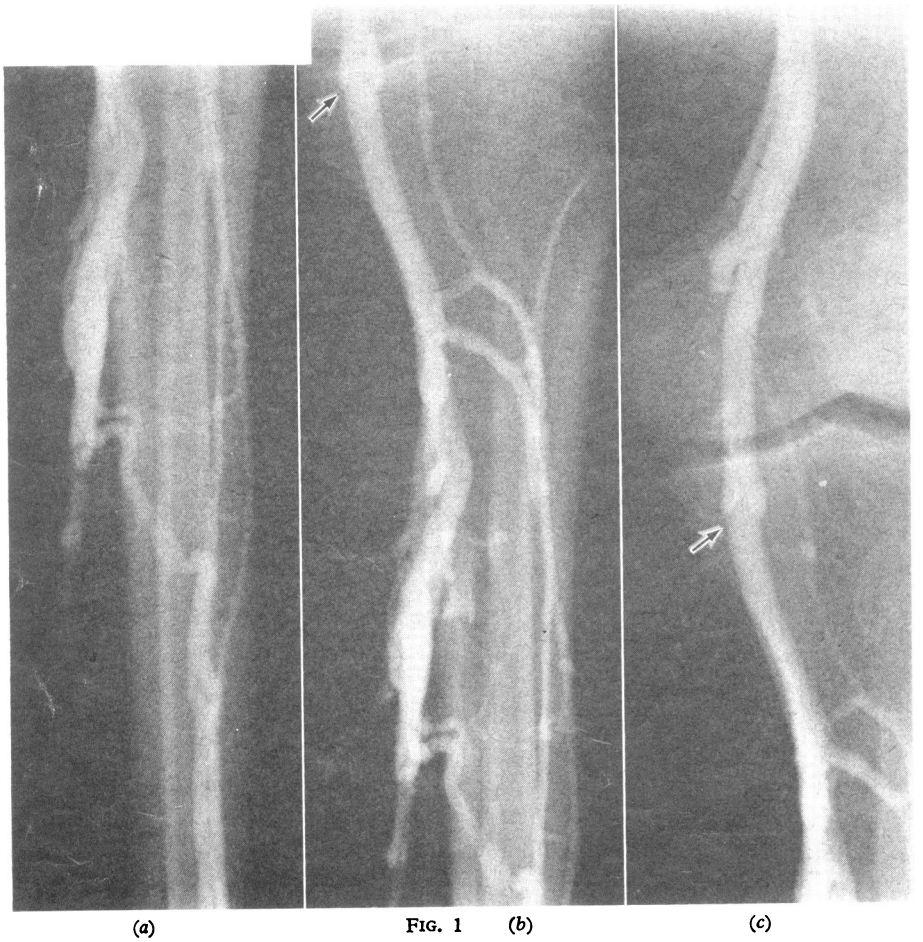
V. V. KAKKAR *ET AL.*: LATE RESULTS OF TREATMENT OF DEEP VEIN THROMBOSIS



(*a*) FIG. 1 (*b*) (*c*)

FIG. 1.—Phlebogram one year after extensive thrombi in the popliteal and tibial veins. The initial treatment was by streptokinase, and this resulted in complete dissolution of the thrombus. (*a*) The valves in tibial veins are competent. (*b*) Arrow indicates the popliteal valve, which is open. (*c*) The same valve, which is closed.

