functional impairment prior to the onset of anuria need only be slight. This encourages one to use more vigorous therapy—for example, dialysis with the artificial kidney—than has been the custom in these cases, in the hope that the anuria may be a reversible state. A further indication for vigorous therapy may be obtained by renal biopsy. If casts are infrequent the secondary obstructive element will be absent and a successful outcome might be more reasonably expected. However, as it is not possible to assess either the importance of the obstructive factor or the reversibility of cast formation, all cases should at present be given every chance for survival, provided that other disabilities from the multiple myeloma are not great.

The usual precautions with renal biopsy should of course be taken, bearing in mind the frequency of a bleeding tendency in multiple myeloma.

Summary and Conclusions

Three cases of acute oliguric renal failure developing suddenly in the course of multiple myeloma are described and compared clinically and pathologically with eight other cases previously reported in the literature.

The cause of this clinical picture is as yet unknown. Obstruction of the tubules by Bence Jones protein casts may play a large part, but the small numbers of these casts in three cases suggests some other cause. There is some evidence for glomerular damage, and this could precede the development of casts and play a greater part in the renal damage of myelomatosis than has previously been thought.

Events likely to lower the filtration rate, such as dehydration and intravenous pyelography, are especially likely to produce acute oliguric renal failure in patients with multiple myeloma and should be avoided. Previous tests of renal function have often shown very little, if any, impairment before the sudden onset of anuria.

There is no specific pathological finding to account for the acute oliguria in these cases, and their renal pathology resembles that found in cases of chronic renal involvement with multiple myeloma.

Because of the previous good renal function in many cases, and because the anuria may be reversible, cases of acute renal failure with multiple myeloma should be treated vigorously, provided other symptoms of the disease are not disabling.

I am indebted to Dr. A. A. Palmer, deputy director, Kanematsu Institute of Research, Sydney Hospital, for his thorough and invaluable assistance in describing the pathology in these cases; and to Dr. E. Hirst, pathologist, Sydney Hospital, for his advice and encouragement in preparing this paper.

ADDENDUM.—Since this paper was submitted for publication another example of acute oliguric renal failure arising suddenly in a previously undiagnosed case of multiple myeloma has been admitted to this unit. He was a man aged 56, and one week prior to the event was thought to be well and was doing heavy work. Anuria developed in two days in association with pneumonia, and the patient died in uraemia a week later, just before a dialysis was about to be performed. Extensive marrow replacement with plasma cells was found, together with secondary amyloid of a number of organs, including the kidneys.

REFERENCES

- Addis, T. (1948). *Glomerular Nephritis: Diagnosis and Treatment*, p. 149. MacMillan, New York.
- Allen, A. C. (1951). *The Kidney*, p. 277. Churchill, London.
- Armstrong, J. B. (1949). *J. clin. Invest.*, **28**, 768.
- Bartels, E. D., Brun, G. C., Gammeltoft, A., and Gjørup, P. A. (1954). *Acta med. scand.*, **150**, 297.
- Berlyne, N., and Berlyne, G. M. (1962). *Ibid.*, **171**, 39.
- Bradley, S. E., and Bradley, G. P. (1947). *J. clin. Invest.*, **26**, 1010.
- Cecil, R. L., and Loeb, R. F. (1959). *A Textbook of Medicine*, 10th ed., p. 1062. Saunders, Philadelphia.
- De Wardener, H. E. (1961). *The Kidney*, 2nd ed., p. 336. Churchill, London.
- Engle, R. L., and Wallis, L. A. (1957). *Amer. J. Med.*, **22**, 5.
- Goldman, R., Adams, W. S., and Luchsinger, E. B. (1952). *J. Lab. clin. Med.*, **40**, 519.
- Harrison, T. R., et al. (1958). *Principles of Internal Medicine*, 3rd ed., p. 1228. McGraw-Hill, New York.
- Holman, R. L. (1939). *Arch. Path.*, **27**, 748.
- Killmann, S., Gjørup, S., and Thaysen, J. H. (1957). *Acta med. scand.*, **158**, 43.
- Kobernick, D., and Whiteside, J. H. (1957). *Lab. Invest.*, **6**, 478.
- Kolff, W. J. (1955). *Med. clin. N. Amer.*, **39**, 1041.
- Macalister, C. L. O., and Addison, N. V. (1961). *Brit. J. Urol.*, **33**, 141.
- Merrill, J. P. (1955). *The Treatment of Renal Failure*, pp. 71 and 133. Grune and Stratton, New York.
- Milne, M. D. (1962). *Brit. med. J.*, **1**, 175.
- Myhre, J. R., Brodwall, E. K., and Knutsen, S. B. (1956). *Acta med. scand.*, **156**, 263.
- Osserman, E. F. (1959). *New Engl. J. Med.*, **261**, 1006.
- Perillie, P. E., and Conn, H. O. (1958). *J. Amer. med. Ass.*, **167**, 2186.
- Smith, H. W. (1951). *The Kidney—Structure and Function in Health and Disease*, p. 657. Oxford Univ. Press, London.
- Vassar, P. S., and Culling, C. F. A. (1962). *Arch. Path.*, **73**, 59.

