Priscilla Kincaid-Smith/A. J. F. d' Apice/R. C. Atkins

PROGRESS IN GLOMERULONEPHRITIS

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Preface

Since the last international meeting on glomerulonephritis in 1972 (Kincaid-Smith P., Mathew T. H., Becker E. L., Eds: *Glomerulonephritis: Morphology, Natural History, and Treatment,* John Wiley & Sons, New York, 1973), the emphasis in glomerulonephritis research has changed from morphological classification to mechanisms of injury. Thus, in planning this second symposium, which was conducted under the auspices of the Australian Kidney Foundation, the Royal Melbourne Hospital, and the Australasian Society of Nephrology, it became clear that we needed a very different meeting from the one held six years ago.

In most areas, we have progressed beyond the discussion of classification and terminology. During the past six years there have been major advances in our understanding of the pathogenesis of glomerular disease. Consequently, much of the second meeting was devoted to recent advances in the understanding of mechanism of glomerular injury and host response. New techniques in investigating glomerular disease, such as identification of glomerular cell surface receptors, glomerular culture, immune complex assays, correlative immunofluorescence, glomerular haemodynamics and glomerular protein permeability, have been developed over the past five years. These techniques are described in their respective chapters.

It is now evident that glomerular injury, initiated by a combination of antibody and antigen, activates many host factors which mediate injury. This experimental progress has been reviewed in Chapter 3. The role of many of the mediators in human disease has yet to be elucidated. However, as outlined by Peters in Chapter 4, it now seems that the main principles of alternate pathway activation have been established while the nature of nephritic factor on IgG auto-antibody has been confirmed. The role of the macrophage in glomerulonephritis has only recently been recognized. Its involvement has been reviewed in Chapters 3 and 5. C3b receptors have been identified in human epithelial cells, but, as outlined in Chapter 6, their role in glomerular injury remains speculative.

Assays for immune complex detection have evolved over the past few years. Richard Glassock, in Chapter 2, has comprehensively reviewed their current status and clinical relevance. He has also described, in Chapter 9, elegant studies of glomerular haemodynamic adaptation to glomerular injury.

The immunopathogenic mechanisms of anti-GBM disease are now well documented, both clinically and experimentally. However, as Rees, Lockwood, and Peters suggest in Chapter 18, nonspecific effects, such as bacterial infection, may

play a major role in increasing damage. Furthermore, as in Goodpasture's syndrome, the concept of a background genetic predisposition with precipitation of glomerular injury by environmental factors, such as exposure to hydrocarbons, is gaining support. Among Peters' patients with anti-glomerular basement membrane disease, 15 of 17 had HLA-DRW2 antigen.

We are no longer hampered by a lack of uniformity in terminology; even the classification of glomerulonephritis has become more standardized. There have been improvements and modifications in classification. The system that Habib first proposed in 1976 may well be adopted by the World Health Organization Committee on Nomenclature and Classification of Renal Disease.

In the field of idiopathic glomerulonephritis, the pertinent chapters are confined to a discussion of areas where controversy still exists, such as in focal and segmental lesions, or where knowledge has advanced considerably, such as membrano-proliferative or mesangiocapillary glomerulonephritis. The latter topic is admirably reviewed in Chapter 10 by Levy, Gubler and Habib, who have seen the world's largest and best documented series of such patients. In Chapter 4, Peters reviews the associated complement abnormalities in depth.

The most exciting therapeutic development in recent years, plasma exchange, was introduced by Peters for the treatment of Goodpasture's syndrome. Rees, Lockwood, and Peters discuss their experience in this group of patients in Chapter 18. Data from the Royal Melbourne Hospital on other forms of glomerulonephritis are presented in Chapter 19. Results in crescentic glomerulonephritis, which is not associated with antiglomerular basement membrane antibody, have been uniformly successful in patients who have not already progressed to anuria. The most important message in both of these chapters is the critical importance of early recognition and referral. Minor local crescents may progress to destroy all glomeruli over a period of days or weeks.

Those investigators who were fortunate enough to hear Stewart Cameron's lecture, "The Natural History of Glomerulonephritis," will be happy to see that it has been published in full in Chapter 1. His comments on the difficulties involved in conducting controlled trials in glomerulonephritis are worthy of careful consideration. The fact that the Australian Controlled Trial Protocols were drawn up in 1972, and that only very preliminary results are presently available, illustrates how much time is required for such multicenter studies. Cameron's story of the elephant and the blind men is unfortunately still too accurate a description of our present understanding of glomerulonephritis, and he points out that there are far more questions than answers. Glomerulonephritis still remains a rich field for basic and clinical investigators.