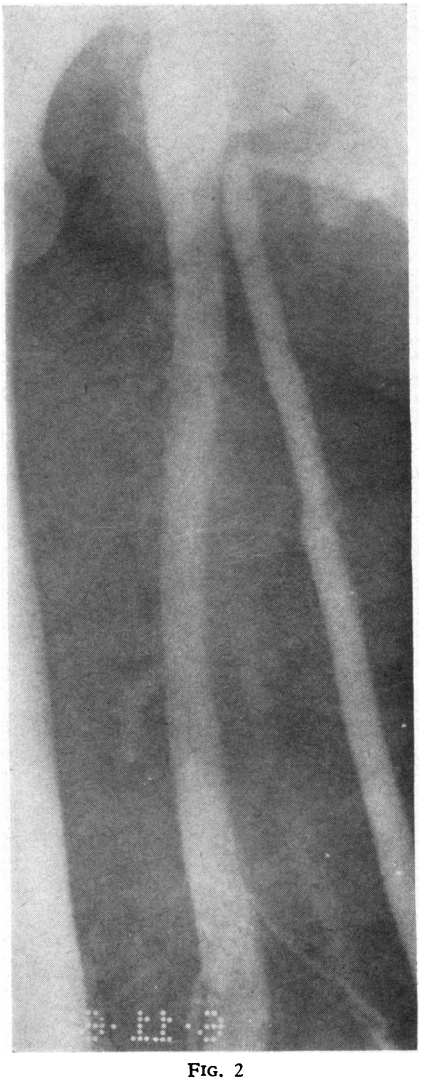


FIG. 2

FIG. 2.—Phlebogram showing completely recanalized vein. This patient was treated initially with Arvin, with a failure to clear the thrombus. Nine months later, after long-term oral anticoagulants, there was complete recanalization but no valves could be seen.

R. D. SPICER *ET AL.*: RENAL MEDULLARY CYSTIC DISEASE

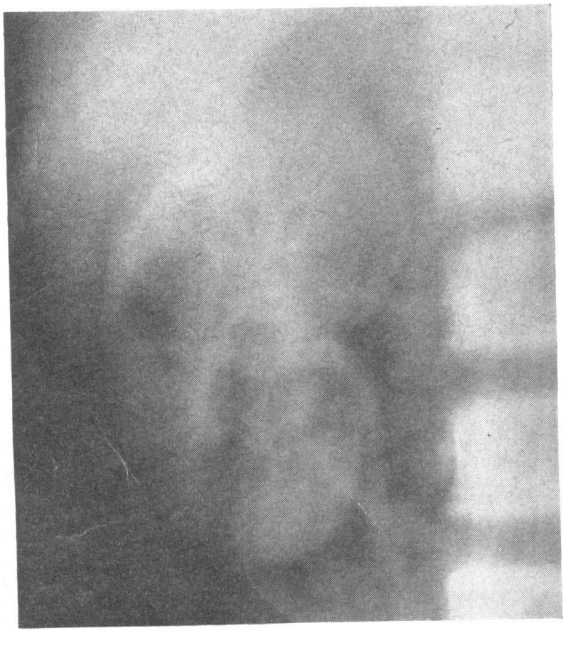


FIG. 1.—Nephrotogram of right kidney.

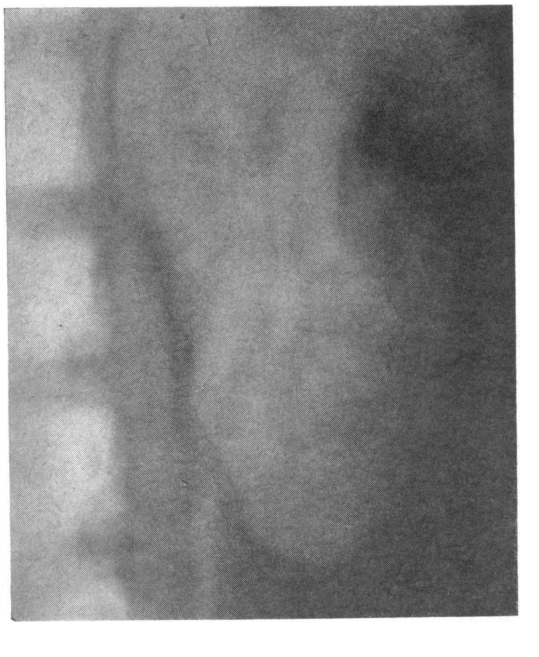


FIG. 2.—Nephrotogram of left kidney.

The longest survivors to date are Case 2 and Case 4, who were first given I.C.R.F. 159 on 5 November and 21 November 1968 respectively. Both still have leukaemic infiltration of the bone marrow, but Case 2 has been weaned off corticosteroids and is clinically well. His peripheral blood picture is virtually normal, and, from being in the terminal stages of his disease when treatment with I.C.R.F. 159 began, he has now been sent back to school.

Case 2 has responded to each of four courses of treatment, and, though he was known as a "good responder," this encourages the hope that there may be other patients in whom the compound—either alone or in combination with other drugs—will control the disease even in the presence of some leukaemic bone-marrow infiltration.

It would appear from this preliminary clinical trial that I.C.R.F. 159 is an effective cytotoxic agent, and as such is of potential interest in the treatment of the leukaemias and lymphosarcomas. Because I.C.R.F. 159 belongs to a new class of antitumour compounds, no cross-resistance was expected and none was seen, even in patients who had received a wide range of antileukaemic chemotherapy.

