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The fate of a child with primary hyperoxaluria (oxalosis)

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The case of a male child with primary hyperoxaluria type I is reported. In spite of many therapeutic trials, haemodialysis treatment for several years and renal transplantation at the age of 11 years, the patient died after the transplanted kidney had failed.

In the "Handbuch der Kinderkrankheiten" 1878, Fol 4, 3rd Section concerning the diseases of the urogenital organs, Johann Bókay Jr wrote his famous chapter about "calculi vesicae", pp. 577–628. The scientific collection of about 200 stones of the Pest Children's Hospital set up with the collaboration of medical assistant Dr. J. Neupauer, was a very important and well-known one. In fact, today the reader of Bókay's chapter is astonished about the high frequency of urolithiasis in children at that time and about the many different techniques in its tratment. Urate, oxalate and phosphate stones were seen very often, while carbonate, cystine and xanthine lithiasis also occurred but were extremely rare. Lithiasis could be found in every age, but it was mainly observed in 2 to 7 year-old children. The aetiology was mostly unknown. Nutrition and water, constitution and inheritance, severe chronic diseases and social conditions seemed to be important. Boys had three to five times more often lithiasis than girls. Stones in the urinary bladder were much more common than in the kidneys. Another fact is that this frequency of urolithiasis has disappeared in these areas, but different papers published in the last decades reported about a high frequency of urinary lithiasis in China, Philippines, Siam, India, Turkey and Syria [3, 6, 14, 18, 20, 21]. The authors found similar aetiologies as did Bókay. Black children seem to be more or less protected because there are few observations on urinary lithiasis in Africa. In European and other western countries, urinary lithiasis in children is now rare but shows other problems. One of these are the genetic disorders, the inborn errors of metabolism, which are characterized by the incapacity of the human organism to eiminate metabolites in normal quantities as a consequence of an enzyme defect, and by the necessity to deposit such metabolites in different organs e. g. in the kidney and/or extrarenally. This is also true for the disorders of oxalic acid metabolism.

Report of a Case

G. St., a boy of healthy parents was born in 1971. The father of the mother had an operation for nephrolithiasis, but is in good health now. No analysis of his concrements was made.

At the age of 8 months the patient had been hospitalized in another hospital because of a febrile disease. He had had pyuria with E. coli, creatinine 0.94–1.8 mg/dl and isosthenuria of 1006. Intravenous pyelography was normal but the isotope-nephrogram and scintigram of the kidneys showed signs which were interpreted as a congenital cystic kidney. At the age of 18 months he weighed 10.7 kg. An infusion-nephrotomogram at the age of 22 months showed many very small opaque shadows in the central region of both kidneys. Serum calcium and phosphate were normal, no acidosis was present. The nephro-calcinosis was explained as a secondary one after polycystic degeneration and chronic pyelonephritis. One year later the situation was the same with the nephocalcinosis being much more distinct.

At the age of 4 1/2 years, the patient had an examination at the Department of Paediatrics in Munich. Tonsillectomy and adenotomy were performed. A creatinine clearance of 51.4 ml/min and oxaluria were found. A biopsy of the kidney was tried without success because of the high resistance of the renal tissue. One year later urinary oxalic acid excretion was twice the normal level. The child had no hyperaminoaciduria or tubular renal acidosis, urinary pH was 5.0–5.8, creatinine clearance 33.8 ml/min. Microhaematuria and some phosphate concrements were found. The ECG was normal; there were no oxalate crystals in the bone marrow, but a discrete shadow in the lens in both eyes and an unusual pigment in the retina were found. Hyperoxaluria with renal insufficency and secondary pyelonephritis was diagnosed.

The prescribed treatment consisted of ingestion of great quantities of water, an oxalic acid-poor diet and 120 mg pyridoxin daily. At 6 3/4 years of age, creatinine clearance was 31.5 ml/min; urea 64; creatinine 1.6 mg/dl; chlorides 99 mval/l; cholesterol 231 mg/dl; uric acid 8.6 mg/dl.

