneys.—These were firm and small with a combined weight of 51 g. (normal, 100 g.). The capsule was adherent, but the underlying surface smooth. The cortex was much reduced in width and the cortico-medullary demarcation was indistinct. Calcium deposits were visible to the naked eye. On histological examination the renal structure was disorganized, with much interstitial fibrosis. Many glomeruli were bloodless and showed endothelial proliferation; in several there were foci of ischaemic necrosis; in others there was hyalinization, capsular adhesions, or periglomerular fibrosis. The tubules were reduced in number, the lining epithelium was flattened, the lumina containing hyaline or granular casts. Some tubules were much dilated, forming pseudocolloid microcysts. Calcium deposits were present in both cortex and medulla, in some cases filling the lumina of the tubules, and in others deposited in the basement membrane and lining cells. There were also many large structureless calcium plaques in the interstitial tissue.

Cardiovascular System.—The heart was greatly enlarged (weight 102 g., normal 60 g.), due mainly to left ventricular hypertrophy. Medial hypertrophy was present in some vessels, such as the interlobular renal arteries. Patchy proliferation of the subendothelial intimal tissue with fragmentation and degeneration of the internal elastic lamina was present in other arteries—the coronary, ovarian, lingual, intralobular, and afferent arterioles of the kidney. There was no calcification in the heart or arteries.

Skeleton.—The density of the skull was much increased. There was a zone of sclerosis near the costochondral junction in the vertebral bodies and in the femoral metaphyses. The femoral shafts were also sclerotic. Histologically, the bone in the sclerotic areas was of normal mature lamellated structure, apart from some necrotic areas in the femoral metaphyses, indicating old microfractures. There was abnormal ossification near the sphenoidal synchondrosis, where islands of calcified cartilage and mature bone presented a mosaic appearance.

Other Organs.—Lungs: There was generalized pulmonary oedema, with small areas of consolidation in the right upper and lower lobes. Widespread calcium deposits were found in the plain muscle of the walls of the bronchi and bronchioles, and in the walls of the alveoli, alveolar ducts, and interalveolar septa. *Stomach:* Calcium deposits were also seen in the fundal glands. *Thyroid gland:* This was small but otherwise normal. *Parathyroid gland:* Only one was discovered, and this had a normal histology. *Liver:* Small centrilobular foci of necrosis were present. *Brain:* There was marked flattening of the gyri but no other abnormality.

Comment

This case showed all the features of severe hypercalcaemia—typical facies, dwarfism, mental retardation, renal impairment, hypertension, and hypercholesterolaemia. Sclerosis of the skeleton was extreme. Death occurred in hypertensive heart failure, and post-mortem examination revealed severe renal destruction and calcification in the kidneys and elsewhere.

Case 9

A female infant, born at term on April 24, 1952, weight 6½ lb. (2,950 g.). She was an only child of healthy unrelated parents. Pregnancy was uneventful, and the mother stated that she had taken only the usual vitamin supplements. The baby's progress was uneventful until 2 months, when complementary feeds of dried milk (700 i.u. of vitamin D per pint: 1,232 i.u. per litre) were begun, and a month later she was weaned completely. From then onwards she became lethargic and difficult with feeds, vomited frequently, and developed constipation. Negligible amounts of cod-liver oil, not more than two teaspoonfuls in all, were the only extra source of vitamin D until 6 months, when twelve drops of "adexolin" (80 i.u. of vitamin D per drop, or 120 i.u. per minim) were given daily for three weeks.

At 7 months she was admitted to the Royal Belfast Hospital for Sick Children. At that time she was pale, hypotonic, and wasted—11 lb. 8 oz. (5,215 g.)—with thirst and polyuria. The skull circumference was normal—16⅝ in. (42 cm.)—but the anterior fontanelle was closed. A loud systolic murmur was audible and the blood pressure was 110/70. Investigations between 7 and 11 months revealed almost persistent hypercalcaemia, the range being 13.8 to 18.7 mg. per 100 ml. The blood inorganic phosphorus level was above 5.5 mg. per 100 ml. on four out of six occasions. There was also azotaemia, the maximum blood urea level being 170 mg. per 100 ml. (Fig. 1). The total serum protein was 8.4 g. per 100 ml., with slight increase of alpha-2-globulin. The urine contained a trace of protein with occasional pus cells in the deposit. *X*-ray examination showed increased density of the bones of the skull, the forearms, and legs. There was no radiological nephrocalcinosis. The course of the illness has been reported up to this time by Creery (1953).

Further Progress

Temporary cessation of vomiting, but no improvement in the biochemical picture, followed administration of a low-calcium diet and the withdrawal of vitamin-D supplements from 9 to 11 months of age. At this time she was transferred to the Hospital for Sick Children, Great Ormond Street, as the family had moved to England. Anorexia, vomiting, and constipation still dominated the clinical picture, and she was severely retarded physically and mentally. The loud systolic murmur was still present and the blood pressure was 90/60. The urine showed no abnormality on microscopy or culture. The base of the skull was still dense, but the radiological appearance of the other bones had returned to normal. The bone age at 11 months was that of a child of 18 months. From about 1 year she improved temporarily and gained a little weight, though apart from a fall in the blood inorganic phosphorus the biochemistry was unchanged.

