RECENT ADVANCES IN RENAL DISEASE

N. F. JONES

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PREFACE

This first edition on Renal Disease in the long-established Recent Advances series indicates the position now held by Nephrology as a specialty in its own right. The growth of Nephrology has resulted in large part from the development of regular haemodialysis and renal transplantation. The medical and immunological aspects of renal transplantation are covered in Chapters 9 and 10, but less attention is given to the details of regular haemodialysis. I thought it inappropriate to consider the technology and highly specialised practice of regular dialysis in a book of this nature. The more general and social aspects of such replacement therapy for terminal renal failure are considered in Chapter 5, while Chapters 6, 7 and 8 deal with special problems in the management of advanced renal disease.

The text is not a comprehensive account of Nephrology but a series of topics considered to be 'growing points'. Particular attention to recent advances is given throughout but in this, the first, edition the contributors also take a broader look at the 'present state of the art' in their subjects.

Most of the authors are clinical nephrologists but histologists, an immunologist and a pharmacologist also contribute. The book is intended primarily for postgraduate students of medicine in general, but nephrologists may well find much of interest outside their own particular fields. The chapters on glomerulonephritis should also prove of use to pathologists interested in the kidney.

It is my pleasure to thank Professor De Wardener and Sir Douglas Black for their advice when I was planning this book. Useful criticism was also given me by many other colleagues, both senior and junior, and I thank them. I am most grateful to Miss Carol Stevenson and Miss Margaret Matthews for their help, given so willingly, with the secretarial and bibliographic work involved. My thanks are also due to the representatives of Churchill Livingstone who have made collaboration with them easy and pleasant. Finally, I will always be grateful to my patient wife and our family for creating an atmosphere in which this extra work could be undertaken without stress.

CONTRIBUTORS

A. W. ASSCHER MD BSc FRCP
Reader in Medicine and Hon. Director, KRUF Institute of Renal Disease, Welsh National School of Medicine, Cardiff

J. R. BATCHELOR MD
Hon. Professor of Transplantation Research, Royal College of Surgeons of England and Director of McIndoe Memorial Research Unit, Queen Victoria Hospital, East Grinstead, Sussex

G. W. BISSET DPhil MB BS
Professor of Pharmacology, St Thomas' Hospital Medical School, London

WILLIAM B. BLYTHE MD
Chief, Division of Nephrology, Department of Medicine, University of North Carolina, Chapel Hill, North Carolina, U.S.A.

G. W. BOYD MD BS PhD(Melb.) FRACP
First Assistant in Medicine and Honorary Senior Physician, Austin Hospital, Heidelberg, Victoria, Australia. Recently Senior Lecturer in Medicine, St Mary's Hospital, London

W. R. CATTELL MD FRCP FRCP(Edin.)
Consultant Nephrologist, St Bartholomew's and St Leonard's Hospitals, London

H. E. de WARDENER MBE MD FRCP
Professor of Medicine, Charing Cross Hospital Medical School, London

J. B. EASTWOOD MB BS MRCP
Lecturer in Medicine, Charing Cross Hospital Medical School, London

BARRY HULME BSc MD MRCP
Consultant Nephrologist and Honorary Senior Lecturer, St Mary's Hospital and Medical School, London

M. S. R. HUTT MD FRCP FRCPath
Professor of Geographical Pathology, St Thomas' Hospital Medical School, London

N. F. JONES MA MD FRCP
Consultant Physician and Senior Lecturer, St Thomas' Hospital and Medical School, London

J. F. MOORHEAD MB FRCP
Director, Department of Nephrology and Transplantation, Royal Free Hospital, London

L. J. MOREL-MAROGER
Maître de Recherche à l'INSERM, Department of Nephrology and INSERM U.64, Hôpital Tenon, Paris

D. K. PETERS MB MRCP
Lecturer, Royal Postgraduate Medical School and Consultant Physician, Hammersmith Hospital, London

PETER RICHARDS MD PhD MRCP
Consultant Physician and Senior Lecturer in Medicine, St George's Hospital and Medical School, London

P. J. VERROUST
Charge de Recherche à l'INSERM, Department of Nephrology and INSERM U.64, Hôpital Tenon, Paris

R. H. R. WHITE MD FRCP DCH
Consultant Paediatrician and Nephrologist, The Children's Hospital, Birmingham

D. GWYN WILLIAMS MD MRCP
Consultant Nephrologist, Guy's Hospital, London

CONTENTS

1. ACUTE RENAL FAILURE

W. R. Cattell

Acute failure of kidney function remains one of the most dramatic, therapeutically demanding, yet gratifying, clinical conditions with which the physician may deal. Its importance lies in the potential for restoration of renal function in patients who except for correct diagnosis, careful and skilled management would otherwise die.

