THE NEPHROTIC SYNDROME IN EARLY INFANCY:

A REPORT OF THREE CASES*

BY

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The nephrotic syndrome is characterized by generalized oedema, hypoproteinaemia with diminution or reversal of the albumin/globulin ratio, hyperlipaemia and gross albuminuria. Haematuria is not prominent; hypertension and azotaemia, except in the terminal stages, are slight and transient and often do not occur at all. Recognition of this syndrome presents no difficulty but in many cases, particularly in childhood, its cause remains obscure. Occasionally certain drugs such as troxidone or mercury, or certain diseases such as amyloidosis, pyelonephritis, diabetes, disseminated lupus erythematosus or renal vein thrombosis, can be incriminated. In cases which develop renal failure and come to necropsy the lesions of glomerulonephritis (Type I or Type II of Ellis, 1942) may be found. Other patients, especially children, may never show any unequivocal features of glomerulonephritis and appear ultimately to make a complete recovery; such cases belong to the group usually classified as lipoid nephrosis, in which the lesions are held to involve predominantly the renal tubules, glomerular damage being slight or absent. However, this condition is relatively uncommon and, by definition, not of itself fatal; descriptions of the morbid anatomy must therefore be based on somewhat limited observation, and the primary cause of the disorder and its relationship to glomerulonephritis are still uncertain.

It is exceedingly rare for the nephrotic syndrome to appear during the first few weeks of life but when this does happen it is reasonable to suggest that the basic disorder may have originated *in utero*. The study of the small group of cases of 'congenital nephrosis' is therefore of particular interest. In the three examples now reported there is, moreover,

evidence of genetic aetiology inasmuch as two of the infants were brother and sister and both sets of parents were cousins. Further points of interest were the demonstration of anisotropic crystalline material in alcohol-fixed tissues from all three infants, and the discovery on renal microdissection of lesions of the proximal tubule recalling those found in Fanconi-Lignac disease (cystinosis).

Case Reports

The parents of the first two patients (and the paternal grandparents) are first cousins. They, and a sister born three years before the first of her affected siblings, have been investigated in detail and show no sign of renal disease. There is no history of renal disease in any other member of the family. The pedigree of this family is shown in Fig. 1.
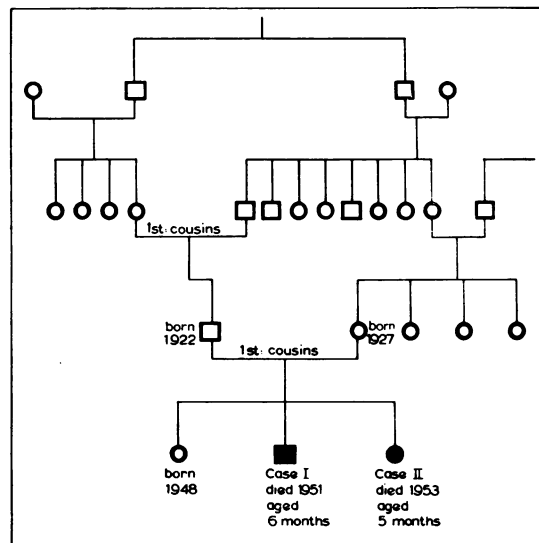

FIG. 1.—Pedigree of Cases 1 and 2.

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* Cases 1 and 2 were presented at a meeting of the Pathological Society of Great Britain and Ireland on January 7, 1956, and Cases 1, 2 and 3 at the Annual Meeting of the British Paediatric Association on April 27, 1956.

Case 1. M.R., a full-term male infant weighing 5 lb. 8 oz., was born on May 9, 1951, and was admitted to hospital on September 6, 1951, aged 4 months. At birth his legs had been swollen and from the waist down his skin had a slightly bluish tinge. During the first two weeks of life the swelling and the blueness gradually disappeared. Subsequently, however, there were repeated attacks lasting a day or two in which he passed very little urine and his legs again became tense and swollen; the attacks ended with the passage of much urine and disappearance of the oedema. He had been breast-fed throughout.

On admission he was a pale, rather ill-looking infant with tense pitting oedema of the legs and abdominal wall; there were purpuric spots and blotches in the oedematous regions. The optic discs and retinae were pale but otherwise normal. Blood pressure was 140/90 mm. Hg. A loud systolic murmur was audible over the precordium, maximal at the apex. The abdomen was tense, and ascites was suspected; the left kidney was palpable and thought to be enlarged. The urine contained 250 mg. protein per 100 ml., and the deposit showed 5-10 red cells per high-power field. Haemoglobin was 7·4 g. per 100 ml. and leucocytes 24,100 per c.mm. with 84% polymorphs. The serum cholesterol was 359 mg. per 100 ml., albumin 0·4 g. and globulin 3·21 g. per 100 ml., potassium 3·1 mEq., plasma chloride 100 mEq., bicarbonate 22·5 mEq. per l. and blood urea 26 mg. per 100 ml. The blood Wassermann reaction was negative and a radiograph of the long bones showed no abnormality.

COURSE IN HOSPITAL. Breast feeding was continued after admission. Oedema subsided, slowly at first but more rapidly after a few days with the passage of a number of loose stools, although it did not clear entirely from the legs. The spleen became palpable 3-4 cm. below the costal margin. Following blood transfusion his haemoglobin rose to 14·3 g. per 100 ml. but the cardiac murmur persisted unaltered. During the second week diarrhoea ceased and oedema returned. On September 18 he had a succession of generalized convulsions for which phenobarbitone was given. On the same day he received two injections of 20 ml. each of 25% salt-poor human albumin solution; there was no subsequent alteration in weight or degree of oedema, but the urinary protein concentration rose to 2 g. per 100 ml. On September 19 serum potassium was 2·8 mEq. per l., calcium 5·6 mg. per 100 ml. and albumin 0·98 g. per 100 ml. Potassium chloride, 1 g. twice daily, and calcium lactate, 1 g. four times daily, were started, and given intermittently for the remainder of the illness. Urea, 1 g. thrice daily, had no diuretic effect.

For the remaining four weeks of life the course was one of alternating oedema, sometimes accompanied by fits, and dehydration associated with diarrhoea. There was no significant azotaemia, blood urea being 32 mg. per 100 ml. three days before death. The blood protein and cholesterol levels and the urinary findings remained typical of the nephrotic syndrome. Hypokalaemia and hypocalcaemia persisted and there was transient hypochloraemia (plasma chloride 80 mEq. per l.). Blood pressure remained about 140/90 mm. Hg. Treatment was directed towards maintaining a reasonable degree of hydration and correcting the various electrolyte disturbances as they occurred. However, the infant did not recover from a final episode of dehydration and died on October 20.

NECROPSY. The necropsy was performed 50 hours after death. The body was that of a male infant in poor general nutritional condition (height 21 in., body weight 7½ lb.) with undue laxity of the skin over the upper part of the body and oedema of the prepuce and the legs below the knees. The fontanelles were patent and depressed.

The middle ears contained a small quantity of slightly blood-stained mucopus. The brain weighed 584 g. and was poorly differentiated and oedematous. On the external surface of the heart there were several small recent subpericardial ecchymoses over the anterior aspect of the right ventricle. The right heart was dilated and the left ventricular wall was of firm consistency and measured 1 cm. in thickness. The anterior portions of both lungs were emphysematous, but posteriorly and in both lower lobes there was congestion and collapse with basal consolidation.

The liver was reduced in weight (150 g. as compared with the expected weight of 200 g.), dull, yellow-brownish and of flabby consistency. It cut easily and the cut surface was swollen, with an ill-defined yellowish coloration at the periphery of the lobules and dark, reddish-brown areas centrally. The gall bladder was small with a thickened fibrous wall and its lumen contained a few small, oval, dark calculi and some whitish mucoid material; one of the calculi was impacted in the cystic duct. The extra-hepatic biliary system was normal. The spleen, which was of average weight, was congested with irregular areas of haemorrhage in the pulp.