By 15 months she developed craniostenosis, sufficient to cause papilloedema. There was now *x*-ray evidence of nephrocalcinosis. Two months later an operative reconstruction of the fused coronal and sagittal sutures was carried out in two stages. This failed to benefit her vomiting, although the papilloedema disappeared and the skull circumference actually increased by ½ in. (1.3 cm.) during the next six months. A biopsy of the brain taken at the time of operation revealed focal calcification in the cerebral cortex and meninges. As she was still vomiting and making no progress, at 26 months a further effort was made to reduce the serum calcium level, this time by a calcium-free diet and an intramuscular infusion of a chelating agent ("disodium versenate," 3.3%). The serum calcium level fell over a six-hour period from 12.1 to 10.1 mg. per 100 ml., but the infant collapsed two hours later and died in cardiac failure five hours after the infusion.

Post-mortem Examination

At post-mortem examination (Dr. Martin Bodian) the body was that of a reasonably well nourished child of 17 lb. (7.7 kg.)—normal, 28 lb. (12.7 kg.)—and height of 17 in. (43 cm.)—normal, 33 in. (84 cm.).

Kidneys.—Both were small, with a combined weight of 26 g. (normal, 93 g.). The capsule stripped easily and left a smooth surface. Numerous white dots and streaks of calcium salts were seen in the cortex and at the corticomedullary junction. Histologically there was advanced shrinkage and disorganization of the cortex, apart from the juxtamedullary zone, where the nephrons were mostly intact and hypertrophic. In the affected areas the glomeruli were crowded and largely fibrosed or hyalinized, and the tubules were mainly destroyed. Those which persisted were degenerate and filled with granular calcium salts. Nephrocalcinosis was also present in the medulla.

Skeleton.—The skull vault was diminished in size, measuring 17 in. (43 cm.) in circumference. The base of the skull and calvarium were unduly thick. The inner and outer tables were fused in many places and the diploic spaces were inconspicuous. The natural sutures and fontanelles were all closed, but the operative suture lines remained open. The vertebrae, ribs, and sternum appeared normal to the naked eye. Histology revealed that in these various sites the trabeculae were thickened, though otherwise of normal architecture. There was abnormal endochondral ossification in the sternum and in the femur, with retarded osteoid production.

Cardiovascular System.—The heart was not hypertrophied (weight 51 g., normal 56 g.). A well-defined focus of calcification 3 by 1 mm. was visible in the mitral valve near the insertion of the posterior cusp. Histology showed a trace of calcium in a few subepicardial muscle fibres. No hypertensive changes were seen in the cardiovascular system, but certain arteries—coronary, for instance—showed partial degeneration and fragmentation of the internal elastic lamina, while other vessels—lingual, meningeal, and renal arteries—showed, in addition, considerable deposition of calcium in relation to the degenerated elastica.

Respiratory System.—There was acute bronchitis with pulmonary congestion and oedema. The bronchial cartilage and alveolar capillary walls showed scattered calcification.

Parathyroid Glands.—These were normal in size and histology.

Metastatic Calcification.—In addition to the areas of calcification already noted, calcium deposits were found in the submucosa of the fundal glands of the stomach and in the ganglion cells of the myenteric bowel plexus. The dura over the cranial base was calcified, with small areas of bone formation. Calcification was also present in the cortical dura and in the arachnoid.

Brain.—The brain weighed 914 g. (normal, 1,064 g.). There was some convolutional flattening, but the gross architecture and histology were normal.

Comment

This case was typical of the severe type of hypercalcaemia, with the peculiar facies and usual biochemical changes, combined with mental and physical retardation. Osteosclerosis

was present and renal function was greatly impaired. Craniostenosis developed during the second year of life and was treated surgically. Death occurred at 25 months, and at necropsy the kidneys were found to be severely damaged by deposits of calcium salts, which were also present in the mitral valve, lungs, and meninges.

The following two cases, both of which survived, are now reported for the first time.

Case 4

This infant, a male, was born on August 20, 1950, birth weight 4 lb. 12 oz. (2,155 g.), after a full-time and uneventful pregnancy. Only the usual antenatal vitamin supplements had been taken by the mother. There were no siblings and no family history of consanguinity or congenital malformation. The baby cried repeatedly from birth and was reluctant to suck, rendering breast-feeding impossible. Thereafter, anorexia persisted, with frequent vomiting and troublesome constipation. Many varieties of dried milk, and, finally, fresh cow's milk, were tried without success. One drachm (3.5 ml.) of Government cod-liver oil (750 i.u. of vitamin D per drachm: 215 i.u. per ml.) was offered daily from the age of 2 months. At the age of 4 months irritability increased, grimacing and facial twitching developed, and he was admitted to hospital. He was then noticed for the first time to have an odd facies. Feeding still proved extremely difficult. A soft systolic murmur was present and the tendon reflexes were very brisk. A raised protein (110 mg. per 100 ml.) was present in the cerebrospinal fluid, falling to 65 mg. per 100 ml. two months later, and finally becoming normal. As the vomiting continued he was readmitted at 6 months, now physically backward and weighing only 12 lb. 15 oz. (5.8 kg.). The blood urea was raised—85 mg. per 100 ml. (Fig. 1)—but no serum calcium estimation was performed. There was slightly increased density at the base of the skull, without any thickening of bone structure.

