

CYSTINOSIS

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The relationship between some cases of so-called renal rickets and disturbances of cystine metabolism was first suggested by Lignac (1924) who described the case of a 3-year-old boy dying with severe rickets and dwarfism. There was a preceding history of polyuria and glycosuria. Post-mortem examination revealed the presence of aggregations of cystine crystals throughout many organs particularly those of the reticulo-endothelial system and the kidneys. Lignac (1937, 1938) subsequently reported two very similar cases, in a boy of 2 years and a girl of 14 months. Cystine stones were discovered in the latter's renal tract as well as diffuse cystinosis of the body tissues. Details of these cases are shown in Table 1.

Russell and Barrie (1936) described two and possibly three further cases which are the only ones in the English literature. Their first was a girl who died at the age of 12 years having suffered from renal rickets since infancy. Glycosuria had been found repeatedly and had been shown to be renal. She eventually died from renal failure. The second was a boy dying at 16 years, also from renal failure, who had been treated in early childhood for rickets. In neither case was there enlargement of the liver or of the spleen. At necropsy cystine crystals were found throughout the reticulo-endothelial system and the kidneys showed glomerular destruction, tubular atrophy and interstitial fibrosis. A severe case of cystinosis was described by Beumer and Wepler (1937). This was a boy who died at 17 months of age from marasmus and rickets. During life hepatosplenomegaly had been noted as well as a renal type of glycosuria.

A most valuable contribution to the subject has been made by Hottinger and his colleagues in Basle (Hottinger, 1941; Roulet, 1941; Bürki, 1941; Esser, 1941; Freudenberg, 1941) who described a boy whom they followed from the age of 20 months to his death at 7½ years. He presented at first with rickets, dwarfism and a renal type of glycosuria. At the age of 7 years the liver and spleen were enlarged and the corneae were seen to be hazy.

Slit lamp and later biopsy examination showed this to be due to the deposition of refractile cystine crystals in the cornea and conjunctiva. The diagnosis of cystinosis was further confirmed during life by the finding of cystine crystals in a smear of the sternal marrow.

In 1936 Fanconi published his important paper on a type of osteodystrophy associated with renal glycosuria, aminoaciduria and hypophosphataemia. These findings were interpreted as being evidence of a renal tubular dysfunction. He described three cases of this syndrome, the first of which was a girl who died at the age of 5½ years with rickets and dwarfism. At necropsy it was noted that the cells of the renal tubules had the appearance of having been packed with a substance which had been dissolved out during the process of fixation either by water or alcohol. Sturzenegger (1939) has suggested that this substance might well have been cystine. Fanconi's third case was a girl of 2½ years who presented with rickets and malnutrition and was found to pass both sugar and organic acids in the urine. This child was kept under observation until her death (in 1939) at the age of 8 years from renal failure with an enlarged liver and spleen (Fanconi, 1946). Post-mortem examination revealed extensive cystinosis throughout the body. In his 1946 paper Fanconi described another case of cystinosis occurring in a girl aged 1 year in whom the diagnosis was made during life by marrow examination and confirmed by necropsy. In his most recent paper on the subject (Fanconi and Bickel, 1949) he reported the case of a 14-month-old girl exhibiting the clinical features of the 'Fanconi syndrome' whose marrow had been found to contain cystine crystals. Very similar to this case is the little boy described by d'Avignon and Vahlquist (1949) who again showed the clinical features of the Fanconi syndrome. The authors failed to demonstrate cystine crystals in the marrow but based their diagnosis on the observation of crystalline deposits in the cornea and conjunctiva exactly resembling those described by Bürki in Hottinger's case. Hottinger (1947) has also

reported a second case of cystinosis. The patient, a boy of 1 year, presented with severe hypophosphataemic rickets and died suddenly from an apparently slight respiratory infection. An older child, who is still alive in spite of progressive renal failure, has been described by Ullrich (1948) who made the diagnosis of cystinosis on the finding of crystalline deposits in the conjunctiva, cornea and iris. A remarkable feature of this case is the family history. The patient is the sole survivor of eight siblings, six of whom have died of symptoms suggestive of cystinosis.