Melbourne, Australia

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Contents

1
The Natural History of Glomerulonephritis

J. S. Cameron

INTRODUCTION

It is a great honor for me to be asked by the Australasian Society of Nephrology to be their Merck Sharp and Dohme lecturer of 1978. In this opening chapter, I would like to develop and expand on some of the themes that will be discussed in the following chapters of this volume. First, I should mention that "natural history," although a very pleasant phrase, is, in fact, an illusion, as will be pointed out later. The most one can hope to discuss is *unnatural* history, and only with difficulty. I shall next examine some of the difficulties involved in the categorization of patients, which is a necessary prerequisite to the study of the various kidney diseases described in this volume: one could not hope to deal effectively with such a vast mass of individual case histories. I shall then take a look at the effects of different factors on natural or unnatural history, particularly treatment, for better or for worse. I will next elaborate on some of the factors that seem to distinguish between those patients who progress and those who do not with apparently similar disease. Lastly, I shall examine the implications of some of these factors for treatment and the inhibition of injury in the glomerulus.

Coming from Guy's Hospital, it is almost a ritual for me to begin with Richard Bright: it has always amazed me, reading Bright's original texts (and indeed his original case notes, which we still have at Guy's), to see the frequency with which he found glomerular disease in the 1820s, the decade in which his classic work was performed. The population that was available to him was small, and referral from great distances was not very common in those days; yet he seemed to be seeing more cases of nephritis in Guy's Hospital in the 1820s than we saw with an elaborate referral system in the 1960s. We still have several kidneys originally studied by Bright at Guy's, off which we periodically take bits and restudy them histologically. It is fairly clear why we do not see patients like the unfortunate girl (Mary Sallaway) who died of nephrotic syndrome in one of Bright's beds in 1824, and whose kidneys we still have: she had amyloidosis, secondary to tuberculosis, and probably bronchiectasis also. With control of infectious diseases, principally

Merck Sharp and Dohme lecture of the Australasian Society of Nephrology, 1978.

syphilis and osteomyelitis, at least in our part of the world, secondary amyloidosis has become uncommon; the small number of patients who remain are nearly all cases of primary amyloidosis.

However, the other two kidneys still in the museum from Bright's time display a pattern that, even after 150 years, first in brandy and then in formalin, one can still recognize: mesangiocapillary glomerulonephritis, probably with subendothelial deposits. It is clear that Bright not only saw more patients with diseases like amyloidosis, whose disappearance can be explained, but also probably saw more glomerulonephritics.

There had been no analysis of data on this disease until very recently, in McKeown's book (1976), tucked away in a table and unremarked by him (Table 1–1). Now, of course, the difficulties of knowing precisely what was meant by those diagnostic categories in these different periods are great. McKeown had been into this study of nephritis fairly conscientiously, and he felt that from 1848 to 1971, they remained reasonably constant: these data show a 15-fold decrease in deaths from nephritis. Workers who run dialysis and transplant programs are indeed grateful that this 15-fold improvement has occurred—assuming that these data represent a real change in the incidence of renal disease of what we can call loosely "glomerulonephritis." What might this change be due to?

We need to construct a hypothesis, and I would like to make a general point over a quotation (which I borrowed from the English translation of Karl Popper's *Logik der Forschung*): "Hypotheses are nets: only he who casts will catch" (Novalis); I think this quotation is appropriate because in studying natural history, we consider far too many observations as *facts*, and not as *questions*, which they should be. For example, *why* does the "minimal change" disease that we see so commonly in childhood have a peak incidence between the ages of 2 and 3 years? Although it may be found up to the age of 80 years, *why* is there such an excess at this age? Is it a disorder of immunologic maturation or of environmental influence that determines the ages at which the bulk of cases occur? *Why* is lupus 12 times as common in women as in men? Is it because (as Mozes and Fuchs have suggested in the New Zealand Black/New Zealand White mouse) the gene that codes for the antibody for antideoxyribonucleic acid is on the X chromosome, or is it a hormonal or an environmental factor, as Talal suggests? I think many researchers have been remiss in accepting quite obvious pointers from the study of natural history, to questions that we should try to answer regarding the nature of glomerulonephritis.