In February 1979, the 7 1/2 years old boy was admitted for the first time to our Department. His data then were: weight 21.8 kg; height 122 cm; blood pressure 110/70; urea 44.4 mg/dl; creatinine 1.24 mg/dl; the urine was sterile bacteriologically; pH 5; leukocyturia, microhaematuria. Clearances (ml/min/1.73 m^3 body surface) were, creatinine 52.6; uric acid 2.6; phosphate 13.6 Concentration of oxalic acid in urine/24 h was 124 mg (= 250 mg/1.73 m^3; normal, 50 mg), respectively 272 mg; glycolic acid 50 mg (= 100 mg/1.73 m^3 = 257 mmol/mol creatinine). X-rays showed nephrocalcinosis and a bone age of 4 1/4 years. ECG: sinus tachycardia, P-pulmonale. Eyes: normal lens and cornea, many clouded pigmentations on the fundus, normal sight. Bone marrow was normal. The isotope-nephrogram and the hippuran scintigram showed a renal parenchymal lesion. Other organs without signs of stored oxalic salts. Diagnosis: Oxalosis type I.

Before the patient had been discharged we talked about the poor prognosis with the mother who was divorced from the father of the patient. She begged us to do everything for her only child. We spoke about the necessity of haemodialysis and the small hope for a kidney transplantation.

During the summer, controls were performed irregularly in another hospital. Then we found concrements in the ureter on the right side, and after another three months the boy developed renal decompensation with urea 450 mg/dl; creatinine 19 mg/dl; potassium 8 mval/l; hypertension between 110/80 and 180/125. He also had a severe anaemia: Hb 7.6 g/dl; Hk 24 vol%, and renal acidosis. Then haemodialysis was performed three times weekly and antihypertensive (diazoxide), digitalisation and symptomatic therapy were instituted. As the boy had convulsions for a few minutes after dialysis and the hypertensive

crisises became more and more critical, with respect to the planned kidney transplantation nephrectomy was performed on both sides at the age of 8 1/2 years. A few days later blood pressure decreased slowly and remained at normal values. In view of the good experience with cadaver-kidney transplantation of E. Leumann at the University Hospital for Children in Zürich (Switzerland), we asked him for such a transplantation, but the probable waiting time was more than a year, so the haemodialysis was continued two or three times weekly. Now we observed a tendency to hypocalcaemia which could be controlled by 0.5 mg 1 25 DiOH-cholecalciferol and 300 mg pyridoxin daily and only very little fluid orally. Immunologic data: HLA-phenotype A1, B8, B17, BW4, BW6, 7b. Antinuclear-factor, negative; HbsAg, positive.

Two weeks before the 9th birthday of the patient, Professor J. Brodehl from the Children's University Clinic, Hannover (GFR) found a donor kidney. Its transplantation went without complications, but the transplanted kidney failed to work. Haemodialysis was performed daily. On the fifth day after the operation a biopsy showed recent oxalosis in the kidney. One week after transplantation the grafted kidney was removed. On the next day the patient was in shock, the ECG-showed an infarction on the anterior side of the heart. The condition improved on morpine and digitalisation. The serum amylase level was high (4.543 SCE/L). Three days later a cerebral insult occurred with unconsciousness, clonic cramps and paresis of the right arm. Computer tomography showed no sign of cerebral haemorrhage. Haemodialyses were done daily. After some clinical improvement, serum levels before haemodialysis were, potassium 3.7; sodium 146; chloride 104 mmol/1; urea 24.4; phosphate 3.15; calcium 2.12 and creatinine. 6.7 mg/dl. The haemodialyses and other treatments were continued. Urea rose to 219 mg/dl, creatinine to 10.84 mg/dl. Many difficulties were encountered in finding possibilities to create a shunt; finally we implanted a Gore-tex loop.

