IDIOPATHIC HYPERCALCAEMIA IN AN INFANT

CLINICAL AND POST-MORTEM FINDINGS IN ONE CASE

BY

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Idiopathic hypercalcæmic syndromes in infancy are now well recognized clinically (Lightwood, 1952a and b; Payne, 1952; Fanconi, Girardet, Schlesinger, Butler and Black, 1952; Creery, 1953; Lightwood and Stapleton, 1953; Lowe, Henderson, Park and McGreal, 1954; Creery and Neill, 1954, and The Lancet, leading article July 17, 1954). They are, in our opinion, separate from infantile renal acidosis, and Lightwood and Stapleton divide them into two groups. The classification is accepted by Lowe et al. In one group the course is transient and benign. There are no significant bony changes, no cardiac murmurs and probably no hypertension. On recovery the intelligence is normal. In the second group the course is prolonged and severe. There are bony changes resembling osteopetrosis, a loud systolic bruit, hypertension, often hypercholesterolaemia, a characteristic facies and impaired mental development. In the papers mentioned above there is one recorded histological report of a renal biopsy in a case which had run a prolonged and severe course (Lowe et al.). In a preliminary communication concerning a similar case (Dawson and Craig, 1954) we had previously tentatively suggested a primary renal origin for the condition. This view has had to be modified as a result of further study. Because necropsy and histological reports on these conditions are rare we think it worth while to present the findings in a single case.

Case Report

Paul D., a boy, was the first child of healthy, unrelated parents. A maternal cousin of the mother had a deformity of the feet. Otherwise there were no known developmental anomalies in the family. Delivery was normal and birth weight 5 lb. 14 oz. Progress in the early months was satisfactory although it was noted that from the age of 3 weeks the baby was unusually quiet, inclined to sleep too much and rather unresponsive to attention. He was first referred to hospital when 23 weeks old on account of anorexia and persistent vomiting for three weeks. On examination the infant was unable to hold his head up. There was generalized hypotonia, gross plagiopcephaly and asymmetry of the face and thorax, right calcaneovalgus, a large umbilical hernia, hypertension and a loud systolic murmur audible over the entire chest (Fig. 1). The cardiac murmur had not been present when the baby was thoroughly examined on two occasions during the neonatal period.

His weight showed an irregular but progressive decline. Unexplained periods of pyrexia occurred at irregular intervals and the child died unexpectedly during one of them at the age of 47 weeks. Apathy and listlessness, lack of emotional response, reluctance to feed and constipation were constant features in hospital. The abnormal behaviour pattern suggested that mental progress might be impaired. Dogmatic conclusions were not justified, however, in view of the child's age, of the associated physical weakness, and of the fact that impaired hearing was suspected by several independent observers.

The baby was fed wholly at the breast until the age of 3 months when a change was made to a full cream dried cow's milk preparation, and when for the first time concentrated orange juice (1 teaspoonful) and pure cod liver oil (5 drops) were given daily. Medicaments given to the child consisted of six teething powders (each containing 1/2 grain of calomel) in the sixth month of life; and from the age of 13 to 23 weeks milk of magnesia (1/2 teaspoonful) on alternate days, and 2 grains of soda.

![Figure 1](http://adc.bmj.com/content/29/148/475RINGA1593A.png)

**Fig. 1.**—Paul D., aged 37 weeks. Note the facial and cranial asymmetry.
and of any occasion
Chromatography
Urea clearance

Frequent
16-4
28.10.53
50-
5.12.53

Nil
10.11.53

Occasional
17.11.53

Desquamated epithelial cells and an occasional
pus cell
Mixed growth of Proteus and staphylococcus
Albumin, trace, pH 6.4

* Frequent use was made of Sulkowitch's reagent but on no occasion did the results suggest excessive calcium excretion.
Chromatography established the absence of reducing substances and of any abnormal amino-aciduria.
Urea clearance was 21% (second hour).

**TABLE 1**

BLOOD SERUM BIOCHEMISTRY (mg., 100 ml.)

