Hospital Topics

Bright's Disease Today: The Pathogenesis and Treatment of Glomerulonephritis*—III

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Most of Bright's patients died suffering from progressive renal disorders rather than some of the more benign forms we can now recognize. Nevertheless, the mortality of any persisting nephrotic syndrome is very high, especially in the old. Even in children, most with "minimal change" lesions, the mortality was 65% until the advent of microbial chemotherapy.¹¹⁶ Control of infection together with effective diuretics and adequate control of hypertension have dramatically altered the outlook for the patients with glomerular disease. Nevertheless, the survival curves (part I, Fig. 1) should remind us that until we have effective specific treatment glomerulonephritis will continue to supply two-thirds of the young adults requiring dialysis and transplantation.¹³

With strong evidence that similar mechanisms of injury at least participate in the genesis and progression of human as well as experimental glomerulonephritis, what can we expect of treatment? Possible levels of therapy are summarized in the Table. This list looks rather impressive until one examines the little that has actually been achieved.

Possible Levels of Treatment for Glomerulonephritis

	Mode of Therapy	Application
Therapy directed at antigen	(1) Avoidance of antigen (2) Removal of antigen (3) Induction of tolerance to antigen	<i>P. malariae</i> Chemotherapy of infection. Removal of tumour ? Cyclophosphamide
Therapy directed at antibody	(4) Suppression of antibody formation	Cytotoxic agents, corticosteroids
Therapy directed at mediators of injury	(5) Inhibition of complement activity (6) Inhibition of fibrin formation (7) Inhibition of platelet aggregation (8) Inhibition and stabilization of leucocytes (9) Inhibition of kinins, histamine, SRS-A release	Heparin Heparin, warfarin Corticosteroids, indomethacin, dipyridamole, heparin, aspirin Corticosteroids, indomethacin, aspirin Cromoglycate, diethylcarbamazine

Applications 5-9 are cytotoxic agents.

Approach to Treatment

In avoidance of antigen, clearly pride of place must go to the elimination of *Plasmodium malariae* (see Table in part II). This

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is probably the commonest cause of the nephrotic syndrome in the world as a whole and is one of the parasites which we can potentially avoid. Other tropical parasites which may be involved in a similar fashion, such as bilharzia (*Schistosoma mansoni*), will probably be even more difficult to eradicate. Anything, however, is easier to avoid than one's own DNA or basement membranes. People who develop lupus probably have an inherited imbalance of immune responses¹⁴ which will require manipulation to circumvent disease. The evidence from the New Zealand Black/New Zealand White mice (NZB/NZW) is that tolerance will not be easy to induce.

The recent description¹¹⁷ of an outbreak of Goodpasture's syndrome in Minnesota among patients exposed to gasoline fumes in closed environments reminds us that there may be many avoidable non-immunological triggers of immune-mediated processes.

ELIMINATION OF ANTIGEN

This is rarely possible, and if most precipitating antigens in chronic soluble complex diseases in man are viral then this may have to await effective antiviral agents. In the very rare bacterial infections leading to this state the infection can sometimes be removed, such as in subacute bacterial endocarditis and infected juguloventricular shunts. One might also mention the disappearance of nephrotic syndromes after removal of the precipitating tumour.¹¹⁸

ANTIGEN TOLERANCE

Rendering the individual tolerant to antigens is obviously particularly important when the antigen is autogenous, as in DNA and anti-kidney-basement-membrane-antibody nephritis. Since viral chemotherapy is also in its infancy this is one of the most promising approaches. Possibly^{119 120} T cells may have a feedback role on B cells in forbidding antibody production against antigen recognized as "self." If in human lupus there is poor T-cell and enhanced B-cell activity, as in the NZB/NZW mouse,¹⁴ then failure of self-tolerance with excess antibody formation might result. Whether prolonged treatment with cyclophosphamide could effect some facilitation of tolerance is not clear, but its short-term effect in lupus can be dramatic.^{90 121} Good results have also been obtained in NZB/NZW mice,¹²² whereas azathioprine and corticosteroids have little effect and antilymphocyte serum actually decreases survival.

Antibody formation should be suppressed by both treatment with corticosteroids and cytotoxic agents. Antibody responses are inhibited by mercaptopurine.¹²³ In the M.R.C. trial plasma total IgG concentrations fell during treatment of glomerulonephritis in man with combined azathioprine-prednisone treatment but no effect on the renal disease was noted.¹²⁴ Lupus nephritis and the immunological manifestations of lupus, such

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as antinuclear antibody and complement concentrations, respond reliably to both corticosteroids and steroid-cyclophosphamide treatment. How much of this short-term effect derives from suppression of anti-DNA-antibody formation, how much from induction of tolerance, and how much from the anti-inflammatory action of the drugs is not clear. The effect, however, in the NZB/NZW mice,¹²² in Aleutian disease of mink,¹²⁵ and on the anti-DNA antibody in man suggests that some effect on the primary responses has been achieved; whether this has a long-term effect on the renal disorder remains to be seen. Azathioprine has a corticosteroid sparing action but does not reverse the immune markers of the disease.¹²⁶ The possibility that triple therapy with corticosteroids plus cyclophosphamide and azathioprine might be more successful is raised by the work of Gelfand *et al.*¹²⁷ in NZB/NZW mice.