During the next two years he continued on haemodialysis. Once a hypocalcaemic tetany occurred. In December 1980, after a haemodialysis, a new hemiparesis appeared on the left side. In March 1981, an abnormal colic crisis with hypercalcaemia

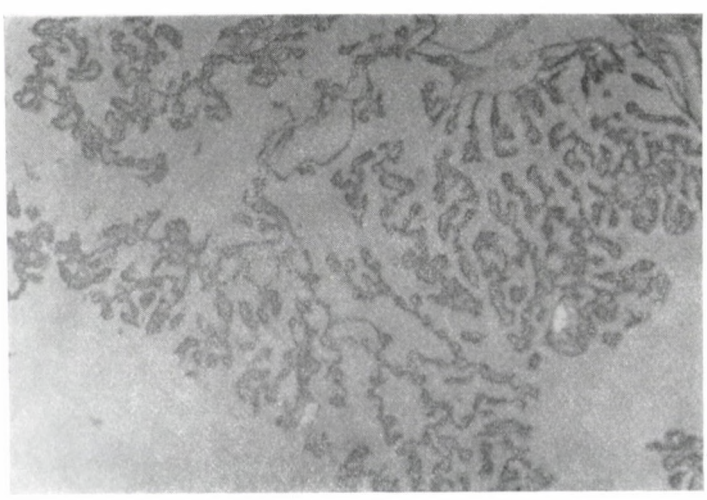


FIG. 1. Oxalate crystals in the kidney

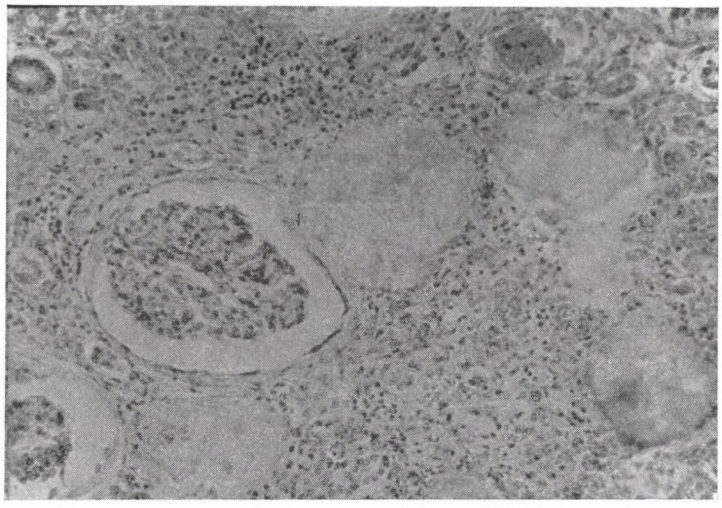


FIG. 2. Oxalate crystals in choroid plexus

of 3.6 μmol/l and muscle pains appeared in the left shoulder and arm. The hypercalcaemia was caused by overdoses of oral calcium and Rocaltrol®. After they had been discontinued, the serum calcium level became normal in 10 days. In June 1982, after a haemodialysis the boy had a third cerebral episode with convulsions, deviation of the eyes to left, cerebral infarction, subdural effusion on the right side, severe pains in all joints, and paresis of the left arm. X-ray showed progressive osteosclerosis and epiphysiolysis in the shoulders and hips. The pains became more and more severe and analgetics were necessary. At this time blood pressure was 85/60, Hb 3.7