Success with renal replacement therapy in patients with chronic renal failure, whether by maintenance dialysis or transplantation, has led to a considerable shift in attention from acute to chronic renal failure, to the extent that acute renal failure may be receiving less than optimum attention. A continuing high mortality, although possibly reflecting a change in the type of case encountered, leaves no place for complacency in the management of these patients.

With respect to aetiology, diagnosis and treatment much remains to be defined. Thus the pathogenetic mechanisms of acute renal failure complicating shock and sepsis remain unclear and in consequence little advance can be made in the development of prophylactic or therapeutic measures. The differential diagnosis of renal failure is often difficult. High dose excretion urography has materially affected the distinction between obstructive and non-obstructive disease, but its role in the differential diagnosis of acute parenchymal lesions remains to be fully assessed. New or changing therapeutic measures, such as the use of high doses of diuretics, peritoneal dialysis versus haemodialysis, and the use of daily dialysis must all be evaluated. Far from being static, the whole field of acute renal failure is constantly changing and it is the purpose of this chapter to attempt to identify where major changes are occurring and to evaluate the present state of knowledge.

THE CHANGING PATTERN OF INCIDENCE AND CAUSATION

It is difficult, if not impossible, to define the incidence of acute renal failure in hospital practice as a whole. A striking feature of the past 10 years has been a change in the nature of the case referrals to large dialysis centres. Thus Kerr, Rabindranath and Elliott (1968) have observed a marked reduction in the proportion of obstetric cases among their patients presenting with acute renal failure—an experience shared by Kennedy et al (1973) and most

renal units in Britain. An increase in the proportion of cases due to surgical and medical conditions has been reported, with a significant increase in median age of the patients. A further trend reported by both British and Scandinavian units (Alwall, 1964) is a decline in overall numbers referred to specialist renal units. Two conclusions can be drawn—that the incidence of acute renal failure in obstetric cases and younger patients has declined—possibly because of a reduction in the number of criminal abortions and better peri-operative care—or that larger numbers of cases are being managed at peripheral district hospitals. With the definition of standard methods of treatment, the training of a new generation of physicians in the management of acute renal failure, and the more general availability of peritoneal dialysis, there is no doubt that increasing numbers of patients with acute renal failure are indeed being managed in non-specialist units.

Experience of battle casualties in Korea and Vietnam has shown a significant reduction in the incidence of acute renal failure with the introduction of early air evacuation and earlier and more effective treatment of shock (Hardaway, 1968; Whelton and Donadio, 1969). While it is difficult to document a similar trend in civilian practice, this wartime experience emphasises the need for early and intensive treatment of patients with major trauma (Kerr, 1972).

While the aetiology of acute renal failure in general has remained much the same over the years, new causes have also been recognised and, with immigration and changing social habits, causes rarely encountered previously have become more common. Some are worthy of special notice.

Drug Nephrotoxicity

Possibly because of its large blood flow and the concentration of drugs in tubular fluid and the medullary interstitium, the kidney is at more risk from the toxic effects of many drugs than other organs (Lant, 1972). The whole subject of drug and chemical nephrotoxicity has in the past been extensively reviewed by Schreiner and Maher (1965) and Milne (1967). Since then, further drug hazards have been identified. The most immediate problem has been the potential nephrotoxicity associated with the introduction of new and powerful antibiotics.

CEPHALOSPORINS

Six antibacterial agents, each based on the same cephalosporin nucleus have been developed—cephaloridine, cephalothin, cephalexin, cephradine, cephacetrile and cephazolin—the latter two not yet being on general release (Wise, 1974). Among this family, cephaloridine appears to have special nephrotoxic properties. The effect is dose-related and reversible. In rabbits large doses (200 mg/kg/day) induce proximal tubular necrosis and renal impairment (Perkins et al, 1968). Proteinuria and hyaline casts have been

observed in the urine of patients given 6 g of cephaloridine/day (Linsell, Pines and Hayden, 1967). Previous renal damage may predispose to further nephrotoxicity due to cephaloridine (Lawson et al, 1970) and the combined use of cephaloridine with frusemide is associated with a significant increase in the incidence of kidney damage (Foord, 1969). Simultaneous administration of gentamycin may also enhance nephrotoxicity.