Freudenberg (1949) quotes Schmidt who states that one of the two children reported by Pache (1940) had died at the age of $7\frac{3}{4}$ years and that cystinosis was found after death. These two children, who were brother and sister, both showed marked rickets and dwarfism associated with cystinuria, but cystinosis was not demonstrated during life. The other child, the sister, has also died but no record of necropsy is available.

Finally Roulet (1941) has argued that a case described by Benoit (1938) as *calcinosis universalis* was probably one of cystinosis. The child, a boy of $3\frac{3}{4}$ years, suffered from severe malnutrition and rickets. At necropsy the tissues were found to contain large numbers of translucent, polygonal crystals which Benoit considered to be calcium but which Roulet has shown might well have been cystine.

In addition to the 16 cases mentioned above in which rickets and dwarfism were shown to be associated with cystine deposition in the tissues, two further cases have been reported in which cystinosis was discovered after death without there being any definite preceding history of rickets. The first of these was a boy who died at the age of 21 months of inanition and was reported by Abderhalden (1903). Kaufmann (1929), who did the necropsy on this case, described the deposition of cystine crystals in the body tissues. Rössle's (1938) case died of renal failure, and extensive deposits of a substance believed to be cystine were found throughout the body.

Table 2 lists five cases of cystinuria in children where a diagnosis of cystinosis has been suggested but not proved. Three of these cases had clinical hypophosphataemic rickets while a fourth died of renal failure.

Case Report

Jacqueline R., aged $7\frac{1}{2}$ years, was admitted to The Hospital for Sick Children, on August 20, 1948. The history indicated that she had been an apparently normal child until the age of 3 years. Pregnancy and labour had been normal; her birth weight was 8 lb. 10 oz.

She was breast fed for the first six months when mixed feeding was begun. The usual vitamin supplements were added to the diet from the age of 1 year. She was a little late in passing the developmental milestones, standing at 11 months and walking at 17 months. She cut her first tooth at 1 year and had a complete set at 2. She had measles at the age of 3 years.

At the age of $3\frac{1}{2}$ years she was taken to another hospital on account of irritability, anorexia and apathy. No bony abnormalities were noted and no radiographs were taken but a diagnosis of rickets was made and she was given vitamin D tablets and ultra-violet light. There was a steady improvement in her condition and she was discharged after attending for 15 months.

When she was 5 years old she started school and was found by the medical officer there to be undersized. She was admitted to a second hospital for investigation. There the dwarfism was confirmed, the weight being only 25 lb. The intelligence seemed normal. There was epiphyseal thickening and she stood with the knees in the valgus position. The eyes appeared normal except that 'very early choroidal atrophy at the periphery of the retina' was noted. The blood pressure was 100/65. The liver and spleen were not palpable. The urine had a specific gravity which varied between 1010 and 1020, and contained small amounts of albumin. No glycosuria was discovered in five examinations. Investigation of the blood chemistry gave the following results: blood calcium, 7.6 mg. per 100 ml. of serum; blood phosphorus, 7.5 mg. per 100 ml. of plasma; blood urea, 175 mg. The alkali reserve was 28.7 vols. of CO₂ per 100 ml. of serum. The serum protein level was 7.8 g. % (albumin 5.0 g., globulin 2.0 g.).

A diagnosis of renal rickets was made and she was discharged. She remained fairly well during the following year except that the knock-knee deformity increased considerably.

One year before admission, when she was 6 years old, she had what appears to have been her first attack of typical carpo-pedal spasms. She had three further attacks during the subsequent six months. Twice weekly calcium gluconate injections and large doses of radiostoleum were given. The appetite had been poor for some time. Thirst was stated to be excessive since infancy but less so during the last six months. Five days before admission she developed a sudden attack of diarrhoea with occasional vomiting and on the preceding day she became drowsy and developed rapid, deep respiration.