The kidneys were of about equal size and were obviously very considerably enlarged. The right weighed 40 g. (expected weight 26 g.) and the left weighed 46 g. (expected weight 25 g.). The appearances were similar in the two and externally the parenchyma appeared paler and flabbier than normal, with some lobation of the surface. The capsules stripped readily and the subcapsular surfaces were very finely granular, with large numbers of raised pale nodules of uniform size distributed evenly on a more congested background. The kidneys cut easily and the cut surfaces were pale. There was marked swelling and widening of the cortices, in which enlarged glomeruli could often be seen as granules. In all parts the cortico-medullary junction zones were blurred. The renal artery was duplicated on both sides. The calyces, pelves and lower urinary tract were entirely normal. Examination of the remaining viscera revealed no significant abnormality.

HISTOLOGY. Tissues were fixed in 10% formol-saline. All sections were stained with haematoxylin and eosin, and by other methods (periodic-acid-Schiff, etc.) as indicated. Small portions of liver, spleen, bone marrow and kidney were also fixed in absolute alcohol and sections were stained with an alcoholic solution of basic fuchsin.

Examination of the formol-saline fixed material revealed significant lesions in the liver and kidneys and confirmed the presence of cerebral oedema and pulmonary congestion and oedema. The consolidated zones at the lung bases were shown to be areas of aspiration pneumonia.

In the liver there was a moderately severe diffuse biliary fibrosis in addition to generalized centrilobular congestion and peripheral fatty infiltration (Fig. 2). The
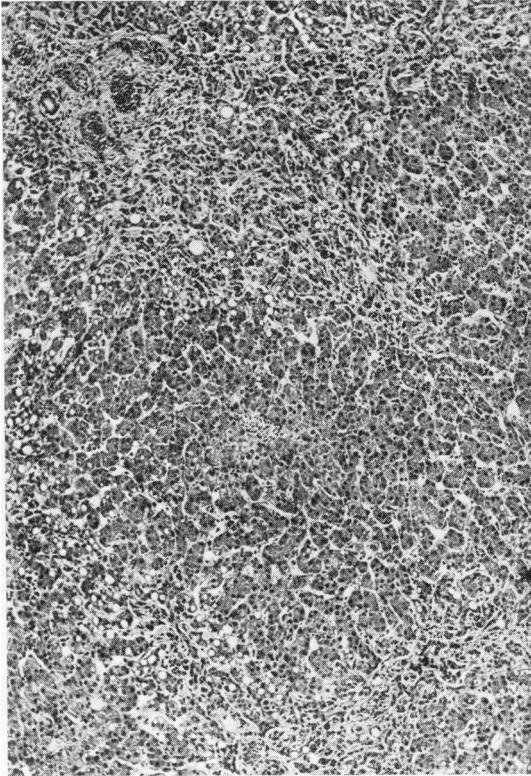

FIG. 2.—Case 1: liver. Diffuse biliary fibrosis with an increased amount of connective tissue in the portal tracts. Haematoxylin and eosin. × 100.

individual lobules were smaller than normal due to proliferation of fibroblastic and fibrous tissues between the portal tracts. The central veins were normal. The perilobular strands contained some proliferated bile ducts, some lymphocytes and plasma cells and many macrophages laden with iron pigment, which was also seen in small amounts in the Kupffer cells, and occasionally within parenchymal liver cells. The liver cells were of normal size, although a few multinucleate forms were seen at the periphery of some lobules. There was no evidence of bile retention within the liver cells, the bile canaliculi, or the bile channels in the portal tracts. In the wall of the gall bladder there were small numbers of chronic inflammatory cells in the submucosa; the mucosa was poorly preserved.

The changes were identical in the two kidneys. The most striking feature was the much greater severity and extent of tubular as compared with glomerular damage (Fig. 3). The glomeruli, however, varied very considerably in size and appearance; some were entirely normal, others were hypertrophied and bulged into the proximal convoluted tubule and many were undergoing ischaemic changes. In these latter there was a variable degree of periglomerular fibrosis as well as some fibrosis of the tuft, associated with irregular thickening of the basement membrane. A few hypertrophied glomeruli showed proliferation of the capsular and glomerular epithelium and increased cellularity due to endothelial proliferation, and here and there small and rather ill-defined epithelial 'crescents' were seen. The periodic-acid-Schiff technique revealed some thickening of the basement membrane in the more central portions of many of the partially ischaemic glomeruli although the peripheral capillary loops were normal. There was no evidence of the glomerular digitation that is such a characteristic feature of Type II nephritis. The tubules were grossly abnormal, the changes being more marked in the cortex than in the medulla. In the cortex there were radially disposed areas of compression, distortion and partial or complete atrophy of the tubules with intervening zones of marked dilatation and hypertrophy. The tubular epithelium varied considerably; in the dilated tubules the cells were flattened and resembled endothelium but in the hypertrophied ones they were plumper and showed all stages of degeneration with cytoplasmic vacuolation, nuclear disintegration and the formation of casts in the lumen. Similar but less regular changes were seen in the medullary tubules. In frozen sections, isotropic sudanophil fat was seen in the lumen and epithelial cells of some of the dilated cortical tubules. In the interstitial tissues there was a diffuse increase of moderately cellular fibroblastic tissue which had a radial arrangement in the cortex corresponding to the areas of maximal tubular damage. Small numbers of chronic inflammatory cells were scattered throughout and there were some zones of partially hyalinized collagen seen here and there (Fig. 4). In the medulla there was a more generalized increase of connective tissue, with fewer inflammatory cells. Vascular changes were not striking and consisted of hypertrophy and, occasionally, hyalinization of the glomerular afferent arterioles, some intimal thickening and elastic reduplication in a number of the intralobular arteries and a little irregular intimal hyperplasia in the main renal vessels. The renal pelvis and lower urinary tract were histologically normal.

Alkaline phosphatase was demonstrated in smaller amounts than normal in the epithelium of the cortical tubules.

Case 2. S.R., a sister of the previous case, was born three weeks prematurely on August 28, 1952 (birth weight 5 lb. 5 oz.), and was admitted to hospital on November 14 at the age of 2½ months.

Except that her mother thought she passed more urine than normal there had been nothing unusual about her progress until four weeks previously when her legs were
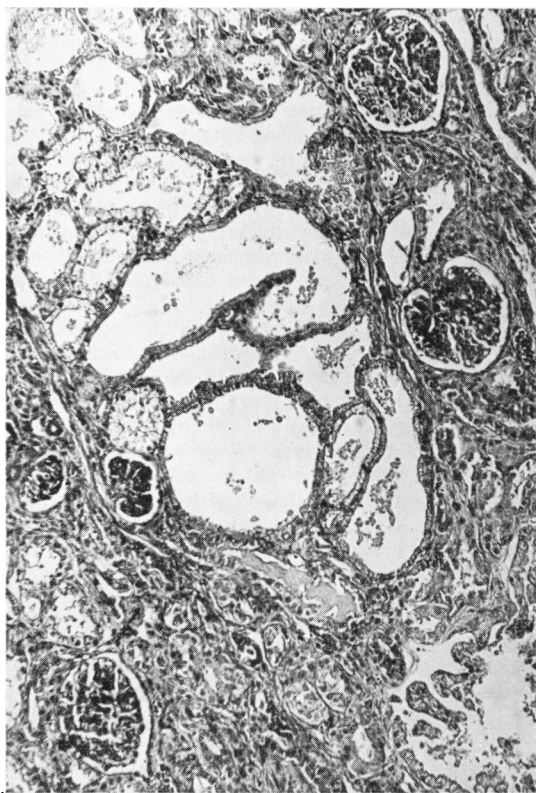
FIG. 3.—Case 1: kidney. The glomeruli are normal or enlarged. The tubules are dilated, with epithelial degeneration and atrophy. Haematoxylin and eosin. × 110.
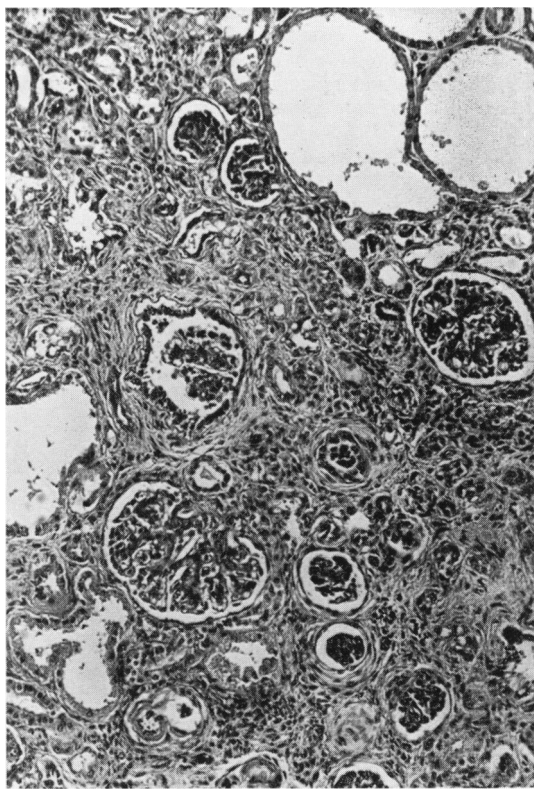