A month later, at 7 months, he was transferred to the Hospital for Sick Children, Great Ormond Street, where the diagnosis of hypercalcaemia was established (Fig. 1). The blood inorganic phosphorus and serum alkaline phosphatase levels were normal and remained so. The E.S.R. was 40 mm. in one hour (Wintrobe). Persistence of renal impairment was indicated by failure to raise the specific gravity of the urine above 1012 after fluid restriction. There was a trace of albumin in the urine, which contained up to 10 pus cells per high-power field in the deposit; *Proteus vulgaris* was grown on culture on six occasions over the next few months. The radiological changes in the base of the skull were still present, and there was increased density in the iliac crests and upper femoral metaphyses. He vomited frequently and remained difficult with his feeds until the age of 1 year, after which his appetite improved and he gained weight steadily. By 15 months the serum calcium level had fallen to normal and he was approaching average height and weight for his age, though his mentality was still severely impaired. The blood pressure was 130/80. Thereafter followed a gradual return to normal of the other biochemical and radiological abnormalities, and the increased density of the skull and skeleton had disappeared by 2 years of age. The blood urea remained elevated until his fourth year, though the urine was now normal. At this time his speech was limited to simple words, he was unable to feed himself, and he was incontinent by day and night; his intelligence quotient was 50.

Comment

This case of infantile hypercalcaemia presented the characteristic facies of the severe type, with typical physical, mental, and biochemical findings, but with minimal osteosclerosis. Most of the abnormalities resolved during the second year of life, but azotaemia persisted until 3 years, and at 4 years his mentality was still severely impaired.

Case 8

This patient was a male infant born in March, 1952. The birth weight was 6 lb. 14 oz. (3,120 g.). He was the first child of unrelated parents. Pyelitis of pregnancy developed at five months, but labour was uneventful. Constipation was troublesome from birth, but otherwise he thrived in the early months, during which the usual vitamin supplements were given. Breast-feeding continued until 6 months of age, when mixed feeding was established without difficulty. Though unable to sit up, he was described as a happy, placid child until 11 months, when an attack of vomiting was followed by gradual failure of appetite, though fluids continued to be well taken. Thereafter, his weight of 18½ lb. (8.4 kg.) remained stationary for the next three months. Cretinism was suspected, but a therapeutic trial of thyroid extract brought no improvement. At 14 months he was admitted to the Derbyshire Children's Hospital, where he was found to be retarded and a soft systolic murmur was heard. *X*-ray examination of the long bones was normal, but the density of the ribs was increased.

The following investigations were carried out: serum calcium, 14 mg. per 100 ml.; blood urea, 84 mg. per 100 ml.; alkali reserve, 41.4 vols. CO_2 per 100 ml.; blood cholesterol, 106 mg. per 100 ml.; serum protein, 6.4 g. per 100 ml. (albumin 3.8 g., globulin 2.6 g.). The urine, *p*H 6.3, contained a trace of albumin and 5 to 80 pus cells per high-power field, and was sterile on culture. The blood Wassermann reaction was negative and the E.S.R. varied between 44 and 67 mm. at one hour (Westergren).

In view of the raised blood urea and slightly lowered alkali reserve a provisional diagnosis of renal acidosis was made, for which alkalis were administered by mouth in moderate dosage over the next ten months. Initially there was a rapid weight gain of 1 lb. (450 g.), but anorexia and constipation returned within a few weeks, and thereafter he again failed to thrive. Pyuria continued intermittently during the second year. The blood urea fell temporarily to normal at this time, but the blood cholesterol rose to 305 mg. per 100 ml. At 2 years he weighed only 21 lb. (9.5 kg.) and had a diminished skull circumference of 18½ in. (47 cm.). The typical facies was noted for the first time when he was seen by Dr. P. R. Evans. He could now just walk alone, and physical retardation was less marked than mental backwardness. The systolic murmur was still present. Skull *x*-ray films, taken for the first time, showed loss of diploic detail with very slight thickening and increased density, involving the base and vault. There were a few transverse lines of increased density at the metaphyses of the long bones. Hypercalcaemia (12.4 mg. per 100 ml.) and hypercholesterolaemia (320 mg. per 100 ml.) were still present. The blood urea had risen again to 133 mg. per 100 ml., though the urine had become normal. The serum protein was also high—9.04 g. per 100 ml. (albumin 5.32 g., globulin 3.72 g.)—but the electrophoretic pattern was normal. One year later, at the age of 3, he was still physically dwarfed, and the parents reported that he had made no mental progress.

Comment

This case of severe hypercalcaemia showed the typical facies with physical and mental retardation, renal impairment, hypercholesterolaemia, and a systolic murmur. Onset of vomiting was late and bone changes were minimal. He was still hypercalcaemic at 2 years and backward mentally and physically at the age of 3.