Renal damage may rarely be observed with other members of this group of antibiotics. Thus there is some evidence that the combined use of cephalothin and gentamycin is nephrotoxic (Fillastre et al, 1973), and renal damage may also arise with the use of cephazolin. Precisely why such nephrotoxicity should be observed with some members of this family of antibiotics and not with others is far from clear, but may relate to significant differences in protein-binding or liver and tissue metabolism (Lant, 1972). The use of cephaloridine should be avoided in patients with renal disease and those undergoing diuretic therapy. If antibiotic sensitivities demand it, cephalothin would appear to combine maximum antibiotic effectiveness and minimum toxicity, but should not be used in combination with gentamycin.

COLISTIN

In recent years there has been increasing evidence of nephrotoxicity, including acute tubular necrosis, with colistin methane sulphonate (colistemethate) (Brumfitt, Black and Williams, 1966; Koch-Weser et al, 1970). Interestingly there appears to be some nephrotoxic synergism when given in conjunction with cephaloridine. Large doses carry an even higher risk of acute tubular necrosis (Price and Graham, 1970).

AMPHOTERICIN B

The nephrotoxic properties of this antifungal agent have been well recognised for many years (Bell et al, 1962; Butler, 1966), but its increasing use in clinical practice requires reiteration of the hazard. Toxicity is manifest in acute tubular damage with impaired concentrating ability, reduced hydrogen ion excretion, a Fanconi-like syndrome and nephrocalcinosis (McCurdy, Frederic and Elkington, 1968). Renal damage following Amphotericin B is not always reversible.

TETRACYCLINE

It has long been known that the administration of tetracycline to patients with renal impairment commonly leads to increasing uraemia (Bateman et al, 1952; Shils, 1963; Wray, Kocen and Wright, 1965). Despite this, most renal units regularly admit patients with acute uraemia which has been precipitated by the administration of this drug (Philips et al, 1974). Pre-existing renal disease was sometimes unsuspected, but on a distressing number of occasions renal insufficiency was known to be present. Such is the frequency of the misuse of tetracycline that it has been our practice for some years to

provide patients who have chronic renal failure with a card specifically warning against the use of this drug.

Some controversy exists as to whether the uraemia induced by tetracycline results entirely from reversible extrarenal mechanisms or is associated with non-reversible kidney damage. There is fairly general agreement that an important factor is reduced protein synthesis and consequent deviation of amino acids to urea formation (Shils, 1962, 1963). Sodium excretion is increased during tetracycline therapy and it has been suggested that salt wasting with secondary fluid depletion may contribute to the uraemia (Philips et al, 1974). Roth et al (1967) reported reduction in creatinine clearance with reduced urine concentrating ability in some healthy subjects given tetracycline while others have reported vasopressin resistant diabetes insipidus after demethylchlortetracycline (Torin, 1967) (see Chapter 14). This renal impairment is quite distinct from the reversible Fanconi-like syndrome produced by degradation products of tetracycline (Benitz and Diermeier, 1964).

In clinical practice there have been many reports of reduced renal excretory function following an episode of acute uraemia induced by tetracycline (Philips et al, 1974). It is commonly impossible to attribute this solely to a direct nephrotoxic effect of the drug, as opposed to the effects of intercurrent infection, dehydration or hypotension, but tetracycline should not be given to patients with renal insufficiency. Doxycycline, although belonging to the tetracycline group of drugs, has been reported not to cause a rise in urea (Little and Bailey, 1970).

HEROIN ADDICTION

While addiction to heroin is not a serious problem in the United Kingdom occasional cases are encountered and acute renal failure resulting from the self-administration of adulterated heroin has been observed. Richter et al (1971) reported four patients with acute rhabdomyolisis following the intravenous administration of adulterated heroin and the author has observed a similar case. Acute renal failure developed in two of the American series and in the patient encountered in London. The dominant feature of the syndrome is acute skeletal muscle necrosis with gross myoglobinuria. To what extent the various adulterants, such as quinine, contribute to the renal lesion is unknown (Richter et al, 1971). This cause of acute renal failure must be kept in mind in patients presenting with bizarre clinical syndromes and evidence of drug abuse.

Acute Renal Failure in Immigrant Populations

Population changes consequent on immigration have brought previously uncommon diseases into British hospitals. Included among these are various haemoglobinopathies and inherited haemolytic anaemias. Rarely, but occasionally, such inherited diseases may be the cause of acute renal failure.

Papillary necrosis is a recognised complication of both sickle cell disease and trait (Harrow, Sloane and Leibman, 1963; Reynolds, 1965), and, particularly when associated with acute urinary infection, may rarely present as acute renal failure. Calcification of necrosed papillae may lead to the erroneous diagnosis of calculus disease. Haemoglobin electrophoresis should always be carried out when obstructive uropathy is diagnosed in negroid patients.