Both parents are healthy. Jacqueline was the first of three children. The second died of 'stoppage of the bowel' at the age of 9 months, and the third, a girl of 3 months, is well. There was a stillbirth two years before.

Examination showed her to be a normally intelligent but drowsy little girl with considerable dwarfing and deformity (height $34\frac{1}{2}$ in., weight 24 lb. 12 oz.). She was afebrile and had deep and rather rapid respirations. The skin was dry and coarse and of an earthy pallor. There were a few scattered ecchymoses. The hair was very fine. She suffered from considerable photophobia and kept her eyes screwed up in all but the dimmest

TABLE
RECORDED CASES

Case	Author	Sex	Age at Onset	Family History	Rickets	Dwarfism	Eye Changes	Liver	Spleen	B.P.	Blood		
											Alkali Reserve (Vol. of CO ₂ %)	N.P.N. (mg.%)	Ca. (mg.%)
1	Lignac (1924a)	M.	1 yr.	—	++++	+	—	o	o	—	—	—	—
2	Lignac (1924b)	M.	18 mo.	?+	++++	—	—	—	—	—	—	—	—
3	Lignac (1924c)	F.	?	—	+	—	—	—	—	—	—	—	—
4	Benoit (1935) Roulet (1941)	M.	?	—	++++	++	—	—	—	—	—	—	—
5	Russell and Barrie (1936a)	F.	14 mo.	?+	++++	++	o	—	o	+	—	(34)	9·7
6	Russell and Barrie (1936b)	M.	18 mo.	o	++	?	o	o	+	+	—	—	—
7	Fanconi (1936) Sturzenegger (1939)	F.	3 mo.	o	++++	++	—	o	o	—	—	40 83	—
8	Beumer and Wepler (1937)	M.	9 mo.	o	++++	+	o	o	o	—	—	26 98	—
9	Pache (1940b)	M.	8 mo.	+	++++	++	o	—	—	+	—	23	10·8
10	Hottinger (1941)	M.	1 yr.	+	++++	++	Conjunctival and corneal deposits	+	+	—	—	29 129	11·5 5·1
11	Fanconi (1946a)	F.	1 yr.	+	+++	+	o	+	o	$\frac{80}{40}$	32	39 214	9·87
12	Fanconi (1946c)	F.	Birth	?	+++	+	o	o	o	$\frac{120}{70}$	46	39 93	10·2
13	Hottinger (1947)	M.	10 mo.	o	++++	o	o	+	+	—	—	—	7·5
14	d'Avignon and Vahlquist (1949)	M.	9 mo.	o	++++	++	Conjunctival and corneal deposits	o	o	—	12·25	32	12·4
15	Fanconi and Bickel (1949b)	F.	14 mo.	+	+	++	o	+	o	$\frac{105}{65}$	34	21	9·0 11·0
16	Ullrich (1948)	M.	1 yr.	++	+++	++	Photophobia. ? Deposits in conjunctiva, iris and cornea	+	—	$\frac{120}{65}$	—	78 135	6·7 4·6
17	Aberhalden (1903) Kaufmann (1929)	M.	—	+	—	—	—	—	—	—	—	—	—
18	Rössle (1938)	F.	2 yr.	—	—	+	—	o	o	—	—	—	—

Where more than one value is reported the figures given represent the extremes.

