Papers and Originals

Diagnosis in Renal Disease*

D. A. K. BLACK,† M.D., F.R.C.P.

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Two things are needed in the choice of subject for a formal lecture. The speaker must be interested in the subject, or he will even bore himself, and he must not know too much about it, lest he risk boring his audience. I am quietly confident of my choice of subject on both these counts. It would be difficult to work among nephrologists, and more important to see personally many patients with renal disease, without becoming interested in the diagnostic problems which they raise. On the other hand, I cannot regard myself as a full-blown nephrologist, for I was brought up in the older tradition of renal disease forming part of internal medicine, and I found my research interest in the disorders of body fluid rather than in the kidney itself. Certainly one cannot study body fluid without paying some attention to the organ which plays the paramount part in homeostasis; but my own personal concern has been more often with the kidney as victim of body fluid depletion, rather than as the prime mover, by virtue of intrinsic renal disease.

A decade or so ago I wrote an essay (Black, 1960) which suggested, in the context of renal disease, that the concept of the syndrome had practical as well as theoretical advantages, in that it opened the way to effective treatment of patients in whom a precise aetiological or morphological diagnosis might not be available. Looking back, it seems clear that I was moving with a tide which has brought to acute renal failure a less anxious course, and to chronic renal failure the hope of prolonged survival through a judicious combination of dialysis and transplantation. This tide is still running strongly, to the great benefit of many a patient; why should it now seem timely to tackle a different aspect of renal disease? I think there are several reasons, of which the following may be paramount. The widespread use of renal biopsy has brought a new and living dimension to the natural history of renal disease. The advent of more powerful, but also potentially hazardous, therapeutic agents has made it necessary to scrutinize more closely the indications for their use which, of course, include a precise characterization of the pathogenic process. Thirdly, and perhaps more speculatively, the whole science of clinical taxonomy is in a phase of development, under the stimulus of the new mathematics of sets or clusters, and the power of computers in the storage and processing of clinical observations (Card, 1967; Feinstein, 1967). I hope to illustrate these themes in the latter part of this lecture; but first I would consider some of the general principles of renal diagnosis.

Approach to Clinical Problems

I have been helped over the years in my approach to medicine by a categorization which is no doubt instinctively used by most doctors, but was first made explicit for me by Paul White, of Boston, in a wartime edition of his textbook on heart disease. He spoke of the aetiological, the structural, and the functional aspects of cardiac disease in the following terms (White, 1944): "While we should thus emphasise etiology and consider it first and generally foremost, we must not lose sight meanwhile of the other two legs of the tripod of cardiac diagnosis; structural change and functional condition. All together the three elements complete satisfactorily our modern idea of analysis of a cardiac case. This represents another step in our progress and a sound one, built upon the experience of the past and of the present. Instead of diagnosing simply mitral stenosis, or auricular fibrillation, or rheumatic heart disease in a given case, we should make the complete diagnosis of rheumatic heart disease (etiological) with mitral stenosis (structural defect) and auricular fibrillation (disorder of function)."

I would like to suggest that in approaching a clinical problem we should have three questions in mind: What type of pathological process is at work? What structural damage is it causing? What disturbance of function is it causing?

Briefly speaking, the knowledge needed to answer the first of these questions is derived from general pathology, including immunology and experimental pathology. The answer to the second is based on morbid anatomy, and it is here that renal biopsy is most germane to the individual patient, though it has also contributed to our general knowledge of renal disease. The third question looks for its answer to the basic and applied physiology of the kidneys and body fluid.

As techniques multiply and become more complex, it becomes less likely that the same man can operate at the fringe of knowledge in a spread of disciplines from electron microscopy and immunoelectrophoresis to micropuncture and isotope distribution. Nevertheless, before I come to particulars, I would like to make the general point that in spite of, and perhaps even because of, the growing mass of various information there is a place for the synoptic view—knowing in general terms what is being done in these various fields, and bringing the knowledge together. This is perhaps part of the justification for the new specialty of clinical nephrology, and I think further that its value can be illustrated from the history of nephrology over the past few decades. When I first became interested in the kidney, before the last war, there was already a mass of information on the morbid anatomy of the kidney, notably from the German school of Volhard; on renal physiology, in which Van Slyke and Homer Smith were opening the way to rigorous quantitative analysis, applicable to the

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† Professor of Medicine, University of Manchester; Physician, Manchester Royal Infirmary.

human kidney; and on the natural history of renal disease, in which the English school was not unworthy to succeed Bright. But these three worlds seemed somehow separated one from another.