To return to our question, if these data on incidence are true, why has the

Table 1–1. Deaths from Nephritis in the United Kingdom*

	Deaths/10^6/year
1848–54	615
1971	41

*Standardized to the 1901 population (after McKeown, 1976).

Table 1–2. Glomerulonephritis is Found in Individuals Who Are:

Relatively immunoincompetent of
Antibody or
Complement or
T cells
and are exposed to a
Chronic antigen load of
Microorganisms
Drugs
Neoplasia

incidence changed so dramatically? Table 1–2 summarizes in rather crude outline our present beliefs regarding the nature of glomerulonephritis, namely, that it is in some way an immunoincompetence, or an inability to eliminate foreign antigen, and that this inability arises in various parts of the immune system, may well be inherited, and therefore lifelong, although possibly modulated by postnatal events, such as the timing of exposure to antigens. Experimentally and clinically, it can involve antibody, complement, or T-cell function, and in the latter, particular attention has recently been given to so-called suppressor T cells. Most of the antigens that we believe to be associated with glomerulonephritis, for which elimination has failed because of this incompetence, are microorganisms, with autologous antigens and drugs representing the remainder. We could thus postulate that a change may have taken place in the type, the incidence, or the nature of microorganisms in the United Kingdom or that a change has taken place in the host, or both.

Clearly, there has been a change in the environment experienced by the average member of the British population in the last 120 years. A vivid description of the appalling conditions in industrial towns in the early nineteenth century is given in Engel's *The Conditions of the Working Class in England* (1844), in Mayhew's *London Life and the London Poor*, and in many other contemporary texts and pictures. My own great-grandfather, an iron miner, died of cholera in Glasgow near the end of the nineteenth century. Clearly, our past microbial environment does not resemble those of Western, so-called developed countries at the present time. However, it does resemble the microbial, parasitic, and other infectious conditions that exist in the Third World today. In the Third World, tens of millions of people exist, in many instances under conditions similar to those found in both rural Britain in the eighteenth century and urban Britain in the nineteenth century after the Industrial Revolution. Exposure to antigens in the form of parasitic, viral, and bacterial diseases is enormously high in the Third World, and we must not forget that on a world scale, the incidence of nephritis is far higher in places like Uganda. In a way, we can look back into our own history, by looking sideways in space to the contemporary Third World, and this tragedy is something of which investigators have not yet taken full advantage.

The incredible admission rate of nephrotic syndrome in the Third World—2–3% of all hospital admissions—is illustrated from the data collected by

Table 1–3. Incidence of the Nephrotic Syndrome*

Continent	*Country*	*Hospital*	*Admission Rate*	*Malaria*
Africa	Nigeria	Ibadan	2.4	+
	Uganda	Fort Portal	1.8	+
		Mulago	2.0	+
	Rhodesia	Harari	0.7	−
South America	Guyana	Mackenzie	2.8	+
		Mackenzie	0	−
North America	USA	Los Angeles County (California)	0.03	−

*After Kibukamusoke, 1973.

John Kibukamusoke in 1973 (Table 1–3). I cannot state the *incidence* of renal failure from nephritis, because these data are not available from countries where malnutrition and infection are rife. John Kibukamusoke was pointing out, in these data, the association between Quartan malaria (*Plasmodium malariae*) infection and these very high incidences. But note that in a completely nonmalarial area—the high plateau of Rhodesia where Harare Hospital in Salisbury is located—there is still a far higher incidence of the nephrotic syndrome than there is in Los Angeles, which might be termed part of the "civilized" world. Particularly interesting in Table 1–3 also is the work of Giglioli (who just died in 1977) in Guyana. He collected admission incidences of the nephrotic syndrome before and after the elimination from the coastal tropical plain of Guyana of endemic malaria. The incidence fell from the usual high tropical figure of about 2–3% to almost nothing. This change suggests that elimination of environmental antigens, in the form of replicating microorganisms, is very important in determining the dramatic differences in incidences of renal disease seen around the world; it probably also explains in part the dramatic fall in incidence observed in the United Kingdom, if McKeown's figures and my interpretation of Bright's data are valid.