ACUTE RENAL FAILURE COMPLICATING A RETICULOSIS REMISSION FOLLOWING HAEMODIALYSIS

BY

H. DUNCAN, M.Sc., M.R.C.P.

W. ELLIOTT, M.D.

M. HALL, M.R.C.P., D.Obst.R.C.O.G.

D. N. S. KERR, M.Sc., M.R.C.P., M.R.C.P.Ed.

AND

A. J. WORT, M.B., B.S.

*From the Artificial Kidney Unit, Royal Victoria Infirmary,
and the Department of Pathology, University of Durham,
Newcastle upon Tyne*

Acute renal failure is a well-recognized complication of leukaemia, the lymphomas, polycythaemia vera, and myelofibrosis (Merrill, 1940; Merrill and Jackson, 1943; Lear and Oppenheimer, 1950; Kravitz et al., 1951; Weisberger and Persky, 1953; Kritzer, 1958; Greenbaum and Hope Stone, 1959). Cellular infiltration and amyloidosis are important contributory causes in some cases, but the usual cause of the renal failure is hyperuricaemia secondary to excessive cellular breakdown. It is therefore most commonly seen after successful treatment with cytotoxic drugs or irradiation, but can occur spontaneously, when it presumably coincides with a sudden increase in the output of uric acid. These peaks of uricosuria are often seen in the course of untreated leukaemia (Sandberg et al., 1956).

Quite large amounts of uric acid are removed when patients with renal failure are treated with the artificial kidney (Goldberg et al., 1960; Kennedy et al., 1961), and haemodialysis has been used in treating the hyper-

uricaemia of gout (Duncan *et al.*, 1962). Haemodialysis might therefore serve two functions in the hyperuricaemia of myelo-proliferative disorders—correction of the uraemia and removal of its immediate cause. It has been employed in the treatment of four reported cases of this syndrome (Firmat *et al.*, 1960); three of the patients died within a few days of dialysis, but in the fourth renal function returned for the six weeks before death from acute leukaemia.

We record here a further instance of the reversal of severe renal failure in a reticulosis following treatment by haemodialysis.

Case Report

A student aged 18 was admitted to hospital in coma. There were no complaints until 12 days before admission, when he began to suffer from malaise, lassitude, nausea, and occasional vomiting. For the last two days he had experienced increasing drowsiness and frequent vomiting. There was no history of urinary complaints. Abnormal findings on examination included arachnodactyly, high arched palate, tachycardia, B.P. 130/0, and coma with response only to painful stimuli.

His urine contained albumin + and increased numbers of white cells. His Hb was 8.7 g./100 ml.; platelets 500,000/c.mm.; W.B.C. 3,300/c.mm.; plasma urea 434 mg./100 ml.; potassium 8.4 mEq/l.; bicarbonate 11 mM./l. The electrocardiogram showed peaked T waves and widened QRS complexes in keeping with the plasma potassium level. Lumbar puncture yielded normal cerebrospinal fluid under normal pressure.

He was treated by haemodialysis with an Alwall artificial kidney for six hours; the plasma potassium fell to 3.2 mEq/l. and the urea to 180 mg./100 ml. Next day he regained consciousness. Cystoscopy, retrograde pyelography, and renal biopsy were performed; bladder mucosa, ureteric orifices, and pyelographic appearances were normal. The renal biopsy was reported as follows: "The glomeruli and tubules are separated by large numbers of deeply staining, fairly uniform cells which are probably neoplastic. Some of the tubules contain polymorphs" (Fig. 1).