<table>
<thead>
<tr>
<th>Date</th>
<th>Sodium</th>
<th>Potassium</th>
<th>Total Calcium</th>
<th>Iodized Calcium</th>
<th>Phosphorus</th>
<th>Phosphate</th>
<th>Chloride</th>
<th>Blood Urea</th>
<th>Urea Nitrogen</th>
<th>CO₂</th>
<th>Cholesterol</th>
<th>Total Protein</th>
<th>Albumin</th>
<th>Globulin</th>
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<td>300</td>
<td></td>
<td>16-0</td>
<td>7.3</td>
<td>5-8</td>
<td></td>
<td>580</td>
<td></td>
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<td>300</td>
<td>6-9</td>
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<td>7.3</td>
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<td>10</td>
<td>560</td>
<td>26-6</td>
<td>350</td>
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<td>28.8.53</td>
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<td>14</td>
<td>16-0</td>
<td>7.3</td>
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<td>9</td>
<td>540</td>
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<td>315</td>
<td>102</td>
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<td>310</td>
<td>110</td>
<td>310</td>
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<tr>
<td>2.12.53</td>
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<td>12-8</td>
<td>5-4</td>
<td>10</td>
<td>540</td>
<td>52</td>
<td>52</td>
<td>250</td>
<td>7-4</td>
<td>55</td>
<td>330</td>
<td>7-1</td>
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<td>7.4</td>
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<td>110</td>
<td>310</td>
<td>110</td>
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<td>249</td>
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<td>4-8</td>
<td>0 : 8 : 1</td>
<td></td>
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</table>

**TABLE 2**

URAL FINDINGS

<table>
<thead>
<tr>
<th>Date</th>
<th>Investigation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>31.8.53</td>
<td>Urocytes, occasional, R.B.Cs occasional Predominant growth Proteus.</td>
</tr>
<tr>
<td>7.9.53</td>
<td>Polymorphonuclear leucocytes, moderate number, some red cells, occasional hyaline casts. Proteus. Albumin, trace, pH 6.3. Calcium, 12.9 mg. per 100 ml.</td>
</tr>
<tr>
<td>24.9.53</td>
<td>Urocytes, moderate number, many cellular casts, granular casts, moderate number. Proteus, profuse growth, occasional colony of staphylococcus Albumin, trace, pH 7-0</td>
</tr>
<tr>
<td>29.9.53</td>
<td>Many polymorphs and some red and epithelial cells Moderate growth of Proteus, light growth of staphylococcus, sensitive to chloromycetin Albumin, trace, pH 6-3 Calcium 12.8 mg.</td>
</tr>
<tr>
<td>16.10.53</td>
<td>Occasional polymorph and red cells. Very occasional granular casts Heavy growth of Proteus and a Gram-positive coccus Albumin, trace, pH 6-4</td>
</tr>
<tr>
<td>10.11.53</td>
<td>Nil Scanty growth of coliform organism of doubtful significance pH 6-3, albumin, trace, calcium, 12-9 mg.</td>
</tr>
<tr>
<td>17.11.53</td>
<td>Occasional leucocyte and red cell Moderate growth of Ps. pyocyanea and a coliform organism</td>
</tr>
<tr>
<td>5.12.53</td>
<td>Desquamated epithelial cells and an occasional pus cell Mixed growth of Proteus and staphylococcus Albumin, trace, pH 6.4</td>
</tr>
</tbody>
</table>

**TABLE 3**

MISCELLANEOUS FINDINGS

<table>
<thead>
<tr>
<th>Date</th>
<th>Age (weeks)</th>
<th>Investigation</th>
<th>Results and Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.9.53</td>
<td>35</td>
<td>Fractional test meal</td>
<td>Acid secretion within normal limits</td>
</tr>
<tr>
<td>12.9.53</td>
<td>34</td>
<td>Wassermann</td>
<td>Negative</td>
</tr>
<tr>
<td>28.8.53</td>
<td>31</td>
<td>Electrocardiograph</td>
<td>Elevation of ST segment in leads 2, 3, V4 and V6. T waves prominent</td>
</tr>
<tr>
<td>17.7.53</td>
<td>25</td>
<td>Radiological Skull and wrist</td>
<td>Fontanelle open Convolutional markings posterior part of skull Three small centres of ossification in wrist</td>
</tr>
<tr>
<td>26.8.53</td>
<td>31</td>
<td>Skeleton</td>
<td>No detectable abnormality in bone structure</td>
</tr>
<tr>
<td>30.9.53</td>
<td>36</td>
<td>Skull Long bones Abdomen</td>
<td>Bands of increased density at ends of long bones particularly at distal metaphyses of radius and ulna Peripheral density in ossification centres of tarsal bones and at knee joints No evidence of renal calcification</td>
</tr>
<tr>
<td>6.11.53</td>
<td>41</td>
<td>Skull Long bone</td>
<td>Skull, basal sclerosis and asymmetry but no abnormality of sutures Long bone, continued deposit of sclerotic bone metaphyses Two ossific nuclei in each wrist Epiphyses of femoral heads well developed Epiphyses and tarsal bone—central core of bone of normal intensity with existing sclerotic changes situated peripherally Skeletal development not delayed</td>
</tr>
</tbody>
</table>
bicarbonate (in a proprietary mixture) daily. The infant was never given sulphonamides.