Clinical Features

Some of the main features in the 10 cases are summarized in Table I and Table II. The latter also includes information on the progress of five of the six survivors. These clinical findings require more detailed comment.

Facies.—The characteristic facies was present in all the cases described. The children had an "elfin" appearance (Lowe *et al.*, 1954), with prominent epicanthic folds, an overhanging upper lip, and underdevelopment of the bridge of the nose and mandible (Fig. 3). It is not exactly known when this facies first develops, but it was noticed as early as 4 months in one case and was still present in the survivors we have followed (Fig. 4). An alternating convergent squint

of a non-paralytic type was found in two children (Cases 1 and 2). Transient facial paresis was noticed in two children (Cases 2 and 3). So far as we can ascertain, this peculiar facial appearance has not been reported in any other condition.

Behaviour.—Several cases were originally suspected to be cretins (Nos. 1, 3, and 8). However, far from being sluggish in their movements, they displayed an extraordinary degree of liveliness, with ill-directed, purposeless movements of the face and limbs. In spite of marked hypotonia, the tendon reflexes were very brisk. Hyperkinesis persisted in at least two survivors, both of whom are easily frightened as well as being mentally retarded.

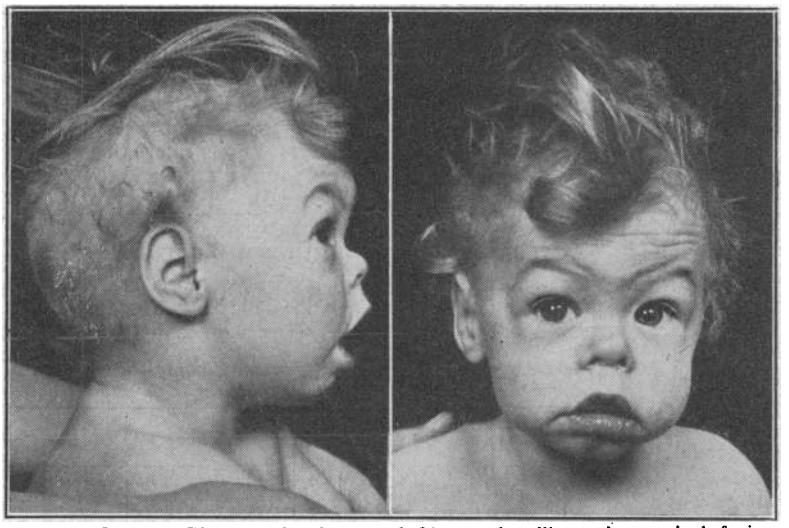

FIG. 3.—Case 5. Photograph when aged 21 months, illustrating typical facies.

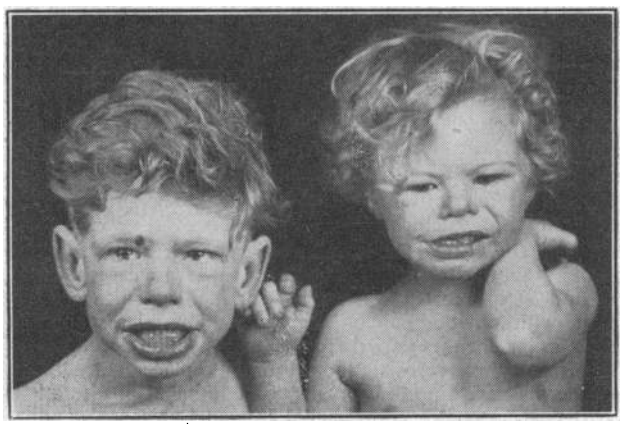

FIG. 4.—Cases 1 and 5. Patients at 6 and 4 years of age, illustrating persistence of characteristic facies.

Skull Size.—A reduction in skull circumference was an invariable finding, persisting even when the height and weight had begun to increase. Although these cases did not have the appearance of true microcephaly, it seems likely that retardation of brain development was responsible for the small size of the skull, which persisted after the resumption of growth elsewhere. Only two cases (Nos. 2 and 9) had evidence of craniostenosis.

Physical Growth.—In all 10 cases there was a marked degree of dwarfing in the acute stage, the weights and heights being below the third percentile. On the other hand, bone age varied considerably. With the criteria of Gruelich and Pyle (1950), it was retarded in three (Cases 1, 5, and 6), normal in four (Cases 2, 4, 7, and 8), and slightly advanced in the remaining three (Cases 3, 9, and 10). In all the survivors the physical growth accelerated soon after the resolution of hypercalcaemia, though only one (Case 4) had reached normal weight within 18 months of recovery. All the children remained small in stature; their progress is shown in Table II. Bone age was normal in two out of four when last seen.

Mental Growth.—Intelligence in young children cannot be estimated very accurately, especially in a sick and hypotonic infant, in whom impairment of physical attainments may influence some of the tests; but by the age of 2 years careful clinical observation is of value. The nine children who reached this age alive were all mentally retarded. Actual intelligence quotients were calculated in three, and none was above 60% (Table II). It seems likely that mental development is permanently affected.