A dose of 25 to 35 mg./kg./day for not more than four days seems to be a reasonably safe and acceptable course. Greater amounts might be given in cases in which a large amount of malignant tissue is present. Further courses may be given depending on the blood picture. It is desirable to give allopurinol at the same time as I.C.R.F. 159 on every occasion. Corticosteroids do not seem to inhibit or promote the activity either experimentally or clinically, and reduction in the dosage of prednisone did not affect the response to I.C.R.F. 159.

Though the number of patients treated so far is too small to be certain of the optimum conditions for administration, it is worth noting that 30 mg./kg./day of I.C.R.F. 159 by mouth is also a very effective antitumour dose in mice. On the other hand, lower doses by mouth of I.C.R.F. 154 are required to achieve the same antitumour effect as I.C.R.F. 159 in mice. It is therefore surprising that in man very large doses of I.C.R.F. 154 were so well tolerated and without any antileukaemic activity. This is probably owing to failure of absorption—a property which, if confirmed, may point to the use of I.C.R.F. 154 in gastrointestinal malignancies.

No direct cytotoxic effects of I.C.R.F. 154 or 159 on resting cells have been noted in animals or in vitro, but it is difficult to believe that the drastic and rapid falls in circulating primitive white cells were due only to an inhibition of their further production, without a direct cytotoxic action on them. This augurs well for the use of I.C.R.F. 159 in other malignancies.

We thank the clinicians who referred patients to us, particularly Drs. K. Hugh-Jones, H. M. T. Coles, and J. S. Staffurth.

We are also indebted to Dr. R. M. Hardisty, of the Hospital for Sick Children, Great Ormond Street, London, for assessing the effects of I.C.R.F. 154 in three cases, I.C.R.F. 159 in Case 8, and for his comments on this paper.

We are greatly indebted to I.C.I. (Pharmaceuticals) Ltd., particularly Dr. A. L. Walpole, for their co-operation in much of the preclinical pharmacology, toxicology, and pharmaceutical development. They also supplied the tablets of I.C.R.F. 154 and I.C.R.F. 159.

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# *Medical Memoranda*

## Renal Medullary Cystic Disease

[WITH SPECIAL PLATE FACING PAGE 809]

*Brit. med. J.*, 1969, **1**, 824–825

Medullary cystic disease of the kidney is a very rare disorder. It is characterized by the insidious onset of uraemia, usually in childhood or adolescence, and is often accompanied by renal osteodystrophy but rarely by hypertension. The diagnosis is usually made at necropsy, but occasionally it is made during life on the basis of the clinical history and the findings on renal biopsy. These patients have always been uraemic when first seen, and it has not previously been thought possible to obtain an intravenous urogram in any case. With the use of high-contrast dosage and tomography we have obtained *x*-ray films of useful quality in a patient with this abnormality, giving appearances which are considered diagnostic.

### CASE REPORT

A 10-year-old girl was admitted to Margate General Hospital and transferred the following day to the renal unit at Guy's Hospital for the investigation and treatment of her renal failure. For the previous two years she had been generally unwell with increasing pallor, polydipsia, and polyuria; during this time there had been several episodes of fever and dysuria which had subsided spontaneously. For one week she had had vomiting, abdominal pain, and increasing lassitude. There had been no episodes of loin pain or haematuria. In the past she had had two operations for congenital dislocation of the hip. She had four siblings, and neither they nor her parents were known to have renal disease.

On examination she was pale, small for her age (height below the 10th percentile, weight below the 3rd percentile), drowsy, and dehydrated. There was no skeletal deformity. Pulse was 110/min. and B.P. 90/60. The lower pole of the right kidney was palpable but not tender.

Investigations revealed anaemia (haemoglobin 5·1 g./100 ml.; M.C.H.C. 34%) and renal failure (blood urea 520 mg./100 ml.;

creatinine clearance 2·1 ml./min.). The plasma electrolytes were: sodium 120, potassium 5·6, chloride 70, and bicarbonate 8 mEq/l. Her urine contained protein (0·5 g./l.) with a normal sediment, and was sterile on culture. A skeletal survey showed renal osteodystrophy with changes of hyperparathyroidism and rickets.