FIG. 4.—Case 1: kidney. Many of the glomeruli are ischaemic and there is irregular tubule dilatation. The interstitial tissues are increased and are denser than normal. Haematoxylin and eosin. × 110.

noticed to be swollen. This swelling had persisted, with some fluctuation in severity.

On admission she was a pale infant with mild pitting oedema of the legs and feet but no other abnormal clinical findings. Her blood pressure was 85/50 mm. Hg; the eye grounds appeared normal. The urine contained 2 g. per 100 ml. of protein and the deposit showed moderate amounts of red cells and some hyaline and granular casts; the specific gravity was 1001. Haemoglobin was 8·7 g. per 100 ml. and leucocytes 5,200 per c. mm. Blood urea was 15 mg. per 100 ml., cholesterol 348 mg., total protein 2·84 g. (albumin 0·7 g., globulin 2·14 g.) plasma chloride 107 mEq. per l., plasma bicarbonate 12·3 mEq., serum sodium 139 mEq. and serum potassium 4·8 mEq.

COURSE IN HOSPITAL. Breast feeding was continued after admission. Heavy proteinuria persisted but the urinary deposit showed only a few red cells ; blood pressure never exceeded 95/55 mm. Hg. About December 17, both weight and the degree of oedema began rapidly to increase, and on December 23 feeds of salt-free milk ('lonalac') were substituted for breast milk, and aureomycin, 65 mg. six-hourly, was started as a prophylactic against infection. On December 12, the serum potassium had fallen to 4·3 mEq. per l., and

bearing in mind the marked terminal hypokalaemia found in M.R., a dose of 1 g. daily of potassium chloride was started and increased on December 28 to 2 g. daily. On January 7, 1953, oedema began to diminish, and during the subsequent two weeks body weight fell from 11 lb. to 8½ lb. Unfortunately, this loss of fluid was accompanied by a rise in blood urea to 82 mg.per 100 ml. and a deterioration in general condition. On January 23, plasma bicarbonate was 11·7 mEq. per l., chloride 114 mEq., and potassium 3·8 mEq.; intravenous infusions of ⅛ molar sodium lactate solution, ½ strength Hartmann's solution with 2·5% dextrose and blood produced temporary improvement, with a fall in blood urea to 40 mg. per 100 ml. on January 29. During the subsequent week, plasma bicarbonate and serum potassium levels remained low in spite of increasing oral potassium intake to 2·5 g. daily and giving regular ¼ molar sodium lactate solution. The infant's general condition remained grave and on February 1 her respirations were gasping and her colour poor ; she died that day.

NECROPSY. The necropsy was performed 22 hours after death. The body was that of a pale, wasted female infant with a large head, puffy face, distended abdomen
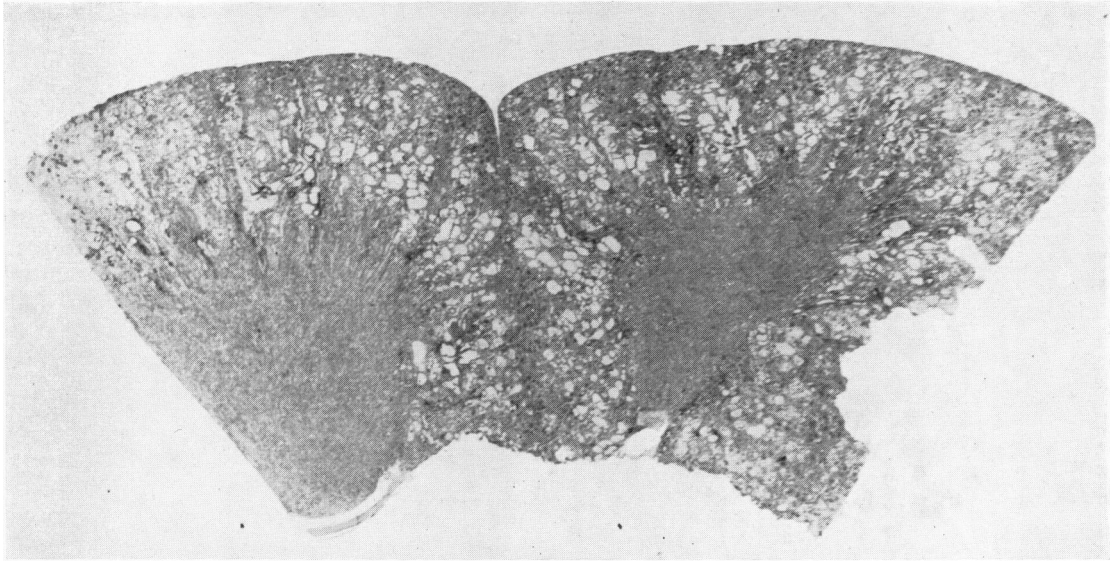
FIG. 5.—Case 2: kidney. Low-power view showing marked dilatation of the cortical tubules. The medulla appears relatively normal. Haematoxylin and eosin. × 5·5.

and pitting oedema of the lower limbs, labia and sacral region (height 20½ in., body weight 9¼ lb.). The cranial sutures were not united and both fontanelles were large and depressed. All the mucous membranes were pale.

The subcutaneous tissues in all parts of the body, as exposed by the routine incisions, contained large amounts of clear oedema fluid. The brain weighed 644 g. (normal for the age) and was oedematous with some simplification of the gyral pattern in the frontal lobes and compensatory dilatation of the anterior horns of the lateral ventricles. The right side of the heart was considerably dilated but the left ventricle was of normal size, its wall measuring 0·8 cm. in thickness. Each pleural cavity contained between 60 and 70 ml. of turbid whitish fluid and the lungs were congested and collapsed but showed no visible or palpable evidence of consolidation. The peritoneal cavity contained 25 ml. of yellowish, slightly cloudy fluid and there was gross gaseous distension of the stomach and large bowel, which appeared to have caused the abdominal enlargement. The liver was increased in weight (224 g. as compared with the expected weight of 188 g.), with centrilobular congestion and some fatty changes at the periphery of the majority of the lobules. The gall bladder and bile ducts were normal. The spleen was enlarged to nearly twice normal and weighed 28 g.; the pulp was intensely congested. The kidneys were very considerably enlarged, the right weighing 60 g. (expected weight 25 g.) and the left 65 g. (expected weight 25 g.). Both showed definite lobation of the surfaces, whilst the capsules stripped readily to reveal pale, finely granular cortices, with some congestion of the stellate veins and many tiny, yellowish elevations upon a darker, brownish-yellow background. The parenchyma cut easily and there was swelling and widening of the cortical tissues, blurring of the cortico-medullary junction zones and

some pallor of the medullae. Closer examination of the cortices showed a fine honeycomb pattern, with large numbers of tiny cystic spaces separated by radially disposed strands of swollen parenchyma; no glomeruli could be distinguished (Fig. 5). The calyces, pelves, renal vessels and the lower urinary tract were entirely normal. Examination of the remaining organs revealed no significant changes.