Biochemical Findings

Hypercalcaemia.—In the acute stage the serum calcium was raised in all cases—that is, over 11.5 mg. per 100 ml. The maximum level recorded varied between 13.3 and 18.7 mg. per 100 ml. This falls almost within the same range of 12.3 to 17.5 mg. per 100 ml. in simple hypercalcaemia described by Creery and Neill (1954). Approximate duration of the hypercalcaemia can be estimated from the interval between the first symptoms and the last recorded raised calcium level. This period varied from 12 to 30 months in four survivors, during which anorexia, hypotonia, and physical retardation were present throughout. The other two were still hypercalcaemic after 13 and 40 months respectively. The illness lasted from 8½ to 22 months in Creery and Neill's series of simple hypercalcaemia.

Azotaemia.—High blood urea levels invariably accompanied the hypercalcaemia. Poor concentrating power or impaired urea clearance was present in eight of the ten cases in which this was investigated during the acute stage. A trace of albumin and a few white and red blood cells in the urinary deposit were frequent findings, while granular casts were occasionally present (Cases 2 and 10). A urinary infection occurred in three instances (Cases 4, 6, and 10). Chromatography showed normal amino-acid excretion in the four cases in which it was undertaken. Follow-up showed that the blood urea level tended to remain raised for many months after the hypercalcaemia had subsided and that some degree of renal impairment persisted (Table II).

Hypercholesterolaemia.—High blood cholesterol levels were recorded at some period in the acute stage in seven out of the ten cases. In two of the others (Cases 4 and 7) only a single estimation was carried out, and this proved normal. High blood cholesterol figures tended to run parallel with the hypercalcaemia, but in the remaining case (No. 5)

TABLE II.—*Follow-up of Five Surviving Cases*

	Case 1	Case 2	Case 4	Case 5	Case 7
Age in years:					
At diagnosis ..	1.8/12	1.10/12	7/12	1.5/12	7/12
At return of serum calcium to normal	3.3/12	Not yet	1.3/12	1.9/12	2 6/12
Findings at last follow-up:					
Chronological age	6.3/12	3.4/12	3.9/12	4	3
Mental age ..	3.3/12 (I.Q. = 60)	1.6/12	1.6/12 (I.Q. = 40)	2 (I.Q. = 50)	1.3/12
Bone ,, ..	5.9/12	—	3.9/12	2 3/12	Normal
Weight ,,* ..	4.4/12	1	3 9/12	1	2
Height ,,* ..	4	2	3	1.9/12	2
Skull ,,* ..	1.6/12	9/12	1	9/12	—
Last available blood chemistry:					
Serum Ca (mg./100 ml.) ..	9·4	13·5	11·3	10·1	10·2
Blood urea ..	47	53	40	100	71
,, cholesterol..	178	281		241	

* These levels represent the age of a normal child with corresponding weight, height, or skull circumference.

the cholesterol level rose for the first time when the serum calcium level had been normal for one year.

Erythrocyte Sedimentation Rate.—This was raised in five of the six children in whom it was estimated.

Other Biochemical Findings.—Blood inorganic phosphorus readings were occasionally above the normal level of 5.5 mg. per 100 ml. in six cases (Nos. 2, 3, 6, 7, 9, and 10), in three of which individual recordings were higher than 7 mg. per 100 ml. It is interesting that the heights of the blood inorganic phosphorus and blood urea readings showed some correlation. Alkaline phosphatase estimations were made in eight of the ten cases by the King–Armstrong method. No reading above 25 units was recorded, but in four cases (Nos. 2, 6, 9, and 10) levels below 10 units were found on one or more occasions. Serum protein figures above 7 g. per 100 ml. were noted in six out of nine cases (Nos. 1, 4, 6, 7, 9, and 10), in two of which levels exceeded 9 g. per 100 ml. The A/G ratio was reversed in two instances only, and in another case (No. 9) the electrophoretic pattern showed an increase of alpha-2-globulin. The same case was repeatedly found to have a normal plasma magnesium level. Occasional low bicarbonate readings below 40 vols. CO_2 per 100 ml. were present in six cases, but in none was there a persistent acidosis.

Cardiovascular System

Hypertension.—The technical difficulties of accurate blood-pressure readings are well known, but, using as criterion for the normal 120 mm. systolic and 80 mm. diastolic, higher figures were recorded in four children (Cases 1, 3, 4, and 10).

Systolic Murmur.—In five of the ten children there was a persistent widely conducted systolic murmur of sufficient intensity and propagation to suggest an organic lesion, though never accompanied by a thrill. It was present as early as 6 weeks in one case (No. 1). In a further three cases there was a soft systolic murmur of a type present in many normal children, which had disappeared in one instance by the age of 1 year.