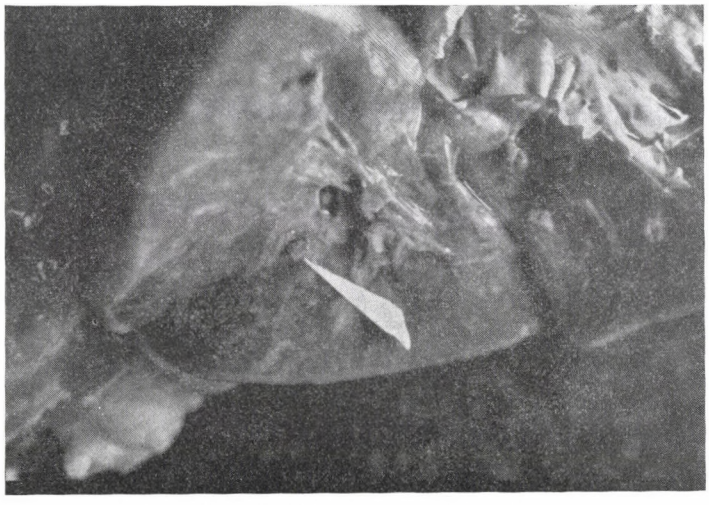


FIG. 3. Pulmonary calcinosis

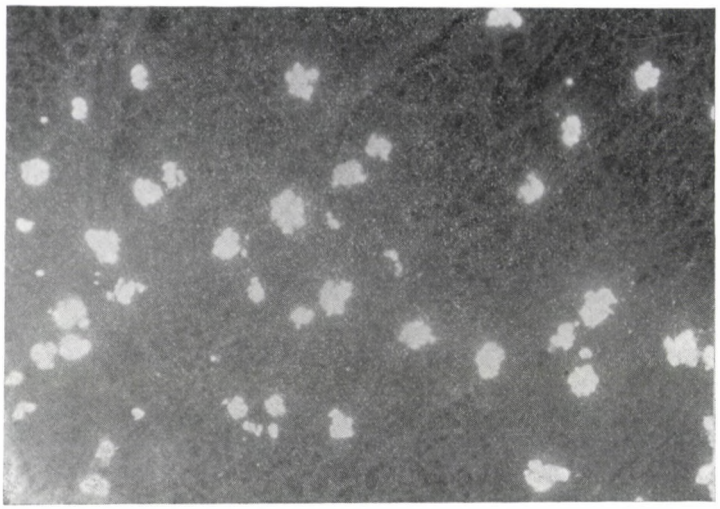


FIG. 4. Oxalate crystals in the myocardium

g/dl, reticulocytes 39%, thrombocytopenia and haemorrhages, BSG 166/170, urea 282 mg/dl, creatinine 6.4 mg/dl. The patient then died at 11 years of age.

The postmortem findings were secondary haemosiderosis in liver, spleen and lymphnodes, heart dilatation, pseudohypertrophy of heart muscles, pulmonary oedema, haemorrhagic pachymeningitis, encephalomalacia in the right hemisphere, poor erythropoiesis in bone marrow, extramedullary haematopoiesis. Many oxalate crystals were found in the heart, lungs, choroid plexus, intracerebral arteries, bones, thyroid glands, testicles, prostate, urinary bladder and adrenals.