One aspect of the progress made since then has been the increasing correlation of anatomical, physiological, and clinical information. Probably no two nephrologists would pick out the same milestones along this road; but for me there were two—the publication of Ellis's Croonian lecture to this College entitled "The Natural History of Bright's Disease: Clinical, Histological, and Experimental Observations" (Ellis, 1942); and the Ciba Foundation symposium on the kidney in 1953, which gathered together renal physiologists, pathologists, and clinicians in common informal discussion (Lewis and Wolstenholme, 1954). Neither of these endeavours reached its goal of integration, but they showed that the attempt was both possible and worth while; and the multidisciplinary approach has continued and extended, by collaboration between individuals, by many small symposia and by discussion in national societies and in the triennial meetings of the International Society of Nephrology.

Evidence on Aetiology

Probably the most important, direct, and practical application of fundamental biological knowledge to renal disease lies in the characterization of the organism in patients with urinary infection, and the determination of its sensitivity to the wide range of bactericidal and bacteriostatic agents now available. This subject has, however, been reviewed a number of times, and I may be allowed to refer to the excellent symposium held in this College, whose proceedings were edited by O'Grady and Brumfitt (1968). In this lecture I can hope at best to be illustrative, and in no way comprehensive; and as my example, in the matter of aetiology, I prefer to turn to the other major disease-complex affecting the kidney, that of glomerulonephritis. I have reviewed elsewhere the general evidence which suggests that glomerulonephritis has commonly an allergic basis (Black, 1970); but here I want to look at the more difficult problem, of how to assess in the individual patient what part, if any, allergy may have played in causing or perpetuating the renal lesion.

It has at once to be admitted that the evidence available is almost always indirect, by comparison with what we may have in pyelonephritis. When there is an outbreak of acute nephritis in a closed community, and when the organism infecting the community, whether the infection be manifest as pharyngitis or pyoderma, has been isolated, then indeed the evidence incriminating that strain of streptococcus becomes strong and direct. Almost always, however, we become aware of the renal involvement only after the antecedent infection has run its course, or when there is no story of such infection. Two questions then arise: (1) given that a component of certain strains of streptococci is the most firmly established allergen in relation to glomerulonephritis, what means have we available for retrospective incrimination of a streptococcus? and (2) in the absence of any evidence of recent or remote streptococcal infection, is there any other acceptable evidence of an allergic basis for renal disease in the individual patient?

Antecedent Streptococcal Infection

Aside from cultures of residual organisms from the throat or skin, the determination of antecedent streptococcal infection depends on finding in the patient's serum antibody to one or more antigens associated with a haemolytic streptococcus. The basic information on streptococcal antigenicity has been available for years, and is reviewed by McCarty

(1954); but details accumulate, and reference may also be made to a symposium on group A streptococci edited by Caravano (1968). In broad summary there are two main groups of streptococcal antigens—enzymatic proteins such as streptokinase, which are active outside the bacterial cell, and the "M-proteins," which are type specific, comparable to the capsular polysaccharide of the pneumococcus.

Extracellular Antigens

Methods are available for titrating the antibody response to streptolysin (the most generally used in this country), and to streptokinase, and to streptococcal hyaluronidase and deoxyribonuclease. Determination of the antistreptolysin O titre alone gives a positive result in about 80% of recent streptococcal infections, but if the other antibodies are also sought, ascertainment of recent streptococcal infection approaches 100% (Glynn, 1969). The time-course of the antibody response to these streptococcal antigens considerably limits their value. They appear one to two weeks after infection with type A streptococci, and thereafter remain raised for two to six months. The transiency of the antibody response to extracellular streptococcal antigens is also demonstrable in population studies, which have shown a mean of 200 Todd units at age 10, but only 100 in old age. Titres are therefore of some value in glomerulonephritis of recent onset, especially if the response to more than one antigen is evaluated; but after six months this value is lost. On the "false-positive" side, macroglobulinaemia can be associated with antistreptolysin O titres in excess of 10,000; also streptococcal infection is not rare, so that a raised antibody titre in renal disease is not a rigid demonstration of streptococcal aetiology.