Radiological Changes

The chief bones affected were the base of the skull, the metaphyses and epiphyses of the long bones, the vertebral bodies, ribs, and iliac crests. In the skull base there appeared to be both thickening and increasing density. The changes sometimes affected the vault of the skull as well,

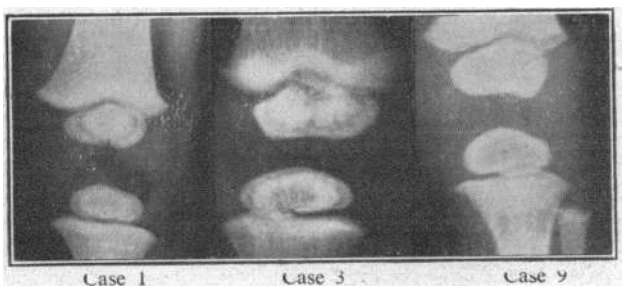

FIG. 5.—Disordered epiphysial calcification of the knee-joint: Case 1, central sclerosis. November 23, 1950. Age 1 year 11 months. Case 3, mid-zone sclerosis. April 1, 1952. Age 2 years 6 months. Case 9, marginal sclerosis. December 20, 1952. Age 8 months.

particularly the frontal bone, where there was loss of diploic detail. Digital markings were present in every case, and the sutures fused prematurely in two.

The changes in the long bones consisted of dense transverse bands in the metaphyses, particularly noticeable at the lower end of the femur and upper end of the tibia. These were irregularly placed at various levels in the shaft, probably corresponding to periods of cessation of growth. Similar bands were present in many instances in the ends of the metacarpals and metatarsals, and in the vertebral bodies and iliac crests. There was no clubbing or lack of modelling distally, such as may occur in Albers-Schönberg's disease, to which the radiological changes bear a superficial resemblance. The shafts of some of the long bones were more dense than normal. The epiphyses were also affected, particularly at the knee, carpus, or tarsus, showing alternate rings of dense and normal bone, indicating presumably exacerbations and remissions in the course of the illness (Fig. 5).

On follow-up, the density of the long bones appeared to return to normal shortly after the acute stage of hypercalcaemia had resolved. In one instance (Case 5) there was a tented appearance in the lower femoral metaphyses, where ossification was defective (cf. post-mortem report in Case 9). Occasionally (Cases 5 and 7) the long bones became slightly osteoporotic later (see also Creery and Neill, 1954). The skull changes also diminished in four survivors, returning to normal in two (Cases 4 and 7) by the age of 2 years. However, in the other two, at the ages of 4 and 6 years respectively, some thickening remained. It is interesting to note that there was slight thickening of the skull and long bones of the mother of one child (Case 3).

Synopsis of Post-Mortem and Biopsy Findings

One short and three full necropsy reports are available, including an account of a kidney biopsy. These are summarized in Tables III and IV. The main changes were renal,

TABLE III.—*Macroscopic Post-mortem Findings in Cases* 3, 9, *and* 10

Case No.	Kidney	Skull	Skeleton	Heart
3	Reduced size (50% of normal). Narrowed cortex. Generalized nephrocalcinosis	Very thick	Ribs, vertebral bodies, femoral shafts, and femoral metaphyses all thickened	Left ventricular hypertrophy
9	Shrunken (30% of normal). Cortex narrow with nephrocalcinosis	Thick. Craniostenosis	Normal	Calcification of mitral valve
10	Reduced size (50% of normal). Architecture normal. No calcium visible	Normal	Femoral shaft thickened	Left ventricular hypertrophy

cardiovascular, and skeletal, in addition to varying degrees of metastatic calcification.

Renal Changes.—The kidneys were considerably shrunken, with a smooth surface. In the three most severe cases (Nos. 3, 6, and 9) the cortex was narrowed, the cut surface being firm, with obvious calcium deposits. On microscopy the glomerular changes varied from patchy hyaline degeneration to ischaemic necrosis and fibrous replacement. Some glomeruli were bloodless, owing to endothelial proliferation, whilst others contained epithelial crescents or capsular adhesions. The tubules showed a degree of destruction comparable to that of the glomeruli. In one case (No. 3) these changes were widespread and the renal architecture was disorganized, but in two (Cases 6 and 9) they were most pronounced in the peripheral area of the cortex, the juxtamedullary regions being less affected. There were aggregations of calcium salts in the cortex and medulla, in the latter within and outside the tubules.

Cardiovascular System.—Left ventricular hypertrophy was found in two cases (Nos. 3 and 10), both of which had hypertension during life; in one of these there was also medial hypertrophy of some of the larger arteries. Metastatic calcification was present in the mitral valve (Case 9) and myocardium (Cases 6 and 9). The smaller arteries showed a patchy fragmentation of the internal elastic lamina, which had led in one instance to degeneration and impregnation with calcium salts. An increase of subendothelial connective tissue occurred beneath these areas in one case (No. 3).