Inherited deficiency of glucose-6-phosphate dehydrogenase has been shown to be prevalent in many parts of the world. It is especially common in Caucasians of Mediterranean origin, Sephardic and Kurdish Jews. Of special interest is the so-called 'primaquine' sensitive type observed in some 10 per cent of Negroes and a variable percentage of individuals of other races. The name is derived from the observation that acute haemolysis can be induced in otherwise healthy individuals with this abnormality following the ingestion of primaquine and other drugs (Table 1). Scattered reports of acute renal failure

Table 1 Drugs which may cause acute haemolysis in 'primaquine-sensitive' glucose-6-phosphate dehydrogenase deficiency

Primaquine, Pamaquine	Sulfones
Nitrofurantoin	Phenacetin, Acetanilid
Vitamin K substitutes	Acetyl salicyclic acid
Sulphonamides	Probenecid
Para-amino salicylic acid	
Naphthalene	Plant poison—Fava bean

in patients with glucose-6-phosphate dehydrogenase have been reported, particularly from endemic areas. The frequency of renal failure complicating acute haemolysis in this condition appears to be low (Symuoulidis et al, 1972). It has been claimed (Owusu et al, 1972) that the association of severe anaemia and urinary tract infection is a special prerequisite for development of acute renal failure but this is not the experience of others (Symuoulidis et al, 1972). Acute renal failure has been described in the absence of infection following the ingestion of large amounts of a phenacetin-containing drug (Brown et al, 1972a). It would seem not unreasonable, however, to expect renal failure more commonly in patients with fulminating infection as the latter may both induce haemolysis and predispose to acute tubular necrosis. The situation may then be compounded by treatment with sulphonamide-containing drugs.

PATHOGENIC MECHANISMS IN ACUTE RENAL FAILURE

The causes of acute renal failure have been the subject of several excellent reviews (Muehrcke, 1969; Kerr, 1972). In many instances the primary mechanism of the renal failure is clear cut, as for example, with acute obstructive uropathy, acute proliferative glomerulonephritis, renal artery occlusion or acute parenchymal disease resulting from nephrotoxins or allergic lesions.

Even in these cases, some controversy exists as to the role of intravascular coagulation. Much greater controversy surrounds the pathogenetic mechanisms involved in the development of acute renal failure following haemorrhage, trauma or sepsis. Definition of the pathogenesis of this condition is not merely of academic interest for, should the mechanisms involved be defined, there then arises the possibility of effective prophylaxis and treatment.

The functional abnormality in 'acute tubular necrosis'

The acute reversible renal failure which may follow a mismatched blood transfusion, haemorrhagic or septicaemic shock, crushing injury and certain poisoning is still referred to by a variety of names, such as crush syndrome, shock kidney, haemoglobinuric nephropathy. Most popular has been the use of the term acute tubular necrosis which stems from the observation that in patients with acute renal failure following shock, the glomeruli and blood vessels appear for the most part histologically normal, whereas the tubular epithelium is extensively, albeit irregularly, damaged (Oliver, MacDowell and Tracy, 1951). It was presumed that the cause of the renal failure was tubular obstruction by cell debris, haemoglobin or myoglobin casts, with back diffusion of filtrate through damaged tubular walls. Doubts regarding this concept were first expressed many years ago. Thus it was repeatedly pointed out that while frank tubular necrosis is evident in the majority of cases, it is by no means always present (Brun and Munck, 1957; Sevitt, 1959; Finckh, Jeremy and Whyte, 1962). Further, comparable degrees of necrosis may be observed in autopsy studies of patients who did *not* have oliguria or uraemia.

Little progress was made for many years because of the inadequacy of conventional clearance methods for distinguishing between impaired blood flow, tubular obstruction and back diffusion of filtrate. As a result of the application of new techniques the emphasis has now shifted firmly towards reduced cortical blood flow and diminished glomerular filtration as the principal functional abnormalities in acute renal failure.

Renal blood flow in acute renal failure

Considerable controversy has existed for years as to the role of altered blood flow to the kidney in inducing and maintaining acute renal failure. Trueta and his colleagues in 1947 reported diversion of blood flow away from the cortex to the medulla following stimulation of the sciatic nerve and splanchnic nerves in rabbits. For many years, this work was criticised and largely discounted on methodological grounds. Studies in man now clearly show that during oliguric renal failure blood flow through the kidney is reduced, but only to levels of 30 to 40 per cent of normal (Brun et al, 1955; Shaldon et al, 1964; Reubi, Gossweiler and Gürtler, 1966), and indeed normal blood flow has been observed (Reubi et al, 1966). Similar rates of renal blood flow are common in non-oliguric patients with chronic renal