Type-specific Antibodies

These have a different time-course, not appearing in diagnostic titre for some months after infection, but on the other hand remaining demonstrable for many years. They are thus of little value in the acute attack of renal disease, but have potential value in the presumption of a streptococcal origin in glomerulonephritis of longer duration. There is the obvious difficulty of a plurality of nephritogenic strains, even among group A streptococci; but given knowledge of the prevalence of nephritogenic strains in a community there is the possibility of a retrospective survey of patients with chronic glomerulonephritis.

Other Evidence of Allergy

Even at its strongest the evidence is indirect, based on the demonstration of general hypersensitivity, of complement consumption, or of the products of an allergic reaction in glomeruli obtained by biopsy. The occasional occurrence of renal disease, particularly the nephrotic syndrome, in victims of hypersensitivity to drugs, pollens, and so forth is well recognized; and so is the prevalence of low levels of serum complement, consistent with consumption of the missing complement in an allergic process. Of these various lines of indirect evidence, perhaps the most interesting stems from the examination of biopsy specimens of glomeruli, using the technique of immunofluorescence.

Fluorescein-labelled antibody has been prepared against a variety of possibly relevant antigens—for example, streptococcal antigens—and also against other components of an allergic response, such as the C'1 and C'3 components of complement. Among the substances which have been demonstrated in this way in diseased human glomeruli are streptococcal cell-wall antigens, several components of complement, and a variety of γ -globulins (Burkholder, 1968). Given

an appropriate ratio of antigen to antibody, soluble complexes are formed, and lodge in the glomerular tuft; but components of the allergic response can also be found in isolation.

Some episodes of acute glomerulonephritis have apparently been preceded by a viral infection (Bates *et al.*, 1957). Much interest thus attaches to the finding by Burch *et al.* (1969) and Burch and Colcolough (1969) of Coxsackie virus B antigen in renal tissue at necropsy. The matter is not yet settled, however, since the associated renal lesions were diverse, including a high proportion of what was regarded as pyelonephritis; and the possibility has not been excluded that antigen from what is after all a common virus might become fixed in tissue previously damaged by some quite independent process.

Evidence on Structural Damage

Before turning to renal biopsy as a means of revealing structural damage, I would refer to the contribution of the radiologist, reviewed by Hodson (1968), who has taught us so much. The radiological demonstration of renal size can be critical in the important practical distinction between acute and chronic renal failure; and as a by-product of the routine practice of a plain film of the renal area an unsuspected calculus may be revealed. A good pyelogram, which may be obtainable only by drip infusion of contrast medium, may allow a distinction between ischaemic and pyelonephritic renal scarring. Both these processes cause a local scar, in contrast to the diffuse renal atrophy of glomerulonephritis or of obstructive nephropathy. The ischaemic scar and the pyelonephritic scar are alike in involving the cortex, giving a depression in the renal outline; but ischaemia does not selectively involve the renal pyramid, whereas in pyelonephritis this is retracted or even destroyed, so that the distance from outer margin to renal pelvis is reduced to a greater extent than in the ischaemic scar.

The technique of renal biopsy is now firmly established in any unit which is dealing with renal disease on a substantial scale. Access to fresh tissue, instant fixation of the small core, the use of a thin section, and the availability of special stains, electron microscopy, and immunofluorescence have transformed our picture of the active disease processes in the renal glomerulus. The "earlier" work on renal biopsy was covered in a Ciba symposium (Wolstenholme and Cameron, 1961), and a more recent general review is available by Muehrcke and Pirani (1968). The most important long-term contribution of renal biopsy to diagnosis probably lies in the improved clinicopathological correlation, over a period of time, which it has made possible. In the present account, however, I must limit myself to the more directly practical aspect, indicating those applications of renal biopsy which are of direct help to the individual patient.

Acute Renal Failure.—When the cause of acute renal failure is patent (mismatched transfusion, accidental haemorrhage, surgical shock) biopsy in the early stages is not justified. When oliguria and nitrogen retention appear without obvious cause, however, and adequate urine flow is not established within say two weeks (the patient meanwhile having been maintained on dialysis), it becomes important to specify the disease process in the kidney, and renal biopsy is called for. Alarming degrees of tubular necrosis may be of little long-term moment, but the key to prognosis lies in the degree of glomerular destruction, fibrosis, or disorganization. Acute infiltrative changes may be reversible, but a totally fibrosed or a totally disorganized tuft and capsule can scarcely be expected to resume useful function. These implications are of course valid only in generalized renal damage—for example, glomerulonephritis—and not in diseases whose impact is patchy (pyelonephritis, some forms of ischaemia), so

that the patient may survive even if many of his nephrons are diseased.