Skeletal System.—Macroscopically the sclerotic changes coincided with the distribution of the *x*-ray findings, affecting mainly the skull base and growing ends and shafts of long bones. The microscopic architecture of the bone was mainly

TABLE IV.—*Histology in Cases 3, 6, 9, and 10*

Case No.	Kidney	Blood Vessels	Skeleton	Other Metastatic Calcification
3	Extensive destruction of cortex and medulla with fibrous replacement. Glomerular ischaemic necrosis with endothelial proliferation. Capsular adhesions. Widespread tubular destruction and calcinosis	Focal degeneration and fragmentation of internal elastic lamina of smaller arteries. Some medial hypertrophy	Sclerotic zones in ribs, femur, vertebrae, and sphenoid, with mosaic structure in the latter. "Micro-fractures" in femur and vertebrae	Lungs. Fundal glands of stomach
6 Biopsy and short necropsy report	Subcapsular cortical destruction. Affected glomeruli hyalinized and fibrosed; capsular proliferation present. Tubular and interstitial calcinosis with focal granulomata	Renal blood vessels normal	Not reported	Lungs. Myocardium
9	Extensive subcapsular cortical damage with glomerular hyalinization and fibrosis; tubular destruction and calcinosis	Focal degeneration, fragmentation, and occasional calcification of internal elastic lamina of smaller arteries	Trabeculae coarse and thickened in the skull, sternum, vertebrae, and femur. Abnormal endochondral ossification in the last two situations	Lungs. Myocardium. Fundal glands of stomach. Intestinal wall. Meninges. Mitral valve
10	Minority of glomeruli destroyed (10%), with patchy hyalinization and occasional epithelial crescents. Vacuolar tubular degeneration and calcinosis	Normal	Structure and ossification normal	Nil

preserved even in the sclerotic areas, suggesting excessive deposition of calcium rather than a primary bone affection. However, endochondral ossification was abnormal, with persistence of cartilaginous areas in the basi-sphenoid (Case 3) and in the sternum and femur (Case 9). Necrotic foci and microfractures were present in one long-standing case (No. 3).

Discussion

Various explanations have been put forward to account for this syndrome. Since our original suggestion of a collection of congenital abnormalities, several necropsy reports have thrown fresh light on the subject. Post-mortem study has shown no evidence of congenital malformations affecting the heart, kidneys, or skeleton. Indeed, present evidence makes it clear that most of the symptomatology and pathological changes can be explained by a combination of prolonged hypercalcaemia and renal impairment.

Severe and probably irreversible kidney damage was found at necropsy in three cases (Nos. 3, 6, and 10), in one of which left ventricular failure was a contributory cause of death (Table III). Glomerular destruction was widespread and severe, consistent with the known effects of hypercalcaemia (Dent *et al.*, 1953). Other renal changes consisted mainly in the deposition of calcium in and around the tubules, and were no doubt due to the same cause. Similarly, the other sites of calcification—in the myocardium, blood vessels, brain, meninges, lungs, and stomach—corresponded to those occurring in hypercalcaemia from any cause, especially when accompanied by a normal or raised level of blood inorganic phosphorus. Calcification of the mitral valve might have explained the systolic murmur heard in Case 9, in which, according to our standards, there was no hypertension. A more detailed histological examination of the mitral and other valves in further cases might reveal evidence of calcification sufficient to cause rigidity of the cusps, as was found in one instance by Hallman (1955). Hypertension has been suggested as a likely cause for these murmurs, but our evidence does not support this conception.

The significance of the bone changes has already been discussed (Fanconi *et al.*, 1952). The histological pattern was normal, but at the growing ends an excessive and often intermittent deposition of heavily calcified bone has been found. These appearances are probably due to hypercalcaemia associated with periods of arrested bone growth, somewhat similar to Harris's lines. Minor degrees of sclerosis have also been described in simple hypercalcaemia (Creery and Neill, 1954). Why it should be more pronounced in the severe type of hypercalcaemia is not clear, but it is probably connected with the more advanced renal damage and the degree and duration of hypercalcaemia. Vitamin-D poisoning is known to produce a similar radiological picture in the long bones (Jeans, 1950).

The coexistence of mental retardation with hypercalcaemia is of great interest. The head circumference of all the children was small, even allowing for the retardation in growth and height. Evidence of raised intracranial pressure was present in only two instances, in one of which papilloedema was transient, so it is unlikely that mechanical causes produced the mental condition. We know of no studies of the effect of hypercalcaemia upon the developing brain, but in adults severe hypercalcaemia can cause mental symptoms (Rogers, 1946). However, the degree of backwardness in our cases was equally severe when the serum calcium fell quickly and skeletal changes were minimal, as in Case 4, so that other factors are probably involved. It is our impression that at least some cases of the severe type were generally retarded at the time when symptoms suggestive of hypercalcaemia were first noticed. Compared with a series of simple cases of hypercalcaemia seen at Great Ormond Street, the severe group we have reviewed had a lower mean birth weight, which was of statistical significance and not due to prematurity (M. N. Karn, 1955, personal communication).

Although hypercalcaemia and renal damage can account for many of the features of the disease, others are more difficult to explain on this basis. The facies, for example, may be the result of abnormal growth of the basi-sphenoid (Russell and Young, 1954), as was in fact found in Case 3 at necropsy. Osteosclerosis is an unlikely cause, as a peculiar appearance was present when increased skull density was only minimal (Case 4) or had not yet appeared (Case 10). A facies with a shallow bridge of the nose has also been ascribed to premature fusion of the spheno-occipital suture (Gray, 1949), but there is no record of this finding in necropsies on the cases we are discussing. Craniostenosis of the vault has already been mentioned.