TABLE
RECORDED CASES OF CYSTINURIA WITH

Case	Author	Sex	Age at Onset	History	Rickets	Dwarfism	Eye Changes	Liver	Spleen	B.P.	Blood		
											Alkali Reserve (Vol. of CO ₂ %)	N.P.N. (mg.%)	Ca. (mg.%)
1	Russell and Barrie (1936c)	M.	4 yr.	—	o	o	Photophobia. Retinitis	o	o	$\frac{240}{170}$	—	(126)	—
2	van der Zijl and Heslinga (1940)	M.	—	o	—	+	o	o	o	—	—	—	10·2
3	Pache (1940a)	F.	8 mo.	+	++	+	o	—	—	$\frac{90}{70}$	—	30	9·4 11·8
4	Lelong (1938) Fanconi (1936)	F.	4 mo.	o	+	+	o	+	o	$\frac{70}{?}$	35	55	8·0 9·5
5	Van Creveld and Grunbaum (1941)	M.	14 mo.	+	++	+	o	+	+	—	34	28	10·8

Where more than one value is reported the figures given represent the extremes.

1
OF CYSTINOSIS

P. (mg. %)	Phosphatase (units)	Urine					Outcome	Age at Death	Evidence of Cystinosis
		Reaction	Alb.	Sugar	Amino- acids	Cystine			
-	-	Acid	+	+	-	-	Died of acidosis and vomiting	3 yr.	At necropsy
-	-	-	+	o	-	-	Died of urinary infection	2 yr.	At necropsy
-	-	-	-	-	-	-	Died Hydrocephalus	14 mo.	At necropsy cystinosis, cystine calculi
-	-	-	-	-	-	-	Died of tetany	3½ yr.	At necropsy ? cystinosis
2.7	-	-	+	+	-	-	Died of uraemia and hypertension	12 yr.	At necropsy
-	-	-	++	o	-	-	Died. ? Uraemia and hypertension	16 yr.	At necropsy
-	-	-	++	++	-	-	Died	5½ yr.	At necropsy ? cystinosis
-	-	-	++	++	-	-	Died of uraemia and marasmus	-	At necropsy
3.9	-	Acid	+	o	-	+	Died of uraemia	7½ yr.	At necropsy
7.2	-	-	++	+	+	o	Died of uraemia and tetany	7½ yr.	Cystine deposits in sternal marrow. At necropsy cystinosis
9.4	-	-	-	-	-	-	-	-	-
2.3 12.3	18	Neutral	+	o	+	100 mg. daily.	Died of renal failure	8 yr.	At necropsy
3.0	7	Alkaline	+	o	-	+	Died of gastro-enteritis and pneumonia	3½ yr.	Cystine deposits in sternal marrow. At necropsy cystinosis
2.38	-	Neutral	+	o	-	-	Died of slight respiratory infection	1 yr.	At necropsy
3.6 4.2	12	Neutral alkaline	+	+	+	o	Improving Treated vitamins A, D and citrates	-	Diagnosis on eye signs. Sternal marrow negative
2.0	5	Neutral acid	+	+	+	o	Alive	-	Cystine deposits in sternal marrow
4.9	-	Acid	++	o	-	-	Alive aged 12 years. Renal failure	-	Diagnosis on eye signs
-	-	-	-	-	-	-	Died of inanition	1½ yr.	At necropsy.
-	-	-	-	o	-	-	Died in coma	4 yr.	At necropsy diffuse crystalline deposits, probably cystine

() = Figure expressed as blood urea. + = Positive finding. o = Negative finding. - = Finding not recorded.

2
SUGGESTED DIAGNOSIS OF CYSTINOSIS

P. (mg. %)	Phosphatase (units)	Urine					Outcome	Age at Death	Evidence of Cystinosis
		Reaction	Alb.	Sugar	Amino- acids	Cystine			
-	-	-	++	-	-	+	Died of uraemia	13 yr.	Cystine calculus removed at 4 years. Biopsy, early nephritis. Necropsy, chronic nephritis, no cystinosis
6.3	-	-	+	o	+	+	Alive aged 12	-	-
2.97 4.1	-	Acid alkaline	+	o	-	9 mg. daily.	Died	8 yr.	No record of necropsy
3.75	7.7	-	++	+	+	+	Died. Pyrexia and constipation	5½ yr.	No necropsy
1.9 2.8	12 34	Neutral alkaline	+	o	+	+	Alive aged 5	-	-