Investigations. The results of investigations are detailed in Tables 1-3 and Fig. 2. There were persistently raised serum calcium, blood cholesterol and urea nitrogen levels. Renal function was impaired, but there was no evidence of renal acidosis or of parathyroid hyperactivity. Radiologically there was moderately increased density in certain bones (Fig. 3) but no nephrocalcinosis. Blood cultures at the ages of 27, 44 and 47 weeks were all sterile, and blood counts between July 11 and November 26 gave: Hb 64-79%, R.B.C.s 3·4-4·2 m., W.B.C.s 7,600-20,400 per c.mm. Numerous blood pressure readings were recorded during the last six months of life. Systolic readings were always in the neighbourhood of 140 to 150 mm. Hg and the diastolic readings between 50 and 60 mm. Hg.

The mother of Paul D. has since given birth to a second baby whose progress has been uninterrupted and who at 9 months of age is in every way healthy. The results of examination of the mother’s blood one month before delivery of her second baby are summarized in Table 4.

![Table 4](http://adc.bmj.com/)

| TABLE 4 |
| RESULTS OF EXAMINATION OF THE MOTHER’S BLOOD |
| Serum (mg. 100 ml.) |
| Calcium | 9·1 |
| Inorganic phosphate | 3·1 |
| Alkaline phosphatase | 12·1 |
| Cholesterol | 295 |
| Urea | 18 |
| Total protein | 5·4 |
| A G ratio | 2·8 : 1 |

Necropsy

Necropsy was performed 18 hours after death. The body was that of a wasted male child, weight 5·0 kg. (10 lb. 4 oz.) and height 63 cm. (25½ in.). The upper and lower incisor teeth had erupted. The facial and thoracic asymmetry were not so noticeable as in life.
Cardiovascular System. The heart weighed 55 g. (expected weight 30-40 g.), and there was moderate left ventricular hypertrophy. The remaining chambers and all valves were normal. The foramen ovale and the ductus arteriosus were closed. The coronary arteries and myocardium were normal on section, as was the pericardium. No atheroma or calcification was seen in the aorta.

Respiratory System. There was no infection of the middle ears or tonsils. The trachea and main bronchi were normal. There was patchy bronchopneumonic consolidation of both lower lobes, with moderate congestion of the rest of the lungs, but no evidence of calcification.

Alimentary System. The mouth, pharynx, oesophagus, stomach and small intestine were normal. There were hard, constipated faeces in the transverse, descending and pelvic colon.

The liver (250 g.) was soft and rather pale, and the cut surface suggested fatty change. The gall-bladder was normal, and the bile and cystic ducts were patent. The spleen (16 g.) and pancreas were normal.

Urogenital System. The kidneys together weighed 35 g., and the capsules of both stripped easily leaving a smooth surface. No grittiness was felt on section, and there were no visible calcium deposits. The cortex and medulla both presented a normal appearance. The renal pelves, ureters, bladder, urethra and prostate were normal.

The left testis was in the scrotum and the right testis in the inguinal canal.

Endocrine System. The neck organs were removed en bloc and fixed, and a careful dissection was subsequently made in a search for parathyroid glands. Some 20 small pieces of tissue from this region were sectioned, but only two small pieces of parathyroid tissue were found. No other parathyroid tissue could be identified. The thyroid and suprarenal glands were normal.

Central Nervous System. The brain, spinal cord, and meninges all appeared normal.

Skeletal System. The base of the skull did not appear thickened to the naked eye, and the lower jaw, which was removed, appeared normal. The shaft of the right femur showed definite thickening of the dense cortical bone. No other abnormalities were seen in the other bones examined.

Histology

Material and Methods. Material was taken from the heart, aorta, tonsil, lung, stomach, intestine, liver, pancreas, spleen, kidney, testis, suprarenal, thyroid, parathyroid, thymus, pituitary, brain, spinal cord, upper and lower jaw, base of skull, femur, ribs and voluntary muscle. It was fixed in 10% formal saline. Blocks of kidney were also fixed in cold acetone and embedded in low melting point wax for phosphatase estimations. Bone was decalcified in 20% formic acid.