Chronic Renal Failure.—When the cause of chronic renal failure can be reasonably inferred from the history and previous observation, and in particular when definite loss of renal substance has been established by radiology, renal biopsy is not called for, and is indeed contraindicated in view of the added danger imposed by hypertension and increased liability to haemorrhage in the uraemic state. If the cause of renal failure is obscure, however, and especially if there is apparently adequate renal substance, then biopsy may be quite justified, provided that hypertension can be controlled and the bleeding diathesis is not in an active phase. In such circumstances biopsy may occasionally reveal deposits of amyloid, calcium, or urates, or other changes which might direct attention to potentially reversible general diseases. I am certainly not advocating renal biopsy as the ideal method of diagnosing diabetes, tuberculosis, gout, or analgesic abuse; but it is better to become aware of these conditions obliquely than to remain unaware of them, should they exist. It may be, of course, that too much damage has already been done to the kidneys to allow full recovery, but at least progression might be slowed.

Protein-losing Kidney (Platt, 1959).—There are many causes of this condition, perhaps more widely known as the nephrotic syndrome. Some of these, such as the collagen disorders, call for general treatment, while others—as in chronic renal failure—may be potentially reversible—for example, toxic and allergic nephropathies. Most patients have some form of glomerulonephritis, but it is important even within this group to be specific about the histology, even if only in the broad categories of "membranous," "proliferative," and "minimal" changes in the glomeruli. These have an obvious bearing on prognosis, and in my view also on management, in the sense that advanced glomerular changes of any kind make one less willing to brave the side-effects of long-term steroid treatment.

These three instances certainly do not exhaust the present and future potential of renal biopsy in the practical management of renal disease, but they may be sufficient indication of the scope of the method.

Evidence on Functional Change

From one point of view the kidneys have as many functions as body fluid has constituent substances, but at the level of clinical usefulness it is perhaps wise to follow Cannon's penetrating analysis, which divides renal function into *excretory* and *homeostatic* operations.

Excretory Function

The elimination of wastes is based on the formation of a large volume of glomerular filtrate, so that substances which may be present only in small concentration in body fluid may nevertheless be potentially available for excretion in significant quantity. Among the practical consequences which follow from the dependence of excretion on bulk glomerular filtration are these:

(1) The assessment of excretory function amounts to an assessment of glomerular filtration rate, though it does not necessarily, or even generally, involve direct measurement of the latter. Evidence of impaired excretory function may be found in a raised concentration in body fluid of nitrogenous wastes (uraemia, azotaemia) or in diminished clearance of substances whose clearance either measures or approximates to the glomerular filtration rate.

(2) Since loss of nephrons, and thus of filtering surface, is a cardinal feature of progressive renal disease, measures of excretory function are relevant to prognosis. They tend to underestimate the degree of loss of nephrons because of hypertrophy of the surviving nephrons; but this matters little from the standpoint of practical

management, since what matters to the patient is his capacity to eliminate wastes, not the means by which he achieves this.

(3) In relation to bio-engineering the need to operate on large volumes of fluid limits the possible minimization of artificial kidneys. An implantable device would have to depart from the kidneys' own method of bulk filtration, unless it could somehow incorporate a concentrating mechanism of comparable efficiency to the renal tubular mass. Though the present artificial kidneys substitute dialysis for filtration, the need to operate with large volumes of fluid remains; but it would be foolish indeed to set limits to the future ingenuity of bio-engineers, who are after all free to depart from nature's methods, so long as they fulfil nature's ends.

In the practical assessment of excretory function the choice of method depends largely on the facilities available and on the end in view. Since the blood urea does not increase unequivocally until urea clearance is depressed to a very great extent (to 20% or less of the normal value), clearance methods have an obvious theoretical superiority to simple estimation of blood constituents. The weakness of clearance methods, however, lies in their dependence on accurate times of collection of urine specimens, which makes them cumbersome as screening tests and vulnerable to faulty bladder-emptying or specimen collection. I have yet to encounter a chemical laboratory of infinite resources; and if the wards and laboratory are submerged by a flood of routine clearances, then accuracy tends to suffer. My own preference is to use the serum creatinine as a screen for a significant degree of renal excretory impairment and to reserve clearance tests for patients with definite renal disease, in whom collections can be closely supervised, preferably by the patient himself. Creatinine is preferable to urea, being less dependent on the intake of protein, which may be unusually low in patients approaching renal failure, either because of medical restriction or because of the patient's own loss of appetite.