() = Figure expressed as blood urea. + = Positive finding. o = Negative finding. - = Finding not recorded.

lights. There was some thickening of the palpebral margins. The corneae were noticed to be clouded and the retinae showed a diffuse black and white reticulation. A more careful examination was made by Mr. J. H. Daggart who reported:

'Both corneae show innumerable punctate opacities in the superficial layers. There is no breach of the surface. Both fundi show widespread choroido-retinal degeneration with partial consecutive optic atrophy.' The tongue was moist with a little brown fur posteriorly. There was gross dental caries. The throat was clean and the tonsils appeared healthy. The lungs seemed normal except for some fine crepitations at the right base. The heart was slightly enlarged but the sounds were normal. The blood pressure was 155/90. The liver and spleen were both enlarged to about three finger-breadths below the costal margins and were firm and smooth but not tender. No enlarged lymph nodes

were palpable. Examination of the skeletal system showed slight frontal bossing of the skull which had a circumference of 19½ in. Some bossing was noted at the costochondral junctions. The spine was normal. Valgus deformity was present at both elbows. The lower ends of the radius and ulna were thickened and there was some ulnar deviation at the wrists. The knees and to a lesser extent the ankles showed valgus deformity.

Pathological investigations showed: haemoglobin 38% (Sahli) 5.2 g. per 100 ml.; red blood cells 1.82 million per c.mm.; leucocytes 12,300 per c.mm. (polymorphs 64%, lymphocytes 33%, eosinophils 3%); platelets 220,000 per c.mm. The blood Wassermann and Kahn reactions were negative.

Blood analysis gave: urea, 229 mg. per 100 ml. blood; protein, 6.3 g. per 100 ml. plasma; calcium, 4.9 mg. per 100 ml. serum; phosphorus, 8.4 mg. per 100 ml. serum; potassium, 11.2 mg. per 100 ml. serum; chloride, 628 mg. per 100 ml. serum; bicarbonate, 27 vols. CO₂ per 100 ml. plasma. The alkaline phosphatase was 29.6 King-Armstrong units.

The urine was acid, with a specific gravity of 1009. An Addis count gave: protein, 500 mg. % per 24 hours; red cells, 7,265,000; leucocytes, 21,311,000; casts, 84,000.

Analysis for the presence of cystine showed 1.1 mg. per 100 ml. The urinary output varied from 14 to 26 oz. per day but accurate

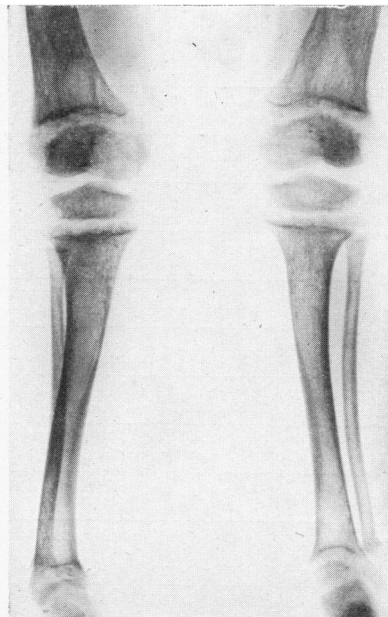


FIG. 1.—Radiograph showing both knees and ankle joints. Note thin cortex and osteoporosis, also enlarged and woolly metaphyses with cupping at the distal end of the tibia.

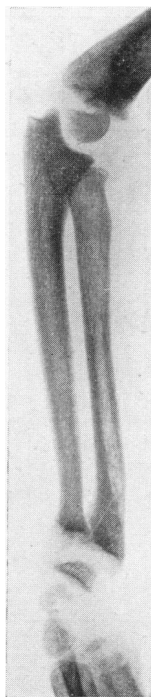


FIG. 2.—Radiograph of left forearm showing similar changes.

measurement was only occasionally possible owing to incontinence.