Haematoxylin and eosin were used for routine staining, and in addition alizarin red, purpurin and xanthopurpurin stains, Von Kossa's method, and the gallamine method of Stock (1949) for calcium; ferri- and ferro-cyanide methods for iron; the azo-dye coupling method of Pearse (1953) using the salt of 4-chloro-o-dianisidine for alkaline phosphatase; and the periodic-acid-Schiff stain, picro Mallory stain, and elastin stain of Weigert for general renal pathology. Sudan IV and Sudan black B were used as fat stains on frozen sections.

The thyroid gland was serially blocked in a further unsuccessful search for parathyroid tissue.

Kidney. Glomeruli are present in normal numbers, and about 90% are normal histologically. In the remaining 10%, the principal abnormality is the deposition of hyaline material in glomerular tufts, in some situations diffusely throughout the tuft, and in others localized to one or more lobules (Fig. 4). Certain tufts have been almost completely replaced by hyaline material. Although some hyaline change may normally be seen in kidneys at this age, these findings were considered to be excessive. Occasional epithelial crescents derived from the parietal layer of Bowman's capsule are present (Fig. 5). There is no glomerular calcification.

While some convoluted tubules are normal, others show severe changes, and it is not always possible to differentiate proximal from distal tubules. Vacuumolysis of proximal tubule cells results in partial or complete occlusion of the lumen in places (Fig. 6). The vakuolysis failed to stain with fat stains, with the periodic-acid-Schiff (P.A.S.) method, or with any of the methods for calcium. The distal and collecting tubules contain eosinophilic hyaline casts, which stain red with P.A.S., and basophilic material, which stains positively with the gallamine stain for calcium (Fig. 7) but does not give a positive stain for iron. In certain situations the epithelium of the tubules is destroyed, while in others a layer of regenerating epithelium extends over the hyaline casts (Fig. 8). Calcified material has been extruded into the interstitial tissues of the cortex from the distal tubules (Figs. 9 and 10). A fibrous reaction has been stimulated in these situations, and in the medullary (but not in the cortical) tissues is associated with occasional giant cells. There are no chronic inflammatory cells. The loops of Henle are compressed by a moderate interstitial fibrosis, but are not otherwise greatly altered. A few small collections of lymphocytes are found beneath the renal capsule. There are no inflammatory changes in the renal pelvis. Renal arteries and arterioles are normal. Sections stained for alkaline phosphatase show no constant relationship between sites of phosphatase activity and calcium deposition.

The calcified material in the tubules stains best with gallamine; staining with von Kossa's method is inconstant, and stains for iron are also negative. On the other hand material which has been deposited in the interstitial tissues of cortex or medulla stains readily with
IDIOPATHIC HYPERCALCAEMIA IN AN INFANT

Fig. 4.—Glomerulus showing a moderate degree of hyaline change. (Haematoxylin and eosin. × 380.)

Fig. 5.—Glomerulus showing epithelial crescent. (Haematoxylin and eosin. × 500.)

Fig. 6.—Proximal convoluted tubule showing vacuolation of the tubular cells. (Haematoxylin and eosin. × 500.)

Fig. 7.—Collecting tubule showing calcium deposit in lumen of tubule. (Stock's gallamine method. × 500.)

gallamine and with ferri- and ferro-cyanide methods for iron (Fig. 11). At no time could any positive staining be obtained with purpurin, xanthopurpurin or alizarin red (Cameron, 1930).

Lungs. There is an organizing pneumonic process around fat droplets, which are almost certainly inhaled milk. There is no calcification present in any of the sections examined.

Skeletal Tissues. Femoral and tibial epiphyses and costal cartilages are normal. The shaft of the femur shows a moderate increase in bony thickness when compared with an infant of the same age group, but the
bone structure is normal. Sections from the base of the skull suggest some thickening but again show normal bone structure.

Sections of the jaws and teeth show normal development and normal calcification of deciduous molars. An unusual and abnormal feature is calcified areas in the pulp of the lower central incisors (Figs. 12 and 13).

**Endocrine Glands.** The two small pieces of parathyroid tissue show a completely normal structure. The pituitary has not been serially sectioned but there is no indication of a disturbance in the customary ratio of chromophil to chromophobe or acidophil to basophil cells in the sections examined.

The remaining tissues examined are normal. There
is no evidence in the stomach or elsewhere of metastatic calcification.