HISTOLOGY. Tissues were fixed in 10% formol-saline. All sections were stained with haematoxylin and eosin as a routine and by other methods as indicated. As in Case 1, portions of liver, spleen, bone marrow and kidney were fixed in absolute alcohol and sections were stained with an alcoholic solution of basic fuchsin.

In the formol-saline fixed material very striking lesions were seen in the kidneys, and the macroscopic findings were confirmed in the other organs. There was no increase of connective tissue in the liver, such as was seen in Case 1. An incidental finding of no relevance in the present context was a number of intranuclear and intra-cytoplasmic inclusions, characteristic of cytomegalic inclusion disease, in the epithelial cells of the ducts of one of the submandibular salivary glands.

Identical lesions were seen in the two kidneys and, as in Case 1, the tubules were more seriously affected than the glomeruli. Moreover, comparison of the two cases showed that the same basic lesion was present in both infants, although it was in a more advanced stage in Case 1. In the present case, the lesions were almost entirely cortical in situation, the only relevant changes in the medulla being vascular congestion, prominence of and increase in the amount of interstitial tissue, and some irregular and slight dilatation of a number of the tubules in the boundary zone. The majority of the glomeruli were of normal size and appearance, although a few were

FIG. 6.—Case 2: kidney. The glomeruli vary in size and are separated by greatly dilated tubules. Haematoxylin and eosin. × 110.
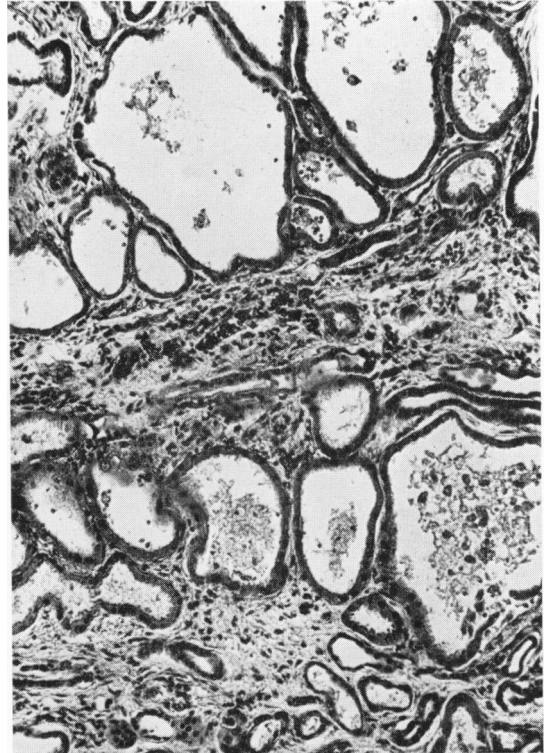

FIG. 7.—Case 2: kidney. The tubules are grossly dilated and separated by oedematous fibroblastic tissue. Haematoxylin and eosin. × 110.

hypertrophied and some, especially in those parts of the kidney where there had been proliferation of the interstitial tissues, showed a variable amount of periglomerular fibrosis and fibrosis of the capillary tuft (Fig. 6). A very few of the cortical tubules were of normal size and appearance, but more commonly there was marked degenerative change in the epithelium, with considerable dilatation of the tubule lumen and flattening or hyperplasia of the lining cells, and with marked vacuolation, cloudy swelling or hyaline droplet degeneration of the epithelium. The dilated cortical tubules were found to correspond exactly with the cystic spaces noted on naked-eye examination. Many tubules, and especially those that were dilated, contained varying proportions of red blood cells, structureless eosinophil casts, desquamated epithelial cells and granular debris in their lumina. Frozen sections showed a small amount of isotropic fat in some of the hypertrophied tubules and small focal collections of fat-laden macrophages interstitially. Throughout the cortex there was a diffuse increase of rather loose fibroblastic tissue (Fig. 7) which tended to have a radial arrangement and was infiltrated with small focal collections of chronic inflammatory cells. The intra- and extra-renal branches of the renal artery were normal and no abnormality could be found in the calyces, pelves and lower urinary tract.

Alkaline phosphatase was present in the cortical tubules but, as in Case 1, in reduced amount.

Case 3. The parents of the third patient are second cousins once removed. Twins, born four and a half years before the patient, are well and apparently normal, as are the parents; the mother has had one miscarriage. There is no family history of renal disease. It has unfortunately been impossible to obtain a full pedigree.

The patient, S.W., was born at term on November 19, 1952, weighing 6 lb. 10oz. He was breast-fed, but sucked poorly and lost weight steadily. He was admitted to hospital on December 14, 1952, aged 3½ weeks, because of failure to thrive. He was then a thin, miserable infant weighing 5 lb., with blood pressure 75/? mm. Hg. There were no other abnormal clinical findings.

COURSE IN HOSPITAL. On December 17, his urine contained protein, 40 mg.%, the deposit showed 20-30 pus cells per high-power field, with an occasional red blood cell, and culture yielded a light growth of coliforms and *Proteus*. Haemoglobin was 12 g. per 100 ml., leucocyte count 22,100 per c. mm., of which 73% were polymorphs, and blood urea 112 mg. per 100 ml. Because of the leucocytosis, a spike of fever up to 100° F. and the onset of paronychia, a course of penicillin was started. On December 20, chloramphenicol was substituted for
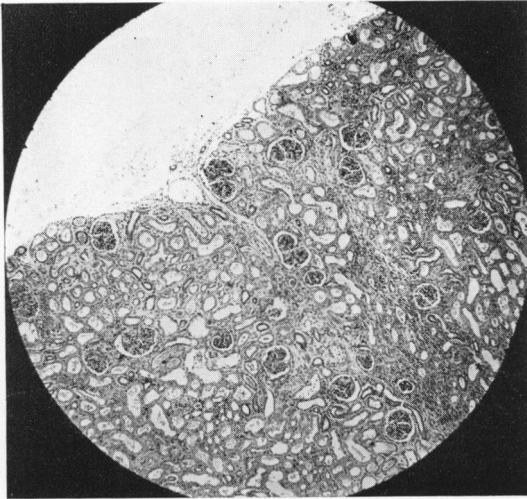
FIG. 8.—Case 3: kidney. Low-power view showing irregularly dilated cortical tubules and normal-looking glomeruli. Haematoxylin and eosin. × 50.

penicillin and was continued for four days. By December 23, blood urea had fallen to 65 mg. per 100 ml., and by December 29 to 34 mg. per 100 ml. On January 7, 1953, however, the urine contained 1,400 mg. per 100 ml. of protein; the deposit showed 4-5 red blood cells per high-power field and culture was sterile. On January 12, urinary protein was 4,000 mg. per 100 ml. and large numbers of red blood cells were seen in the deposit; blood urea was 40 mg. per 100 ml., serum albumin 1·65 g., globulin 2·59 g., cholesterol 291 mg. and phosphorus 7·8 mg. per 100 ml. In view of these findings and the development of oedema, it was felt that the infant should be treated as a case of the nephrotic syndrome, and his diet was changed from expressed breast milk to a synthetic low-sodium milk. The oedema stopped increasing, but there was no improvement in his general condition and he took feeds very poorly. On February 1 he developed rapid grunting respirations, passed some loose stools and looked very pale. The liver was palpable two finger-breadths below the costal margin, and both kidneys were palpable and felt enlarged and hard. Haemoglobin was 4·5 g. per 100 ml., blood urea 72 mg., serum potassium 3·2 mEq. per l. and plasma bicarbonate 5·4 mEq. per l. The urine contained protein, 2,400 mg. per 100 ml., and moderate numbers of red and white blood cells. He was given a blood transfusion of 120 ml. and an attempt was made to correct the electrolyte disturbance with appropriate intravenous fluids. In spite of this his condition deteriorated, he became increasingly oedematous and oliguric, and died on February 3.