Homoeostatic Function

The kidney is the main effector organ in the complex of neuroendocrine feed-back systems which conserves the water

and electrolyte composition of the body fluids. It is manifest from this that it is meaningless to talk of assessing "the homoeostatic functions of the kidney" in the relatively simple terms we have been using of the excretory function; homoeostasis must be atomized into the regulation of individual constituents before it can be operationally assessed. The constituent whose study is relevant has to be decided from the general clinical situation. For example, the thirsty patient raises the issue of excessive water loss, the oedematous patient that of sodium retention, and the patient with Kussmaul breathing that of impaired hydron excretion. In these different situations tests of urine osmolality, of sodium excretion, and of renal output of ammonium and titratable acid would be appropriate.

When a defect of homoeostatic function becomes apparent, either clinically or on testing, the question arises whether it is a manifestation of general renal failure or a more specific derangement which might be of critical importance in diagnosis—for example the amino-acid wasting or glycosuria of a specific tubular syndrome. The type of analysis required to answer the question in depth is well exemplified, in respect of renal acidosis, by Wrong and Davies (1959). It might be thought that a simple answer could be obtained merely by searching for evidence of renal excretory failure, but in adult practice at least it is unusual to find the primary tubular syndrome uncomplicated by some degree of nephron deletion.

Assessment of renal homoeostatic function can, of course, be highly relevant to diseases which are not primarily renal. The most obvious examples would perhaps be diabetes insipidus and Addison's disease, where the normal endocrine stimulus to appropriate renal activity is defective. In gout, and in calculous disease, investigation of the renal handling of urate, calcium, and hydrogen ion is relevant both to pathogenesis and to management. Examples could be multiplied, but perhaps those given suffice to show both the importance of the regulatory aspects of renal function and the impossibility of discussing them here in any detail.

[The conclusion, with a list of references, will be published next week.]

Late Brain Recovery Processes after Drug Overdose

IJAZ HAIDER,* M.B., B.S., D.P.M. ; IAN OSWALD,† M.D., D.Sc., D.P.M.

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Summary: Though recovery of consciousness after drug overdose may occur within a day or two, the drug itself may not finally leave the brain for another one to three weeks, and at this late time a withdrawal syndrome can occur, with insomnia, restlessness, raised paradoxical (R.E.M.) sleep, epileptic phenomena, and even delirium. It is proposed that a high degree of drug-tolerance and dependence can be rapidly acquired after overdose.

Abnormal sleep features of 10 patients resolved only slowly over a period of up to two months after overdose. The data support the view that R.E.M. sleep is concerned with processes of brain repair.

Introduction

Self-administered overdose of drugs today constitutes one of the most common reasons for hospital admission. Comatose patients generally recover consciousness within a few days, but in this paper we present evidence that full restitution often takes weeks.

* Supported by a research grant from the Secretary of State for Scotland.
† Senior Lecturer, Department of Psychiatry, University of Edinburgh, Edinburgh EH10 5HF.

A study of electrophysiological and other features of drug-induced coma (Haider, 1970) was coupled with follow-up in which a number of patients mentioned poor sleep and nightmares in the weeks immediately after the coma. Studies of brain function during sleep after tricyclic drug overdose (Lewis and Oswald, 1969) showed abnormalities which rose to a peak after 10 days and took a month to subside, and so it was decided to conduct similar studies after other overdoses in patients receiving psychotherapeutic and social help without physical treatment where those patients were known not to have taken a mixture of different drugs.

Methods

Patients were drawn from those admitted in 1969 to the Regional Poisoning Treatment Centre, Royal Infirmary of Edinburgh, under the care of Dr. H. J. S. Matthew, and later transferred to a psychiatric ward of the Royal Edinburgh Hospital.

The patient prepared for sleep each night and had electrodes attached above and below each outer canthus, to the scalp, and over the submental muscles, making possible recording of electroencephalogram (E.E.G.), eye movements, and muscle