**Discussion**

Butler, Wilson and Farber (1936) described renal lesions in children with hypercalcaemia and acidosis. They saw calcium deposits between the basement membrane and epithelial cells of collecting tubules, a few deposits in proximal tubules, degeneration of tubular epithelium and calcified deposits surrounded by fibrosis and giant cell infiltration around affected tubules. Their cases appear to belong clinically to the renal acidosis group or possibly to the transient and benign group of idiopathic hypercalcaemia which may sometimes show acidosis. Govan (1950) described hyalinized glomeruli, vacuolation of proximal tubular epithelium, calcified casts in distal and collecting tubules, and deposits of calcium associated with fibrosis in the surrounding tissues in a case of renal acidosis in a girl of 29; death may have been complicated by sensitivity to sulphonamides. The histology of both of these cases is not dissimilar to our own, though there are no calcium deposits between basement membranes and epithelium in our case. Govan attributed the vacuolation of proximal tubules to possible phosphorus absorption, and we were at first inclined to think of the tubular vacuolation in our case as primary, representing a nephron nephrosis of the type seen in sulphonamide or mercury poisoning. The fact that Albright, Consolazio, Coombs, Sulikowitch and Talbott (1940) and Albright, Burnett, Parson, Reifenstein and Roos (1946) postulated a primary tubule defect in infantile renal acidosis, often associated with hypercalcaemia, seemed to support this possibility. Further study has changed this view.

Large amounts of calcium-containing material in distal and collecting tubules justifies acceptance of the view that calcium precipitates out as the filtrate becomes concentrated, and that the interstitial fibrosis and probably the tubular epithelial degeneration are secondary to the extrusion of calcium into surrounding tissues. The positive staining for iron as well as calcium in extratubular but not intra-tubular material supports this view (Cameron, 1952). Vacuolation of proximal tubules need not be primary, but occurs under appropriate osmotic conditions (Allen, 1951) which may well obtain here. Hyaline glomerular changes, besides occurring normally in infancy, have been described as secondary to hypercalcaemia (Dent, Flynn and Nabbro, 1953). In the case of Paul D. no cause for a primary nephron nephrosis was found. On balance it is considered that the renal changes are to be regarded as secondary manifestations of hypercalcaemia, a view which would explain the similarity of lesions in renal acidosis and a severe and prolonged hypercalcaemia.
which are clinically, radiologically and biochemically distinct.

Lowe et al. (1954) describe the results of renal biopsy in a child presenting clinical features similar to Paul D. Their findings resemble those in our case in the nature of the cortical and medullary changes, but differ in the presence of a granulomatous reaction around calcium deposits in the medulla as opposed to the cortex and in the presence of many abnormal glomeruli. It cannot be claimed that histological studies have as yet provided conclusive positive evidence concerning the aetiology of idiopathic hypercalcaemia in infancy. Increased alimentary absorption of calcium must be accepted as a possible explanation. If this be the explanation the facts concerning our case lend no support to the view that sensitivity to vitamin D may have been a contributory factor. Excessive intake of alkalai has been suggested as having a bearing on aetiology. The child, the subject of this paper, did receive alkalai in considerable amounts but not until symptoms had already become established. Alkalai may have had an aggravating effect but cannot be regarded as having any aetiological significance. Abnormal histological changes in bone and metastatic calcification were found in a case resembling that of Paul D. in other respects (Baar, 1954). The absence of such findings in the present case cannot be explained.

Summary

A case of idiopathic hypercalcaemia of a severe and prolonged type in a boy was studied clinically and at necropsy.

Clinical and biochemical findings included failure to thrive, lassitude, generalized hypotonia, irregular pyrexia, hypertension with a pronounced cardiac murmur, cranio-facial asymmetry and excessive irregular deposition of bone. Serum calcium, blood cholesterol and blood urea levels were raised, and there was evidence of renal impairment.

Histological findings in the kidneys included deposition of calcium in and around distal and collecting tubules, vacuolation of proximal tubule cells and hyaline glomerular changes. Abnormal histological changes in the bones were not seen. There was no evidence of metastatic calcification. An unexplained feature was calcium deposits in the pulp of certain incisor teeth. The parathyroid glands were normal.

Renal changes are regarded as secondary to hypercalcaemia, which it is suggested may have resulted from excessive absorption of calcium by the alimentary tract.

We are grateful to Professor F. S. Fowweather, Professor R. A. Willis, and Dr. W. Goldie of Leeds, and Dr. W. W. Payne of London, for help and advice; to the nursing staff of Princess Mary Ward, Leeds General Infirmary, for their cooperation in clinical observations; to Mr. W. H. Lawson for the photomicrographs, and to Mr. D. F. High for technical assistance.

We are particularly indebted to Professor T. T. Read of the School of Dentistry, Leeds, for his advice and opinions and also for Figs. 12 and 13.

References