NECROPSY. The necropsy was performed seven and a half hours after death. The body was that of a male infant in rather poor general nutritional condition with gross facial oedema, especially in the periorbital regions, and moderate to gross oedema of the upper and lower limbs, the scrotum and of the soft tissue at the base of the neck.

The abdomen was distended, with eversion of the umbilicus. Height was 21 in. and body weight 8 lb.

The brain weighed 536 g. (as compared with the expected weight of 516 g.) and was congested and oedematous with flattened convolutions. The myocardium was firm but not hypertrophied. The right pleural cavity contained 5-10 ml. of straw-coloured fluid, both lungs were moderately oedematous and there was some emphysema anteriorly in the right upper and middle lobes. The peritoneal cavity contained 10-15 ml. of straw-coloured fluid and the retroperitoneal tissues were oedematous. The liver was very slightly increased in weight (148 g. as compared with the expected weight of 140 g.) and congested. The gall bladder and bile ducts were normal. The spleen was deeply congested.

The kidneys, ureters and bladder were removed *in toto* and the kidneys were not weighed, although they both appeared to be moderately enlarged. The left kidney was slightly larger than the right and there was some dilatation of the right ureter, pelvis and calyces with compression and thinning of the kidney tissue on that side. The capsules stripped with a little difficulty from both kidneys and the subcapsular surfaces were irregular with many fine yellowish-brown nodules and some congested depressed areas. On the cut surfaces many irregular, radially disposed striae of bright yellow colour were seen in the cortex. The lower urinary tract was normal. There was irregular mucosal congestion throughout the intestine.

HISTOLOGY. Tissues were fixed in 10% formol-saline. All sections were stained with haematoxylin and eosin as a routine and by other methods as indicated. As in Cases 1 and 2 portions of liver, spleen, bone marrow, lymph nodes and kidneys were fixed in absolute alcohol and sections were subsequently stained with an alcoholic solution of basic fuchsin.

In the formol-saline-fixed material significant lesions were found in the bowel and kidneys and the naked-eye findings were confirmed in the remaining organs. In the lower oesophagus there was an extensive acute oesophagitis with congestion, inflammatory cell infiltration and patchy mucosal ulceration. Throughout the small and large intestines the submucosa contained an increased number of pleomorphic inflammatory cells.

The changes in the two kidneys were essentially the same. There were a few small, wedge-shaped foci of chronic pyelonephritic scarring but the most significant abnormality was a marked irregular dilatation of the tubules throughout the cortex and sometimes in the outer medulla as well. By contrast the glomeruli, except in the pyelonephritic scars, were entirely normal for a child of this age (Fig. 8). The dilated cortical tubules (Fig. 9) were lined by a low, flattened type of epithelium which was often irregularly vacuolated and, in frozen sections, was found to contain considerable amounts of isotropic sudanophil fat. The lumina contained desquamated epithelial cells and debris. There was no appreciable increase in the interstitial connective tissues except in the wedge-shaped areas of scarring. Here and there, however, the interstitial tissues contained a little iron pigment,
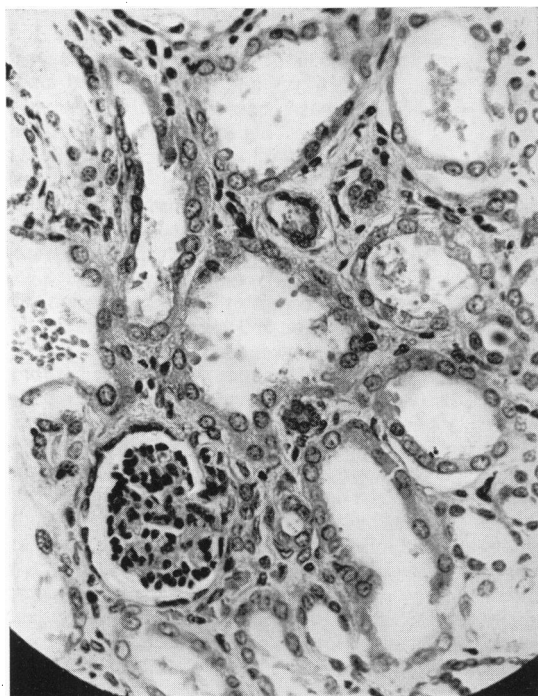
FIG. 9.—Case 3: kidney. Shows a single normal glomerulus surrounded by partially necrotic and dilated tubules. Haematoxylin and eosin. × 300.
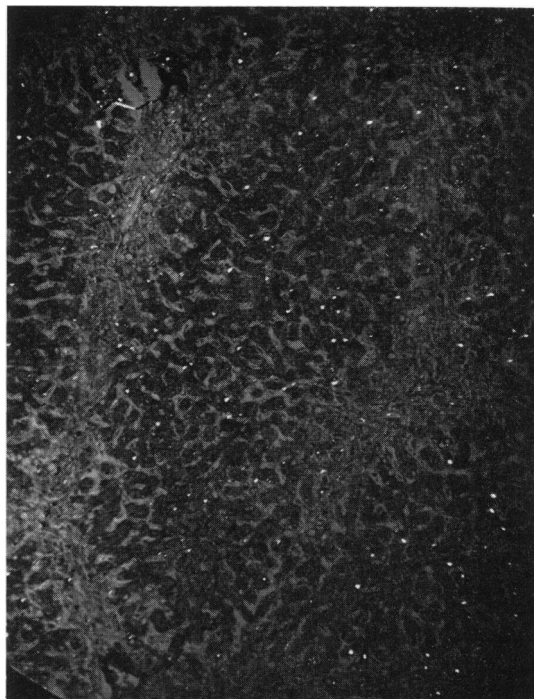

FIG. 10.—Case 1: liver. Photographed under partially polarized light; the crystalline material is clearly visible. Alcohol fixed, stained with basic fuchsin. × 60.

small collections of haemopoietic cells and focal aggregates of calcified material in the cortex and boundary zone (nephrocalcinosis). The renal vessels and their branches were normal. The renal lesions in this case resembled very closely those seen in Cases 1 and 2 although they were in a less advanced stage ; in addition there was evidence of a co-existing chronic pyelonephritis and nephrocalcinosis.

Special Studies

Examination of the Alcohol-fixed Tissues. The alcohol-fixed portions of liver, bone marrow, spleen and kidney from each infant were stained with alcoholic basic fuchsin. In Case 1 faintly bluish, unstained, doubly refractile crystalline material was found in all four tissues. The crystals were of a roughly square shape, measuring approximately $5\mu \times 5\mu$, and were soluble in water, dilute acids, ammonia and aqueous formaldehyde. They occurred in greatest concentration in the liver, where they were found most frequently within the hepatic cells, but were also seen in the Kupffer cells, and occasionally in the portal tracts (Fig. 10). Small numbers were present in macrophages in the marrow and spleen. An occasional crystal lay, apparently extracellularly, in the interstitial tissues of the kidney. *X*-ray crystallography confirmed the crystalline nature of the material but attempts at exact identification were inconclusive because of the low concentration in the tissues.

However, the substance with solubilities and *x*-ray crystallographic properties closest to those observed is cystine.