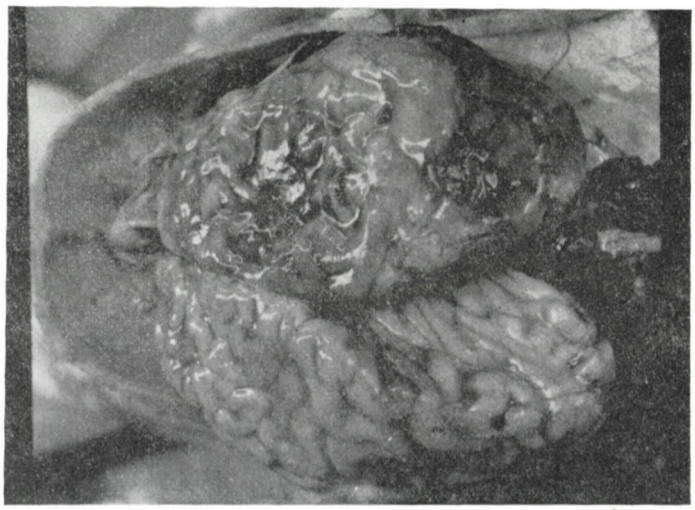


FIG. 5. Areas of softening in the brain

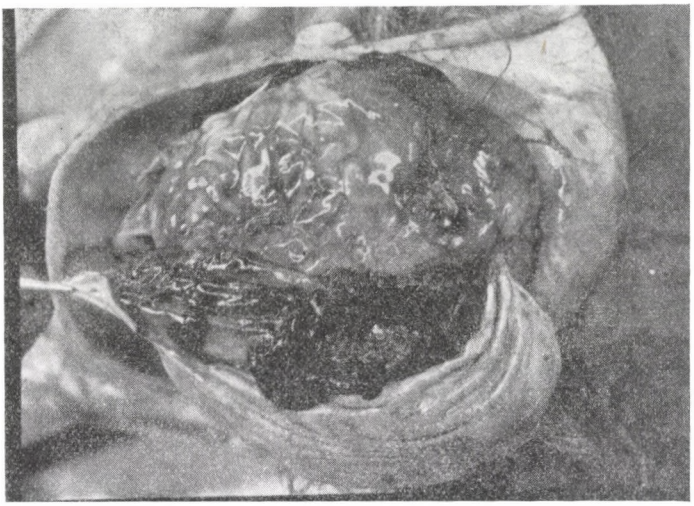


FIG. 6. Subdural haematoma

DISCUSSION

There are six different kinds of hyperoxaluric conditions [23].

I. Inherited:
- A) Primary hyperoxaluria type I — glycolic aciduria
- B) Primary hyperoxaluria type II — glyceric aciduria

II. Acquired:
- A) Increased ingestion of oxalate
- B) Increased intake of an oxalate precursor, such as

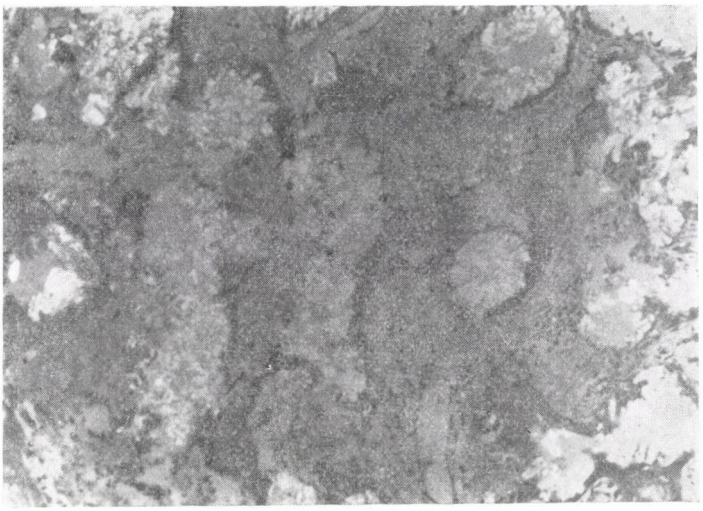


FIG. 7. Oxalate crystals in bone

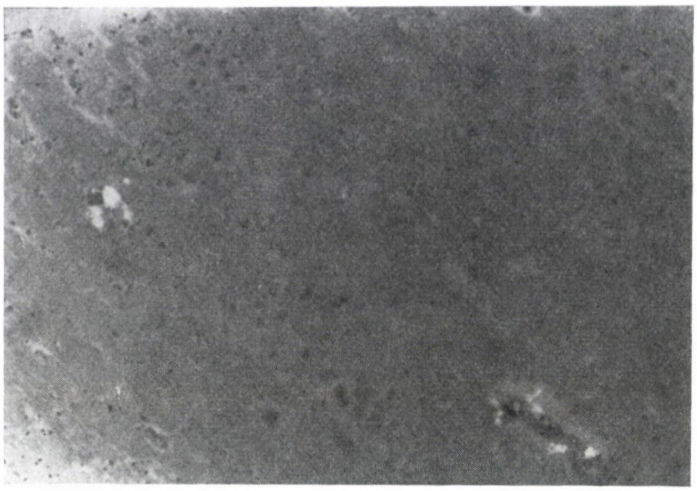


FIG. 8. Oxalate crystals in the brain

1. methoxyflurane
2. ethyleneglycol
3. ascorbic acid
4. xylitol

C) Pyridoxin deficiency

D) Hyperabsorption of oxalate, enteric hyperoxaluria.