But what of the host? The reader would think from the preceding text that immunoincompetence was always programmed genetically, arising from perhaps histocompatibility locus A and other immune response gene-related material. The reader would think, further, that immunocompetence would be difficult or impossible to manipulate, the message being that one must choose one's ancestors carefully! But there is one factor present in the Third World today that was also present in rural Britain until the Agricultural Revolution and that persisted in urban Britain through the Industrial Revolution, and that factor, of course, is hunger. We know that protein calorie malnutrition depresses every aspect of the immune response, which functions in the elimination of antigens from the body: antibody, cellular activity, complement activity, phagocytosis, and also reticuloendothelial activity. Here, then, is a reversible and treatable cause of immunosuppression, which may have contributed to the high incidence of nephritis in Britain of 1820 and to the persistently high incidence in parts of the Third World where there are no particular precipitating antigens that we can

identify, such as *Schistosoma* or *P. malariae*. It may be that for the bulk of patients, the treatment of glomerulonephritis has already been found and that its prevention is possible and has already been achieved in our own countries—that treatment is food. What we observe in developed countries is the small residue of patients who still develop nephritis after the bulk of cases have been prevented: scarcely "natural" history.

Now I shall turn to some of the difficulties that we encounter in trying to describe patients and in trying to categorize them. We cannot describe individual cases and simply amass 20,000 case histories. Ian Mackay mentioned recently, quoting the letters of Charles Darwin, that "at this rate a man might as well go into a gravel-pit and count the pebbles and describe the colours. How odd it is that anyone should not see that all observation must be for or against some view if it is to be of any service." We must remember, if we try and arrange these pebbles in some kind of pretty pattern that pleases us and that we find useful, that these patterns are arbitrary and that they are derived from fundamental data in a fashion that is determined by the way we think and by the way our concepts are working at that particular time in the evolution of ideas. My picture of glomerulonephritis is shown in Figure 1–1. It is a rather elegant picture of an elephant from the British Museum, and I show it to illustrate the story of the blind men who met an elephant one day. One of them came against the side of the elephant (let us call him observer A) and said, "What is this?" One of the others said, "I think it is an elephant." "Ah—I know what the elephant is like—the elephant is clearly like a *wall*." But the other blind man was feeling the leg of the elephant (B), and he said, "No, the elephant is quite clearly like the trunk of a *tree*." The third blind man had hold of an ear (D), and he said, "No, the elephant is like a *sail*," while a fourth blind man had hold of the tusk (E) and said, "The elephant is like none of these things, the elephant is in my opinion like

Figure 1–1. One view of glomerulonephritis: interdisciplinary.

a *spear*." What the man said who had hold of the trunk is not recorded in the story.

There is a point to this little tale, of course, in that we all behave like the poor blind men when confronted with an elephant, or with glomerulonephritis. There are many levels of description (Table 1–4), each of which has its own validity, each of which has its own truths, and none of which tells us the *whole* truth about the elephant, or about glomerulonephritis. What we have to try and do is correlate these different levels of description and *amplify* the quality of our information by using as many levels of description as possible together in individual cases, and in groups of patients. Of course, most of our effort to date has gone into the areas of histopathology and clinical syndromes. We do, however, have some data about response to treatment, and I will come back to these data later.

What of the quality of the information that allows us to propose categories histopathologically and clinically in the syndromes of glomerulonephritis? First, let us consider histopathology (Fig. 1–2). We must remember that when we subdivide into categories, we must not start treating these categories as though they actually exist. They are abstractions that can be derived from the data within a certain framework of ideas, and they represent only our attempt to make sense of the chaos that surrounds us. As D.H. Lawrence wrote, "the map becomes to us more real than the land." We must not forget the "land" underlying our constructs, which to some extent remains unknown and unknowable.

Keith Peters described histopathology recently as a "battlefield," a description that is true in more than one sense of the word! What one does is rake around among the rubble, trying to reconstruct what happened to this shattered building (Fig. 1–2). I think what Keith Peters, Richard Glassock, and all of us are working toward is some understanding of what happened before the wreckage in Figure 1–2 occurred: did the gas main blow out or are there bombers disappearing out of the corner of the picture? Histopathology does not tell. It does not tell us where the patient has been, but I will try and establish its value.

Table 1–4. Levels of Description in Glomerulonephritis

Etiology
Pathogenesis
Mechanism
Mediation of injury
Histopathology
Optical microscopy
Ultrastructure
Immunohistology
Biology
Clinical syndrome
Stage of evolution
Behavior
Spontaneous
Response to treatment