In Cases 2 and 3 occasional doubly-refractile crystals were seen in alcohol-fixed material from bone marrow, spleen, liver and kidneys. The crystals were similar to those seen in Case 1 but were present in such small amount that positive identification was again impossible.

Paper Chromatography of Blood and Urine. Random post-prandial samples of blood and urine from each case were examined for amino-acids and sugars, using the methods described by Woolf (1951) and Woolf and Giles (1956). The results are summarized in Table 1. Two specimens of urine from Mr. R. and one each from Mrs. R. and L.R. (respectively father, mother and sister of Cases 1 and 2) were similarly examined; all were protein-free and showed no excess of amino-acids or sugars.

Microdissection of Kidneys. Microdissection of the kidneys was hampered in all cases by a moderate amount of irregularly distributed interstitial fibrous tissue. The changes in Cases 1 and 2 were essentially the same (Fig. 11). The glomeruli were normal. The first part of the proximal tubule was replaced by a long and narrow neck lined by thin and flattened epithelium for about the first third of its course. The remainder of the proximal tubule was ballooned in many areas, and considerably

TABLE 1
PAPER CHROMATOGRAPHY OF URINE AND BLOOD

Subject	Material	Date	Creatinine (mg/100 ml.)	Chromatographic Findings
Case 1 (M.R.)	Urine	6.10.51	28	Proline, leucine, valine, taurine + +. Other amino-acids +. Glucose 200 mg. per 100 ml.
	Urine	12.10.51	23	Ethanolamine, β-amino-isobutyric acid + +. Leucine, phenylalanine, tyrosine +. Other amino-acids normal.
	Blood	12.10.51	—	Leucine, phenylalanine +. Other amino-acids normal.
Case 2 (S.R.)	Urine	15.11.52	7	No excess amino-acids or sugars
	Urine	21.11.52	21	No excess amino-acids or sugars
	Urine	12.12.52	20	Ethanolamine + +. Taurine, β-amino-isobutyric acid, +. Sugars normal. Other amino-acids normal
	Urine	10.1 53	37	Ethanolamine, β-amino-isobutyric acid, leucine, valine +. Sugars normal. Other amino-acids normal
	Urine (post-mortem specimen)	1.2.53	18	Leucine, valine, proline + +. Other amino-acids +. Glucose 37 mg. per 100 ml.
	Blood	12.12.52	—	Ethanolamine, taurine, β-amino-isobutyric acid +. Other amino-acids normal
	Blood (post-mortem specimen)	1.2.53	—	General increase in amino-acid levels
Case 3 (S.W.)	Urine	12.1.53	30	No excess amino-acids or sugars
	Urine	2.2.53	18	Leucine + + β-amino-isobutyric acid, valine +. Other amino-acids normal
	Blood (post-mortem specimen)	3.2.53	—	No excess amino-acids

+ Indicates a moderate, + + a marked increase over the normal concentration.

wider than normal. The lumen of the tubule was dilated throughout its course, and the epithelium flattened and irregular and in places vacuolated. The ballooning of the proximal tubule was much more advanced in Case 1 than in Case 2. The loops of Henle were normal but in the distal tubules the lumen was dilated, and the epithelium flattened. The collecting tubules were normal.

In Case 3, the changes were somewhat different in that the nephrons were of two types. In the first type the changes were similar to those seen in Cases 1 and 2 except that the narrowing and thinness of the first part of the proximal tubule was less in degree and extent, and the ballooning of the remainder of the tubule less apparent. The overall width of the proximal tubule was in fact normal for an infant of this age but the lumen was dilated and the epithelium flattened. In the second type (Fig. 12) the proximal tubule was similar to that seen in premature infants, that is to say, it was shorter than normal and lacked convolutions. It showed a slight narrowing of the neck for a short distance but the proximal tubule was of uniform diameter throughout. The loops of Henle were normal in both types but the distal tubules showed epithelial flattening and dilatation of the lumen.

Discussion

Nephrotic Syndrome in the Newborn. The nephrotic syndrome is remarkably uncommon during the first few months of life and indeed during the first year; thus in the large and well-documented series of 208 cases reported by Barness, Moll and Janeway (1950), although precise figures are not quoted, the graph showing age at onset indicates only one case aged less than 12 months. Other series (Block, Jackson, Stearns and Butsch, 1948;

Galán, 1949) similarly include very few cases in infants. This almost complete immunity in the first year is the more striking in that the second to fourth years are the period of maximum incidence.

The first published account of the nephrotic syndrome in the neonatal period seems to be that of Gautier and Miville (1942). This infant had facial oedema at birth, at 17 days showed marked generalized oedema, and died three days later. No necropsy was obtained. There were no siblings; the mother had been pregnant once before but the embryo died at 6 weeks.

Fanconi, Kousmine and Frischknecht (1951) reviewed the problem of congenital and familial nephrosis and described a family of five siblings, three of whom developed nephrotic symptoms at 4, 10 and 24 days. All these babies died, but in only one, who died in uraemia at 2¾ years, was a complete necropsy obtained. In this case the kidneys showed glomerular hyalinization and epithelial crescents, periglomerular lymphocytic infiltration, and atrophy or striking dilatation of the tubules; the liver was fatty.

Eiben, Kleinerman and Cline (1954) reported the case of a premature baby who was oedematous from the sixth day of life and died at 15 weeks. Glomerular changes were relatively slight but there was some periglomerular fibrosis and fibrosis of the tufts with irregular basement membrane thickening. The renal tubules showed considerable dilatation and hypertrophy with epithelial degeneration; they contained small amounts of lipoid, and alkaline phosphatase was present. Changes of benign

FIG. 11.—Case 1: microdissected nephron.   Phase-contrast mosaic shows that the glomerulus is joined to the proximal tubule by a narrow neck, the epithelium of which is regular.   The remainder of the proximal tubule is distended and ballooned, with flattening of the epithelium.   Case 2 shows similar changes.   × 200.