She was treated with intravenous saline and sodium bicarbonate with rapid improvement, and her blood urea fell to a minimum of 150 mg./100 ml. Subsequently she needed a high fluid intake, a diet restricted in protein, and an oral supplement of sodium bicarbonate.

The first radiological investigation of her urinary tract was a micturating cystogram. This showed a large (700 ml.) bladder which emptied normally. There was no ureteric reflex. Urography was then carried out with 60 ml. of sodium iothalamate (Conray 420) and immediate tomography. This showed normal-size kidneys with smooth outlines. The pelvicaliceal systems were faintly opacified but appeared normal. The most striking finding was the presence of numerous translucent cysts in the corticomedullary region (Figs. 1 and 2). The appearances were thought to be characteristic of medullary cystic disease.

## Comment

Clinically this patient showed features typical of medullary cystic disease. The age of presentation, failure to conserve sodium and water, lack of hypertension, and the presence of severe renal failure with renal osteodystrophy are all characteristic, but not diagnostic. Among several conditions which may present in this way is familial juvenile nephronophthisis (Royer *et al.*, 1963), which is felt by some (Strauss and Sommers, 1967) to be pathologically indistinguishable, though a positive family history is found less often in medullary cystic disease (Strauss and Sommers, 1967). The condition is distinct from medullary sponge kidney (Strauss and Welt, 1963; Heptinstall, 1966), though several authors have confused the two conditions (Mulvaney and Collins, 1956; Lowen and Smythe, 1964). The main differences are in the age groups affected, in the course of the disease, and in the fact that the cysts in medullary cystic disease are at the corticomedullary junction (Strauss, 1962), while those in medullary sponge kidney are in the collecting ducts, and are at the tips of the papillae. Moreover, in medullary sponge kidney most nephrons are normal, while in medullary cystic disease the whole kidney is affected.

This would appear to be the first recorded example of the urographic diagnosis of this condition. The radiological changes are striking and seem to be diagnostic, since they correspond exactly with the morbid anatomy. A case report by Faigel (1964) mentions normal appearances on retrograde pyelography, which is in accord with the pathological findings. The diagnosis can therefore be made only by using a urographic technique designed to demonstrate the renal parenchyma. High dosage of contrast and tomography are now recognized as being of value both in renal failure (Schwartz *et al.*, 1963) and in patients with suspected abnormalities of the renal parenchyma (Saxton, 1968). In the subject with renal failure, as in the normal subject, the nephrogram shows continuous improvement with increasing dosage after opacification of the collecting systems has ceased to show any increase (Doyle *et al.*, 1967). Thus abnormalities of the parenchyma may be demonstrable in renal failure, and the case described above is an excellent example of the diagnostic value of this method.

We would like to thank Dr. T. S. Rogers, of Margate General Hospital, who referred this patient to us.

Requests for reprints to be sent to Dr. C. S. Ogg.

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# Malabsorption Induced by Para-aminosalicylate

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Oral para-aminosalicylate (P.A.S.) is often associated with gastrointestinal disturbances, and, though diarrhoea is not uncommon (Goodman and Gilman, 1965), frank steatorrhoea is not usually recognized in clinical practice. Oral P.A.S., however, has been shown to increase faecal fat excretion experimentally in normal subjects (Levine, 1968). The following report is that of a patient who received P.A.S. and isoniazid therapy for tuberculosis and developed steatorrhoea, which remitted when the P.A.S. was stopped.

## Case Report

In 1946 a brewery clerk aged 33 underwent a Polya partial gastrectomy for peptic ulcer. In 1965 an iron-deficiency post-gastrectomy anaemia was diagnosed. As the serum vitamin $B_{12}$ concentration was low cyanocobalamin was given in addition to oral iron therapy. In February 1968 he developed a left pleural effusion. Pleural biopsy suggested tuberculosis. In view of an admitted high alcohol intake and abnormal liver function tests liver biopsy was performed, which showed early cirrhosis and disseminated tuberculosis. Antituberculous therapy was started with anhydrous sodium P.A.S. 12 g. and isoniazid 300 mg. daily as Inapasade granules. After 12 weeks' treatment he developed frequent blood-stained semi-formed stools. On readmission in June, after 15 weeks' therapy, he had a distended abdomen with visible painless peristalsis. The bowels were open 10 times a day, stools being characteristic of steatorrhoea and streaked with blood and mucus. The pleural