An x-ray report (Dr. L. G. Blair) stated: 'Marked and extensive rachitic changes in the long bones (Figs. 1 and 2). No abnormality in the skull. The heart is enlarged; lung fields congested: bilateral minimal pleural effusions.'

In view of these findings a diagnosis of renal rickets with uraemia was made though the possibility of cystinosis was later considered. The child was treated with 30 ml. of a mixture containing sodium citrate 100 g., citric acid 60 g., water 1,000 ml., in four-hourly doses. She also received large doses of calcium lactate and vitamin D. A small blood transfusion was also given. In spite of these measures the child's condition steadily deteriorated. She developed heart failure with oedema, ascites, and bilateral pleural effusions, and increasing uraemia. She died on

September 17, 1948.

A post-mortem examination by Dr. Martin Bodian showed that the body was that of a stunted and wasted child with moderate oedema.

There was slight frontal bossing of the skull. Whitish deposits were found on the pia arachnoid membrane, especially along the sagittal edge of the occipital and parietal lobes. The brain was normal. The tonsils were enlarged, and on section showed a greyish-white finely reticular pattern.

There were bilateral small pleural effusions. The fluid contained hexagonal and rod-shaped crystals. In the lungs were pinpoint subpleural deposits of shimmering white material, some pulmonary oedema and lobular consolidation. There was some pericardial effusion. The fluid resembled that found in the pleural cavities. The visceral pericardium appeared frosted. There was some hypertrophy and dilatation of the left ventricle. There was a small amount of ascites in the abdomen, and the fluid again contained crystals. Numerous chalky patches were seen on the parietal peritoneum and greater omentum.

The liver was enlarged, pale and smooth. Beneath the serosa there was a punctate, fern-like pattern of silvery-white deposits uniformly distributed throughout the whole surface. These were less noticeable on cut section.

The gall-bladder and pancreas were normal. The spleen was enlarged and salmon pink.

There were two or three circular white plaques on the surface. On section the normal markings were replaced by a finely linear and punctate silvery-white pattern interspersed with pale brown areas on a salmon pink background.

The suprarenals were normal.

The kidneys were very small and firm with numerous small cortical cysts. On section the normal pattern was completely lost. The cortex was very thin and there were radially directed linear markings of pale cream colour in the medulla.

There were small white specks on the mucous membrane of the stomach and small intestine.

The reproductive organs were normal.

Four parathyroid glands were discovered and considered normal in size and shape.

Lymph nodes were enlarged and pale, containing opaque white deposits.

There was broadening and heaping up of the epiphyseal plates. The red bone marrow contained bright yellowish streaks and flecks of chalky material. The sternum contained only four small islands of marrow.

Histology. There was a widespread deposition of double refractile crystals within the cells of the reticulo-endothelial system. There was no foreign body giant cell reaction to the presence of these crystals, which were found in the choroid, iris and cornea of both eyes, in the duodenum and caecum within phagocytes, in the liver in Kupffer cells and within phagocytes in the portal areas, in the medullae of the adrenals, in the spleen and in numerous lymph nodes, in the medullae of both kidneys, in the urinary bladder and in one section of femur. These crystals were identified as cystine by x-ray crystallographic analysis. There was extensive destruction of the nephrons as well as marked changes in the renal vessels attributable to gross renal destruction. Changes observed in the bones were consistent with renal rickets.

Discussion

The diagnosis of cystinosis depends on the demonstration of cystine crystals in the tissues. In 13 of the recorded cases this was shown at necropsy, the diagnosis not having been suspected during life. In these cases cystine crystals were found throughout the body, notably in the organs of the reticulo-endothelial system and in the kidneys. In only five reported cases has the diagnosis been made during life. In Hottinger's (1941) first case the corneae were hazy due to the presence of large numbers of minute refractile crystals in the cornea and conjunctiva. Histological examination at a later date showed these crystals to be cystine (Bürki, 1941). Ullrich (1948) and d'Avignon and Vahlquist (1949) have used similar clinical observations in their cases to substantiate the diagnosis of cystinosis. In our patient an almost identical appearance was seen in the cornea but conjunctival deposits were not observed. The

retinal changes have not been previously described. Russell and Barrie (1936) mention retinitis in their third case but this was probably albuminuric in type.