The two inherited disorders of hyperoxaluria are rare, especially few observations were published of type II [10, 22, 25]. The excretion of excessive amounts of L-glyceric acid in type II suggests an abnormality in hydroxypyruvate metabolism where

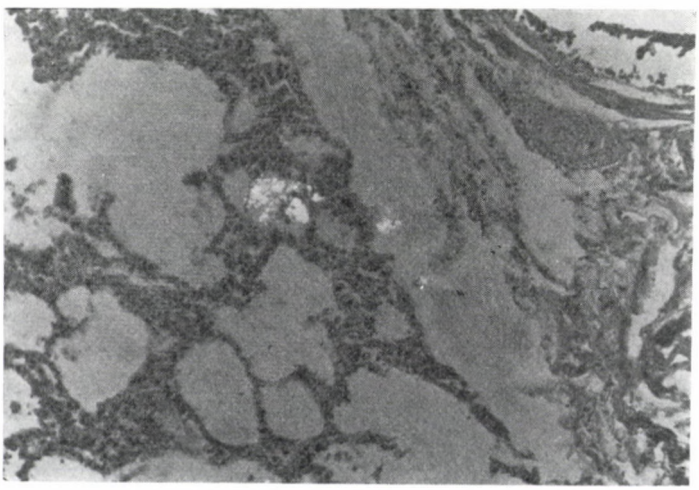


FIG. 9. Oxalate crystals in the lung

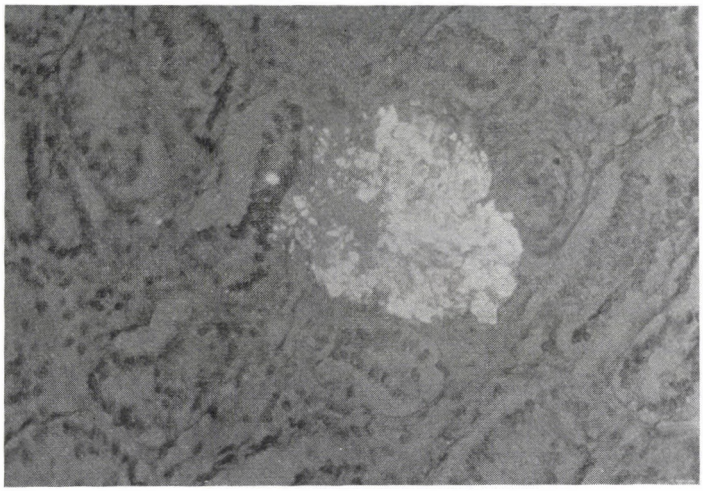


FIG. 10. Oxalate crystals in the testicle

the secondary reduction is catalysed by lactic dehydrogenase [23]. Type I with glycolic aciduria is a rare disease but somewhat more common than type II. It is characterized by the urinary excretion of large amounts of glyoxylic and glycolic acids.

The major precursor of oxalate is glyoxylate, which is formed primarily from glycine and glycolic acid, and alpha-keto-gamma,-hydroxyglutamic acid (Table I).