On receipt of this unexpected report a search for other evidence of reticulosis was carried out. No enlarged lymph nodes were palpable, or were visible on chest radiograph; films of blood, buffy coat, and bone-marrow and biopsy of liver were normal. At laparotomy liver, spleen, and abdominal nodes appeared normal; the kidneys were moderately enlarged.

There was a further rise in blood urea post-operatively (Fig. 2), but a spontaneous diuresis then occurred and blood urea fell to normal levels. For three months he remained in excellent health, regained 10 kg. of lost weight, and had no urinary or other symptoms. At the end of this period nausea, vomiting, and loss of weight recurred. He was

readmitted with drowsiness, hiccup, abdominal pain, rectal bleeding, acidotic breathing, and oliguria. His plasma urea was 491 mg./100 ml.; potassium 7.1 mEq/l.; bicarbonate 7 mM./l.; Hb 11.5 g./100 ml.; W.B.C. 12,200/c.mm. (no atypical cells seen); platelets 250,000/c.mm. Urine contained albumin and a heavy deposit of urates.

FIG. 2.—Plasma urea (solid line) and uric acid (broken line) levels during the course of illness. D=Haemodialysis.

A further haemodialysis was carried out, and after this procedure the urine output rose to 2 l./day. Two days later he began to complain of pain in the big toe, and within a further two days developed a typical gouty arthritis of the metatarsophalangeal joint. His plasma uric acid on four occasions over the following week was between 10 and 13 mg./100 ml., although his blood urea was now below 50 mg./100 ml.

Further marrow films showed numerous blast cells, and he was treated with blood transfusion and 6-mercaptopurine but continued to develop attacks of gout in his feet and hands. The plasma uric acid steadily increased. At first the urine volume was well maintained and the plasma urea rose more slowly. Two months after the second dialysis, when the plasma uric acid reached 50 mg./100 ml., there was an abrupt fall in urine output and a rapid rise in plasma urea until his death four days later (Fig. 2). Blast cells were present in his blood for the last two weeks of his life, and in view of this haematological deterioration further haemodialysis was deemed unjustifiable.

At necropsy the kidneys were enlarged to twice normal size (total weight 650 g.). On section there were areas of infiltration by dense white neoplastic tissue and some uric-acid infarcts in the pyramids. The capsule stripped easily, leaving a smooth surface.

Histological examination of the kidneys showed that the glomeruli and tubules were widely separated, the intervening spaces being infiltrated by neoplastic cells, giving an appearance identical with the original biopsy. Sections of tissue fixed in absolute alcohol and stained by the Schultz-Schmidt technique showed scattered crystals of uric acid (Fig. 3).

Similar neoplastic infiltration was found in the bone-marrow, pancreas, liver, and periadrenal fat. Other organs, including the spleen and several lymph nodes, were normal. A diagnosis of reticulum-cell sarcoma was made.

Discussion

Although plasma uric acid was not measured during the first two episodes of acute renal failure the clinical pattern of these was so similar to the final one, and also to hyperuricaemic crises described by previous authors, that it is highly probable the pathogenesis was

FIG. 1.—Biopsy specimen of kidney showing malignant cellular infiltration. (Haematoxylin and eosin. $\times 400$.)

identical on each occasion. In the final episode the rise in plasma uric acid to levels which involved marked supersaturation of the plasma was followed by oliguric renal failure with crystallization in the renal medulla.

FIG. 3.—Post-mortem specimen of kidney showing uric acid and urates in tubule. (Schultz-Schmidt. $\times 500$.)

Removal of a considerable proportion of the excess uric acid from the patient by haemodialysis might be expected to result in a temporary improvement in renal function. Presumably this is the explanation of the return of normal urine output and sustained fall in plasma urea level after the second dialysis, since there was no evidence of haematological improvement at this stage.

The longer and more complete return of renal function after the first dialysis was probably due in part to a remission in the underlying reticulosis, for during the dialysis and following his liver biopsy and laparotomy he received a total of 5 litres of blood. A temporary remission of acute leukaemia is known to occur in about 30% of adults treated by blood transfusion alone (Hayhoe and Whitby, 1955), and during such a remission there is a striking fall in uric-acid output (Dickinson, 1960). As with our patient, the response to a second transfusion is usually less complete.