An interesting symptom observed in our case was marked photophobia. This symptom is emphasized by Ullrich and the photograph of Hottinger's first patient (Bürki) would suggest a similar occurrence. It is conceivable that the presence of refractile crystals in the cornea might increase the dazzle effect produced by bright lights. Bürki recommends the use of a slit lamp as an aid to diagnosis in all cases of renal osteodystrophy.

A somewhat easier means of establishing the diagnosis of cystinosis during life seems to be the examination of smears of bone marrow. In cystinosis large reticulum cells containing refractile cystine crystals may be observed. This finding was first described by Esser (1941) in Hottinger's first case and observed again by Fanconi (1946) in his third case and by Fanconi and Bickel (1949). d'Avignon and Vahlquist, however, were unable to demonstrate cystine crystals in the small amount of marrow aspirated from the tibia in their case and we were unable to obtain any marrow from the sternum in ours. At necropsy it was seen that the sternal marrow had become confined to four small islands. It is unfortunate that the procedure of iliac crest puncture was not being practised at that time. The diagnosis of cystinosis might also be established by means of biopsy of some suitable tissue, for instance a lymph node. In Russell and Barrie's third case a biopsy was taken from the renal cortex at the time of operation for removal of a cystine calculus but no evidence of cystinosis was demonstrated. In this connexion it is important to remember that cystine is soluble in the ordinary fixatives such as formalin, used in the preparation of histological sections (Roulet, 1941). All biopsy and post-mortem material should be fixed in alcohol only. In our case the examination of the fluid which had collected in the various serous cavities would presumably have confirmed the diagnosis.

The finding of increased amounts of cystine in the urine does not in itself justify the diagnosis of cystinosis. Cystinuria has been demonstrated in only four of the described cases. In our case the single estimation gave a value only slightly in excess of normal. On the other hand several of the cases of cystinosis have a family history of cystinuria. Lewis (1932) examined 10,500 healthy students and found cystine crystals in the urines of four, while a further 14 gave a strongly positive reaction to tests for cystine. According to Linder (1944)

approximately 10% of cystinurics develop cystine calculi in the renal tract. Table 2 gives details of five cases from the literature in which cystinuria has been found to be associated with either rickets or dwarfism and a diagnosis of cystinosis has been suggested. Three of these have died. In two of them necropsy was either not performed or not reported, while the third showed no evidence of cystinosis. The fate of the other two has not been reported and without further evidence it seems wrong to include any of these as cases of cystinosis. Of a milder nature are the two cystinuric sisters reported by Hickmans and Smallwood (1935) who had associated albuminuria, and, though not dwarfed, are described as being slender and delicate.

The clinical picture of cystinosis may perhaps be divided into three stages. These stages are not sharply delimited and usually overlap one another considerably. Up to the age of about 2 years the child fails to thrive. There may be a tendency to excessive reaction to infection or intoxication with undue thermolability, dehydration and constipation. Examination will show an underweight infant whose urine is alkaline and contains albumin and perhaps a little sugar. In spite of the urinary reaction the alkali reserve of the blood is much reduced. The condition thus somewhat resembles the syndrome of nephrocalcinosis described by Lightwood (1935). It appears that confusion between these two conditions may also occur at necropsy. Roulet has shown that Benoit's (1935) case of calcinosis universalis was in all probability one of cystinosis. Both calcium and cystine give a positive von Kossa reaction.