The conversion of glyoxylate is catalysed by the three enzymes glycolic acid oxidase, xanthine oxidase and lactic dehydrogenase. In both types of

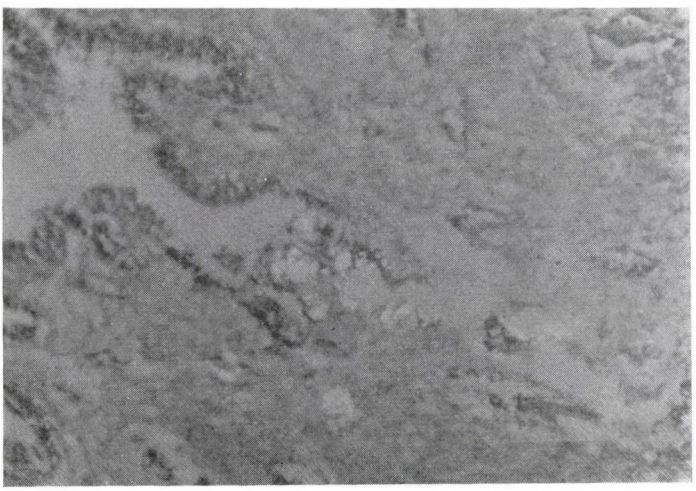


FIG. 11. Oxalate crystals in the bladder wall

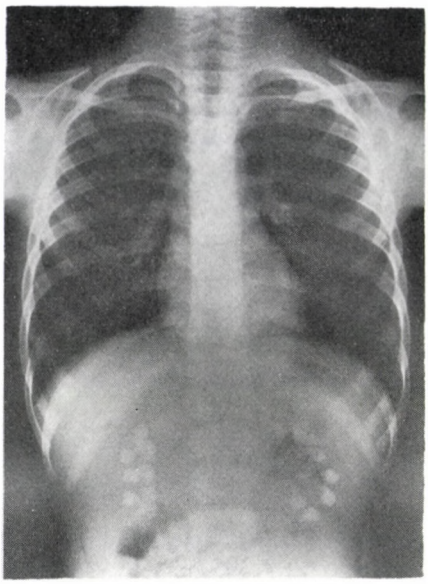


FIG. 12. Oxalate concrements in small renal calyces

primary hyperoxaluria an excessive synthesis of oxalate results from a metabolic block. In type I the cause of the block seems to be a deficiency of the soluble enzyme alpha-ketoglutarate: glyoxylate carboligase. In type II there seems to be a deficiency of D-glyceric-dehydrogenase. A defect in hydroxypyruvate metabolism results in its excessive reduction to D-glyceric acid, catalysed by lactic dehydrogenase [23].

Our patient had a type I primary hyperoxaluria or oxalosis. This in-

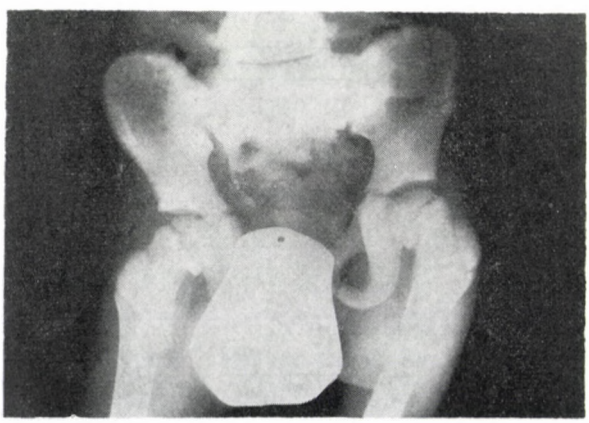


FIG. 13. Massive oxalate storage in bone marrow. Fracture of neck of femur. Oxalate stones in ureter