Conclusions

Haemodialysis has a useful place in the treatment of hyperuricaemic crises. Normal or near-normal renal function may be restored for a few weeks, during which the original cause can be treated. It should therefore be particularly useful in the crises that sometimes follow the start of treatment in polycythaemia vera and chronic myeloid leukaemia. Since older children and adults can now be treated on the artificial kidney with minimal discomfort it may even be indicated in occasional cases of acute leukaemia.

We acknowledge the help of Professor G. A. Smart and Mr. J. Swinney in the clinical management of the patient; of Professor A. L. Latner in the biochemical investigations; and of Dr. R. O. Schade, who reported the renal biopsy.

REFERENCES

- Dickinson, C. J. (1960). *Brit. med. J.*, **1**, 1027.
 Duncan, H., Elliott, W., Horn, D. B., Kerr, D. N. S., Pearson, D. T., and Robson, A. M. (1962). *Lancet*, **1**, 1209.
 Firmat, J., Vanamee, P., Klauber, L., Krakoff, I., and Randall, H. T. (1960). *Cancer (Philad.)*, **13**, 276.
 Goldberg, M., Castleman, L., and Wallace, S. L. (1960). *J. Lab. clin. Med.*, **55**, 268.
 Greenbaum, D., and Hope Stone, H. F. (1959). *Lancet*, **1**, 73.
 Hayhoe, F. G. J., and Whitby, L. (1955). *Brit. J. Haematol.*, **1**, 1.
 Kennedy, A. C., Grav, M. J. B., Dinwoodie, A., and Linton, A. L. (1961). *Lancet*, **2**, 996.
 Kravitz, S. C., Diamond, H. D., and Craver, L. F. (1951). *J. Amer. med. Ass.*, **146**, 1595.
 Kritzer, R. A. (1958). *Amer. J. Med.*, **25**, 532.
 Lear, H., and Oppenheimer, G. D. (1950). *J. Amer. med. Ass.*, **143**, 806.
 Merrill, D. (1940). *New Engl. J. Med.*, **222**, 94.
 — and Jackson, H. (1943). *Ibid.*, **228**, 271.
 Sandberg, A. A., Cartwright, G. E., and Wintrobe, M. M. (1956). *Blood*, **11**, 154.
 Weisberger, A. S., and Persky, L. (1953). *Amer. J. med. Sci.*, **225**, 669.

Preliminary Communications

Transfer of Erythropoietin to Amniotic Fluid in Rh-immunized Pregnant Women

Studies on the plasma erythropoietin (erythrocyte-stimulating factor) levels in cord blood from normal and anaemic infants indicate that the regulatory mechanism of erythropoiesis through erythropoietin is intact in the last part of intrauterine life (Halvorsen, 1963). Normal newborn infants have slightly elevated plasma erythropoietin levels in cord blood, while severely anaemic erythroblastotic infants may have markedly elevated erythropoietin levels (Halvorsen, 1963).

It has previously been reported that erythropoietin is excreted in the urine of anaemic children (Piliero *et al.*, 1956). Whether or not this is true also in the foetus and the newborn infant is unknown, but may be suspected. Although the formation and resorption of the amniotic fluid are only partially understood, there is general agreement that the foetus passes urine into the amniotic fluid. The volume of urine passed and the part this excretion plays in the amniotic fluid balance is, however, unknown.

The prenatal diagnosis of the severity of erythroblastosis has been increasingly important since it has been suggested that induction of labour before term may be essential in reducing the mortality rate of erythroblastosis. Besides the maternal anti-Rh titres, the bilirubin content of the amniotic fluid has been proposed as a useful guide (Walker, 1957), but fails in many cases. It will therefore be of importance if other indices can supplement the present tests used in the prenatal diagnosis of erythroblastosis.

These facts and considerations raise the following questions: Do anaemic erythroblastotic newborn infants excrete erythropoietin in the urine? Does erythropoietin occur in the amniotic fluid in Rh-immunized pregnant women? If erythropoietin is transferred to the amniotic fluid, is it excreted with the foetal urine or transferred through the foetal membranes? Does the amount of erythropoietin in the amniotic fluid have any relationship to the anaemia of the foetus and the severity of erythroblastosis?

MATERIAL AND METHODS

Amniotic fluid was collected from normal and Rh-immunized pregnant women either by trans-abdominal amniocentesis before term or by membrane rupture during delivery or during caesarean section. Cord blood and blood withdrawn during the first part