The second and perhaps most important stage is clinically indistinguishable from the syndrome described by Fanconi (1931), De Toni (1933), and Debré, Marie, Cléret and Messimy (1934) and called by the first author amino-diabetes. McCune, Mason and Clarke (1943) give a detailed analysis of cases of this syndrome reported before 1943, and of the 40 cases included seven had cystinosis. The characteristic features of this stage are rickets and dwarfism associated with excessive thirst, polyuria and certain biochemical disturbances. The urine, which is usually alkaline, has a low specific gravity and contains a small to moderate amount of albumin, large quantities of phosphates, amino-acids and occasionally sugar. The study of the various amino-acids excreted has been aided recently by the introduction of partition chromatography. Examination of the blood shows a normal calcium level but reduced phosphorus. The level of the alkaline serum phosphatase may be slightly raised. The blood urea is normal. The fasting blood sugar is normal

but there may be a diabetic type of response to the administration of glucose. Radiologically the changes differ from those seen in ordinary vitamin D deficiency rickets. There is rarefaction of the bone structure and widening of the epiphyseal line without any proliferation of osteoid tissue. Nor is there any increase in the distance between the epiphysis and the metaphysis. According to Fanconi (1946) these findings resemble those seen in Gaucher's disease and certain chronic anaemias.

The final stage is one of renal failure with uraemia and hypertension. The level of the serum phosphorus rises while that of the calcium falls so that several of the children have suffered from tetany. At this stage there may be some enlargement of the liver and spleen. The clinical picture now resembles that of classical renal rickets as described by Barber (1921) and others, with the addition perhaps of hepatosplenomegaly and the appearances of cystine deposition in the eyes.

No treatment so far suggested appears to have had any markedly beneficial effect. It seems to be wise to avoid cystine- and cysteine-rich foods. Alkalies in the form of Albright's (Shohl's) mixture might help to reduce the acidosis. Large doses of vitamin D should be used to combat any superimposed deficiency rickets which is said to occur.

The prognosis is hopeless. If the child survives the first stage of thermolability he will succumb later to renal failure.

Aetiology and Pathogenesis. It is not proposed to discuss the pathogenesis and biochemical relationships of cystinosis in any detail. Our own case was unfortunately under observation for too short a time to permit relevant study.

It is evident that the condition has a genetic basis. Many of the recorded cases have a family history of either cystinosis, cystinuria or consanguinity. It is perhaps significant that eight of the cases come from Switzerland where intermarriage is relatively common.

According to Fanconi (1946) the disease is primarily one of disordered protein metabolism, there being abnormal amino-acid production following the breakdown of albumin. He postulates that the resulting albumin deficiency gives rise to retarded growth and to the characteristic osteodystrophy. The amino-acids produced are excreted by the kidneys and may be found in the urine but are at the same time nephrotoxic. Experiments by Curtis and Newburgh (1927) and others have shown that young animals fed on a diet containing large amounts of cystine develop renal lesions resembling glomerulo-nephritis. The renal damage is progressive and eventually the patient

will succumb to uraemia with contracted kidneys. As in all cases of chronic renal failure in childhood classical hyperphosphataemic rickets develops. The renal failure also tends to hold back the excretion of cystine which is already being produced in excess, with the result that it is deposited throughout the tissues especially in the reticulo-endothelial system. Freudenberg (1949) has argued that this blocking of the reticulo-endothelial system is responsible for the very poor response which these children show to 'intoxication' and infection.

An entirely different conception of the disorder is held by Debré (1946) who believes that the primary pathology is in the renal tubules.

Summary and Conclusions

The literature relating to cystinosis (cystine storage disease or Lignac's disease) is reviewed.

A case of cystinosis in a girl dying of uraemia at the age of 7½ years is described. The diagnosis had been suggested during life by the finding of crystalline deposits in the corneae. Changes in the retinae are also described. A description of the clinical features of the condition is given and the aetiology briefly discussed. The treatment of the disorder is of little value and the prognosis hopeless. It is felt that although cystinosis is undoubtedly very uncommon, cases are probably overlooked because the condition is not borne in mind.

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