FIG. 12.—Case 3: microdissected nephron.   Phase-contrast mosaic showing a premature type of nephron.   The glomerulus is joined to the proximal tubule by a short narrow neck; the proximal tubule is shorter than normal, lacks convolutions and is reduced in width.   × 140.
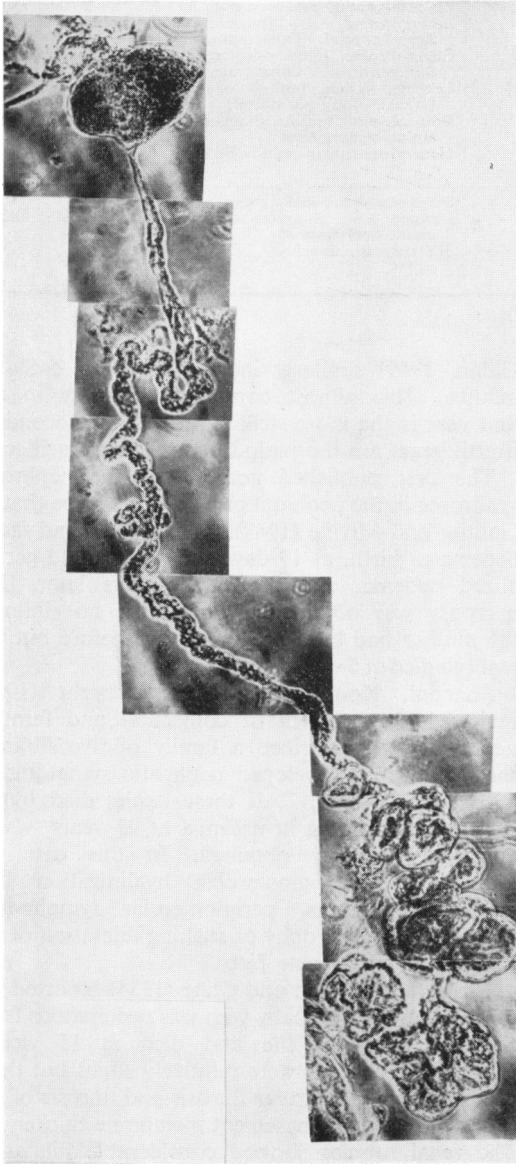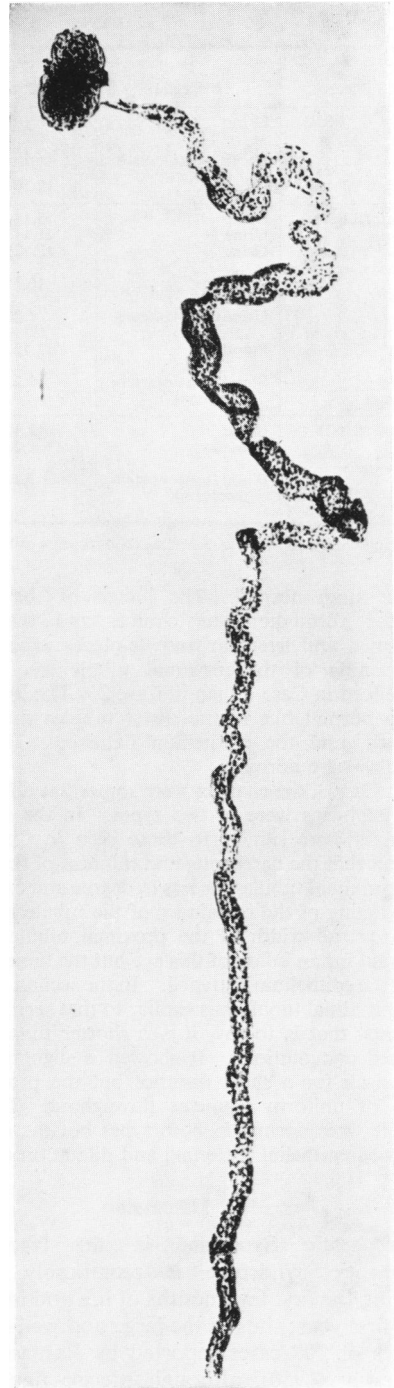

FIG. 11.

FIG. 12.

TABLE 2

NEPHROTIC SYNDROME IN EARLY INFANCY

Author	Sex	Premature	Age at Onset (days)	Age at Death (weeks)	Healthy Siblings	Necropsy Diagnosis
Gautier and Miville (1942)	F.	No	Birth	3	0	—
Fanconi et al. (1951)	M	?	24	7	} 2	No histology
	M	?	10	26		—
	M	No	4	2¾ years	}	Glomerulonephritis
Eiben et al. (1954)	M	Yes	6	15	5	Lipoid nephrosis
Kunstadter and Rosenblum (1954)	M	Yes	9	10	4	Glomerulonephritis
Frischknecht et al. (1954)	F	Yes	? Birth	15	3	Glomerulonephritis
Hallman et al. (1956) (8 cases)	5M 3F	7 pre- mature	Birth-31	1-44	7 (3 families)	6 Glomerulonephritis 2 Lipoid nephrosis
Hudson (1956)	F	? No	21	5	} 0	'Nephrosis'
	M	? No	42	32		'Nephrosis'
Dobbs and France (1956)	M	Yes	Birth	7	2	Congenital 'nephrosis'
Present series	M	No	Birth	24	} 1	Congenital 'nephrosis'
	F	Yes	40	17		Congenital 'nephrosis'
	M	No	? Birth	11	2	Congenital 'nephrosis'

hypertension were present in the blood vessels. The gall bladder contained several soft black calculi and a single similar calculus lay in the cystic duct. This patient had five healthy siblings.

Kunstadter and Rosenblum (1954) also observed a premature infant who became oedematous on the ninth day and died at 10 weeks. Microscopically the kidneys showed swollen and hyperaemic glomeruli with proliferation of Bowman's capsule and degeneration of tubular lining cells. There were four healthy siblings.

Frischknecht, Zollinger and Keiser (1954) described a further case, again a three weeks' premature infant, who was noticed to be oedematous almost immediately after birth, and died at 3½ months. Slight but definite inflammatory changes were found in the glomeruli, including thickening and splitting of the basement membrane; some of the tubules were dilated and hypertrophied, others atrophied. The patient had three healthy siblings.

Hallman, Hjelt and Ahvenainen (1956) have recently presented a group of eight infants who developed the nephrotic syndrome within the first few weeks of life. Seven of these were premature; all died, their ages at death ranging from 7 days to 10 months. Full pathological details are not yet available but six cases were classified as glomerulonephritis and two as lipoid nephrosis. Three of the infants had one or more healthy siblings; five (including two of the three with healthy siblings) had siblings who were born prematurely and died.

Hudson (1956) encountered two siblings who developed the disorder at 3 weeks and 7 weeks, and died at 5 weeks and 7½ months respectively. The infants were mature by dates, although their birth weights were only 4½ lb. and 5½ lb. The parents were healthy and not consanguineous; they had no

other children. The renal lesions in both cases were thought to resemble those of the present series.

Dobbs and France (1956) observed a three weeks' premature infant who was noticed to be oedematous within a few hours of birth and died at 7 weeks. The patient had two healthy siblings; there was no parental consanguinity. The kidneys showed a remarkable degree of tubular dilatation; the majority of the glomeruli were normal, although a few showed pericapsular fibrosis with occasional slight capsular proliferation.

These case reports are summarized in Table 2, which also includes the diagnoses submitted by the respective authors.

Other accounts have been published of various clinico-pathological syndromes associated with renal disease in the neonatal period (Mitchell, 1930; Collins, 1954; Lapage, 1932) but these do not in general provide sufficient clinical and biochemical information for full classification.

Familial Incidence of Nephrotic Syndrome. The familial occurrence of renal disease has frequently been observed (Mitchell, 1930) but in most cases it is impossible to be certain of the exact nature of the disorder. There are few reports of a well-defined nephrotic syndrome occurring more than once in a family. Blechmann (1934) observed two brothers, both of whom developed 'lipoid nephrosis' at 4 years. The first died less than a month from onset; the second recovered. Forge (1950) reported four cases in male and female sets of uniovular twins. In the female set the age at onset was 18 years in both twins, in the male set 13 and 17 years respectively. The 13-year-old died two years later; the outcome in the remaining three cases was not certainly known. Prader (1950) observed a further set of male uniovular twins, both of whom became

ill at 15 years and both of whom died. Goettsch (1948) only once encountered nephrosis in siblings. Fanconi *et al.* (1951) reported the family already referred to, another in which two brothers developed the disease at $3\frac{1}{2}$ years and 6 years, surviving eight months and three months respectively, and a third family in which a sister and brother became ill at 9 years and 14 years, both eventually recovering. As already mentioned, Hudson (1956) observed the disease in a brother and sister. Except in Hudson's cases and one case of Fanconi's no necropsy findings were recorded. Parental consanguinity was not demonstrated in any of the families.

Classification of Present Cases. It seems almost certain that the three cases described in the present report all suffered from the same basic disorder. This view is based on the uniformity of the morbid anatomical changes, the presence of anisotropic crystalline deposits in tissues from all three infants, the demonstration of broadly similar abnormalities in the microdissected nephrons and, in two of the cases, the sibling relationship. There are, however, quantitative histological differences, the changes being most advanced in Case 1 and least advanced in Case 3. This may well reflect the duration of the illness, since the ages at death were $5\frac{1}{2}$, 4 and 2 months in Cases 1, 2 and 3 respectively.