Hypercholesterolaemia is another feature of the severe type of hypercalcaemia, but it can occasionally arise in the simple type (Creery and Neill, 1954). Nephrosis immediately comes to mind, as being so commonly associated with a raised blood cholesterol, but the clinical picture and renal pathology in infantile hypercalcaemia, mild or severe, are not compatible with this condition. Nevertheless we believe that in some way it is connected with renal damage. It is interesting to note that hypercholesterolaemia has been reported in hypercalcaemia due to excess vitamin-D dosage (Fanconi and de Chastonay, 1950).

Naturally the key to the whole problem would be the discovery of the cause of the hypercalcaemia. There has been no biochemical, radiological, or histological evidence of hyperparathyroidism. It is also clear that neither bone destruction nor immobilization plays any part in the production of the hypercalcaemia. We have been unable to find any evidence of an abnormally high intake of vitamin D by the infants under discussion, nor by their mothers during pregnancy in the four cases we were able to investigate fully. Four of our infants had been fed on dried milk —700 i.u. of vitamin D per reconstituted pint (1,232 i.u.

per litre)—for some months before the development of symptoms, with the addition of vitamin supplements in normal amount (Cases 1, 5, 6, and 10). Overdosage with vitamin D having been excluded, the possibility of hypersensitivity to the vitamin must be carefully considered (see also Andersen and Schlesinger, 1942). It is known that the amount of vitamin D required to prevent rickets varies enormously from individual to individual, and it is also possible that there is a similarly wide range in the amount which will produce hypercalcaemia. Apart from individual sensitivity, exogenous factors causing retardation in growth may determine the requirement and action of vitamin D.

Hallman and Ylppö (1954) have described a series of cases with hypercalcaemia developing in premature infants who had recently recovered from plasma-cell pneumonia. All the premature infants had been given varying amounts of vitamin D, but only those who had suffered from pneumonia actually developed hypercalcaemia. Some of their cases were also observed to have squints, a curious facies, and mental retardation, and appeared to be similar in many ways to the cases we are describing. Hypercalcaemia has also appeared in a child with miliary tuberculosis (D. H. Wallace, 1955, personal communication), and in a case of infantile hypothyroidism, where bone growth is also retarded (Naylor, 1955). In neither of these had an excess of vitamin D been given.

In view of the bad prognosis of the severe type of infantile hypercalcaemia, treatment should aim at reducing the serum calcium to normal as soon as possible. In our experience the omission of vitamin D from the diet is an ineffective method of reducing the serum calcium. A low-calcium diet, as given to two of the cases in the present series by Russell and Young (1954), may be effective, and special milk is now available for the purpose. Recently Anderson *et al.* (1954) have shown that certain cases of sarcoidosis are hypersensitive to vitamin D and that this effect can be reversed by cortisone. In hyperparathyroidism, however, cortisone had no effect. The successful use of cortisone in simple infantile hypercalcaemia has been reported by Creery and Neill (1954) and Fanconi and Spahr (1955). In the light of these results, cortisone should be given a more extended trial in the severe type, as has also been recommended by Bonham Carter *et al.* (1955).

There has been some doubt concerning the exact relationship between the two forms of hypercalcaemia which have been mentioned, and intermediate grades may well occur. Comparison between the present cases and a series of simple hypercalcaemia, published by Creery and Neill (1954), reveals that the method of feeding and vitamin intake were similar, but symptoms tended to begin earlier and last longer in the sever type. Most of the differences can be explained on the assumption that in the severe type derangement of calcium metabolism and renal impairment begin earlier and are greater. For example, azotaemia was not always present in the benign group, and none died of renal failure.

Osteosclerosis is a striking feature of the severe type, though more than half the cases of simple hypercalcaemia showed transverse bands of increased density at the lower ends of the long bones. A loud systolic murmur was heard in some of the severe cases, though soft systolic murmurs were present in both series. Hypertension developed much more often in the severe group and a raised blood cholesterol was more than three times as common. A typical facies and mental retardation appear to be clinical signs confined to the severe type, but their exact relationship to hypercalcaemia remains to be determined.

From our present knowledge, it seems clear that a child with hypercalcaemia and the additional features we have discussed in the severe type is in danger of death through renal failure or hypertension, and if it survives is likely to be permanently retarded mentally.

Summary

Seven published cases of the severe form of hypercalcaemia of infancy are reviewed and three new cases are added. The morbid anatomy in four fatal cases is discussed. Present evidence indicates that most of the pathological changes are secondary to the hypercalcaemic state. Two distinguishing features in the severe type—the facial appearance and mental retardation—are stressed and their aetiology is discussed.

Excessive vitamin-D intake was regarded as a possible cause, but no evidence of this could be found. An abnormal sensitivity to vitamin D, determined by individual metabolic requirements or by growth disturbance, is suggested.

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Hospitals in Great Britain have over 4,000 vacancies for male nurses. 2,500 of these are for trainees, the most urgent need for whom is in mental and mental deficiency hospitals. The Ministry of Labour points out that young men under 18½ or who have left school within three months, who train for registration on the general, mental, or mental deficiency parts of the register, for the certificate of the British Tuberculosis Association, or for enrolment as assistant nurses, may obtain deferment of their National Service. After training they will have the opportunity of being employed on nursing duties during their service.