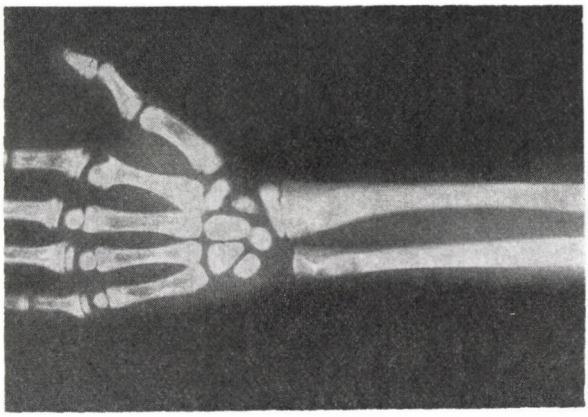


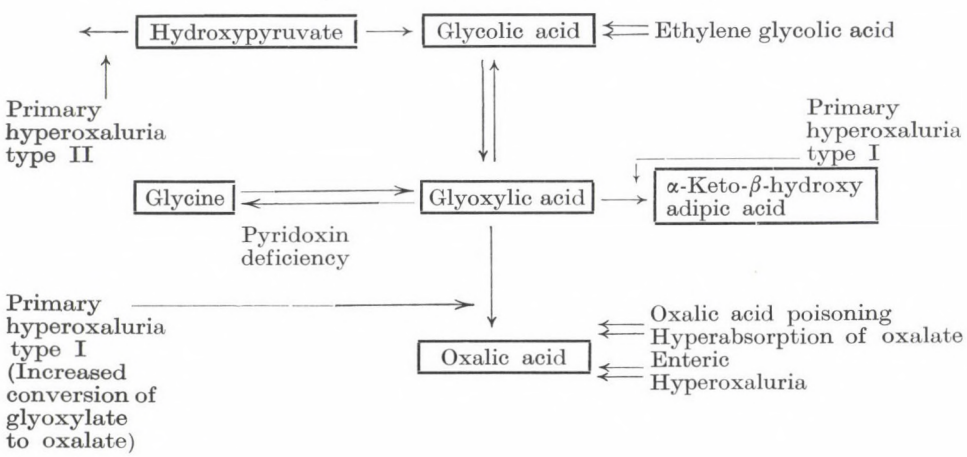
FIG. 14. Oxalate storage in bones, cystoid spaces in distal metaphysis of radius and ulna

herited disease begins with renal symptoms, pyuria and hyperoxaluria with calcium oxalate urolithiasis and nephrocalcinosis in early childhood. The next signs are current infections of the urinary tract, renal insufficiency and hypertension. The metabolic defect leads to an overproduction of oxalate, the renal insufficiency to a progressive decrease of oxalate excretion and an increase in extrarenal calcium oxalate deposits, especially in the bones, heart, vessels and the male urogenital system. Crystals in the walls of veins, arteries and arterioles have been noted particularly in hyperoxaluric patients undergoing long-term haemodialysis for chronic renal failure [2].

The clinical diagnosis is based on

TABLE I

Oxalate metabolism in humans (23)



the excessive urinary oxalate excretion before renal failure would have developed. With the renal failure the urinary excretion of oxalate, glycolic and glyoxylic acid decrease. The next symptoms are nephrolithiasis and nephrocalcinosis and the presence of oxalate crystals in extrarenal organs, e. g. in bone marrow and the bones.

No efficient treatment exists. The aim should be to normalize the metabolism of oxalic acid early in life. The high doses of pyridoxin were given for such a purpose; it diminished the urinary oxalate excretion, but the conversion of glyoxylic acid to glycine by pyridoxin was never sufficient [7, 8]. Trapping of glycine with benzoate was also attempted; it may reduce oxalate excretion, but too modestly [19]. The same is true for the attempt to inhibit the oxidation of glycine to glyoxylate by D-amino acids]16].

It remains to try, as in other forms of nephrolithiasis, to give large quantities of water to maintain a great volume of urine with the aim of dissolving the oxalate salts and to use magnesium oxide for inhibiting the storage of calcium oxalate [4, 15]. We have not attempted to apply this treatment. The recommended phosphate supplementation was applied in a case with some success [17], but it failed in our patient. The last therapeutical means are haemodialysis and renal transplantation, The prolonged survival after renal transplantation in a case of primary hyperoxaluria [11] was encouraging, but we were less lucky.

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