In none of the cases are the classical changes of Ellis Type I or Type II nephritis seen. In Case 1, some basement membrane thickening is demonstrable with the periodic-acid-Schiff technique, but the lesion, although similar to that found in Type II nephritis, is not so diffuse. Moreover, the pattern of the interstitial proliferation is unlike that seen in Type II nephritis and the changes are almost certainly of ischaemic origin. There is no evidence that hypertension *per se* has produced any changes in the kidney. The relative paucity of inflammatory cells in the renal parenchyma is a striking feature of all three cases, and pyelonephritis is clearly not the primary disease. The tubular lesions, comprising atrophy, hypertrophy with dilatation, and epithelial degeneration, are very much more marked throughout than the glomerular changes, and it is postulated that there is a primary tubular lesion which has resulted in proliferation of the interstitial tissues, which in turn has had a secondary strangulating effect upon the glomeruli. This concept is supported by consideration of the ages at which the children died, and by comparison of the renal lesions which show, in Case 1, interstitial collagen and quite severe glomerular sclerosis, in Case 2, fibroblastic interstitial proliferation and only minimal glomerular sclerosis, and in Case 3,

no increase in the interstitial tissues, except in the wedges of pyelonephritic scarring, and normal glomeruli.

In summary, the renal changes are thought to be consistent with a 'nephrosis', using the term in the sense of a primary tubular disorder with secondary and relatively minor glomerular lesions. The absence from the kidneys of significant deposits of anisotropic fat would, however, seem to make the qualification 'lipoid' not strictly appropriate.

Unfortunately, chemical analysis of the biliary calculi found in the gall bladder of Case 1 was not carried out. In appearance they were more like pigment than cholesterol calculi. It seems probable that the biliary cirrhosis was due to intermittent calculous obstruction of the large bile passages. Whether these hepatic and biliary lesions are coincidental is unknown. There is no obvious basis for associating them with the renal disease, but the occurrence of gallstones in the closely similar case of Eiben *et al.* (1954) raises the possibility that there is more than a chance relationship.

Genetic Aspects. It is impossible to pinpoint the date of onset of nephrosis and we cannot state categorically that the cases now reported were truly congenital. However, there are reasonable grounds for accepting them as such. Thus, in Case 1 oedema was present at birth; in Case 2 oedema was not noticed until the age of 6 weeks, but by this time the nephrotic syndrome was fully developed, and must have begun much earlier; in Case 3, although again nephrosis was not confirmed until the baby was 7 weeks old, he had been ill since birth. In no instance was there anything unusual about the mother's health during pregnancy, and no extraneous cause for the infant's illness could be found. In such circumstances it is logical to consider a genetic aetiology. In fact, inheritance of a Mendelian recessive characteristic would well explain the occurrence of a disorder, of extreme rarity in the neonatal period, in two newborn siblings (Cases 1 and 2) whose parents are first cousins and in whose family there is no history of renal disease. This hypothesis is strengthened by the existence of a cousin relationship between the parents of Case 3.

Anisotropic Crystalline Material. The significance of this finding is difficult to assess. It is unfortunate that the material could not be positively identified; no more can be said than that it was very possibly cystine. No similar crystals have been found in appropriately fixed and stained tissues of children dying from glomerulonephritis or from causes unrelated to renal disease, but we cannot say

whether or not such crystals may be present in the tissues of children with lipoid nephrosis until further cases have been studied.

Chromatographic Studies. An increased urinary amino-acid concentration was found at one time or another in all three cases. This accords with the observations of Woolf and Giles (1956) who described two types of abnormal urinary amino-acid pattern in the nephrotic syndrome. The first of these, characterized by increased excretion of ethanolamine, β-amino-isobutyric acid and other amino compounds, suggested a disturbance of intermediary amino-acid metabolism. The second type, approximating to that of normal blood and associated with glycosuria, and with azotaemia, hypertension or other evidence of renal failure, was attributed to renal tubular insufficiency, Among the present cases, this latter pattern was found only in the post-mortem urine specimen from Case 2 and in one ante-mortem specimen from Case 1; these were also the only samples containing an increased concentration of glucose. The remaining specimens from all three cases either showed the first pattern or were within normal limits.

Both patterns differ from those of cystine storage disease in their variability, in the presence of increased amounts of ethanolamine, β-amino-isobutyric acid and taurine, and in the absence from the majority of specimens of significant amounts of glucose. The relatively high urinary creatinine concentration found at least once in all of the cases is a further point of distinction from cystine storage disease, in which the creatinine rarely rises above 20 mg. per 100 ml.

We are unable to draw any conclusions from the amino-acid patterns found in the blood of Cases 1 and 3. In Case 2, the pattern found during life resembled that sometimes seen in the nephrotic syndrome in older children (Woolf and Giles, 1956).

Significance of Changes on Renal Microdissection. The similarity of the lesions to those previously described by some of us (Clay, Darmady and Hawkins, 1953; Darmady, 1954; Darmady and Stranack, 1955) in Fanconi-Lignac disease (cystinosis) is of interest. The principal difference would seem to be in the lower end of the proximal tubule, for in Fanconi-Lignac disease ballooning and dilatation of the lumen of the lower part of the proximal tubule have not been a feature in the cases so far examined. It is possible that the anatomical abnormality of the proximal tubule may be due to the genetic linkage of the families concerned, since this is apparent in Fanconi-Lignac disease also. Nevertheless the obvious differences in glycosuria, amino-aciduria and proteinuria correlate more closely with a specific reabsorptive tubular defect, and cannot be attributed entirely to the less specific micro-anatomical lesion. It is therefore probable that the genetic linkage affects the specific reabsorptive enzymes as well as the development of the proximal tubule. The persistence of the foetal type nephrons in Case 3 may not be of significance, for examination of kidneys of normal infants show that foetal nephrons can be found in small numbers in infants up to 8 months. This finding has also been confirmed by Peter (1927).

Aetiology of Congenital Nephrosis. A review of the reported cases of the nephrotic syndrome in newborns shows that apart from the essential clinical and biochemical similarities, the most notable common features are an invariably fatal outcome, usually within the first six months and, as pointed out by Hallman (1956), an association with prematurity. Somewhat unexpectedly, the underlying pathology is almost as heterogeneous as in older children and adults. However, the cases of Eiben *et al.* (1954), of Dobbs and France (1956) and of Hudson (1956) do show renal changes closely resembling those found in the present group. Hudson's cases were also familial, but in the others the familial incidence and genetic background are missing, nor were the tissues examined for crystalline deposits or by microdissection. The diagnosis made by Eiben *et al.* (1954) was lipoid nephrosis, and although the authors could advance no explanation for such an early onset, they believed it unlikely that there could have been an antecedent acute nephritis and felt that this argued for the existence of lipoid nephrosis as an independent entity. Frischknecht *et al.* (1954) interpreted their case as one of intracapillary glomerulonephritis, and attributed the incompleteness of the histological picture to inadequate antibody production in the young infant.

As already indicated, there are occasional references in the literature to the occurrence of the nephrotic syndrome in siblings; but most of these concern older children. Parental consanguinity has not previously been described. There has therefore been little evidence hitherto for a genetic aetiology in neonatal nephrosis. In the cases presented in this report, however, there is strong evidence for such aetiology; and the inherited defect may be manifested by an anomaly of the renal tubules and by the deposition in certain tissues of anisotropic crystalline material.

It is evident from these findings that any attempt at differentiation and classification of neonatal nephrosis demands the most detailed study and the use of every appropriate investigative technique.

Summary

The cases are reported of three infants who manifested the nephrotic syndrome at or within a few weeks of birth and died before the age of 6 months. Two of the cases were siblings whose parents were first cousins; the parents of the third case were also cousins. Each case showed (i) a similar abnormality of the renal tubules on microdissection; (ii) doubly refractile crystalline material in alcohol-fixed tissues; (iii) predominant lesions in the renal tubules, glomerular damage being minor and probably secondary. The severity of the histological changes could be correlated with the presumptive duration of the illness. These findings suggest that all three infants suffered from the same, and probably genetically determined, primary disorder.

Other reported cases of neonatal nephrosis show differing morbid anatomical patterns but have had a uniformly fatal outcome.

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