CORTICOSTEROIDS AND CYTOTOXIC AGENTS

The results of corticosteroids and cytotoxic agents in progressive types of glomerulonephritis other than lupus have, after initial optimism, proved disappointing. I have discussed the results in detail elsewhere¹²⁸⁻¹²⁹ and will do no more than summarize here. There is no adequately controlled information that any long-term effect whatsoever is achieved by corticosteroids, azathioprine, or cyclophosphamide, alone or in combination, in any variety of glomerulonephritis that does not have a natural tendency to remit or heal. Neither proteinuria nor glomerular filtration rate was affected in either membranous nephropathy or proliferative glomerulonephritis in the M.R.C. trials of prednisone and of prednisone and azathioprine.¹³⁰⁻¹³⁴ Similar negative results were obtained in other controlled studies on azathioprine and corticosteroids.¹³¹⁻¹³² Perhaps some as yet unidentified subgroup of patients may benefit, but retrospective analysis has so far failed to find them.¹³³

COMPLEMENT ACTIVITY

Inhibition of the complement activity looks at the moment one of the promising areas for investigations of new drugs. Much of the glomerular damage seen in human glomerulonephritis seems to be complement-dependent, at least in the early stages, and in animals complement depletion protects against nephritis.⁸²⁻¹³⁴ Unfortunately there are as yet no effective safe anticomplementary agents suitable for use in man, although the widely-used anti-trypanosomal drug suramin has been shown to be a powerful in-vitro inhibitor¹³⁵. Heparin and heparinoids have both anti-kallikrein¹³⁶ and anticomplementary activity¹³⁷ as well as anti-thrombin and platelet-stabilizing activity, and this makes them slightly more attractive as anticoagulants than warfarin, which has no such activity. This point is discussed further below.

FORMATION OF FIBRIN

Inhibition of fibrin formation has been much discussed recently. Kleinerman¹³⁸ and Halpern *et al.*¹³⁹ inhibited renal damage in animals given anti-kidney antibody by treatment with heparin, and Vassalli and McCluskey¹⁴⁰ showed that warfarin was also effective. Naish *et al.*¹⁴¹ showed that previous defibrination of rabbits with anrod also protected them against anti-kidney antibody nephritis. These findings, and the prominent fibrin deposition in the glomeruli and glomerular crescents of proliferative glomerulonephritis, lead to the use of heparin and other anticoagulants in this condition.¹⁴²⁻¹⁴⁴ On most occasions these anticoagulants have been combined with platelet-stabilizing agents, such as dipyridamole and cyproheptadine, and often with cytotoxic agents or corticosteroids. These results are still controversial and no controlled information is yet available. Probably little effect can be expected in patients with glomerulo-

nephritis and already established anuria, but we have observed that in patients treated earlier, during rapid decline of renal function, stabilization or improvement occurs, which it is tempting to attribute to the drug. Only further careful clinical study can suggest whether these forms of treatment have a place in the management of glomerulonephritis.

We must be cautious also in extrapolating from the animal models to human therapy. While in Masugi anti-kidney antibody nephritis both heparin and warfarin protect, in the NZB/NZW mouse heparin protects¹⁴⁵ while warfarin does not,¹⁴⁶ nor does warfarin anticoagulation affect the lesions of antibody-antigen complex nephritis in rabbits.¹⁴⁷ Our own results in patients with established anuria and extensive crescents and in mesangiocapillary glomerulonephritis have been very disappointing.¹⁴⁸

A major problem now is to identify patients who might benefit as early as possible; the excretion of fibrin degradation products in the urine may give some guide.¹⁰⁸

INHIBITION OF INFLAMMATION

This has been the approach most exploited. Probably whatever action corticosteroids, azathioprine, cyclophosphamide, and related drugs may have principally depends on their anti-inflammatory properties.¹²⁸⁻¹²⁹ We might expect that they would have some effect on diseases where there is chronic inflammation of the glomeruli; the irony is that the condition which reliably responds to treatment is the one in which there is no clear evidence of immune involvement or of inflammation. This is the "minimal change" lesion or "lipoid nephrosis." This reversible disorder of permeability is unaccompanied by any permanent glomerular damage or disorganization. We still have no idea how corticosteroids and azathioprine act to produce the prompt, but often temporary remission in this syndrome. The prolonged remission induced by cyclophosphamide is even more fascinating (see part II, Fig. 4), especially as it can be induced after the patient has been put into or kept in remission by corticosteroid treatment.

Other less toxic anti-inflammatory drugs have been advocated for the treatment of glomerulonephritis. These include indomethacin,¹⁴⁹⁻¹⁵⁰ which inhibits leucotaxis, phagocytosis, platelet aggregation and release of platelet factors and stabilizes lysosomes, possibly by inhibiting prostaglandin synthesis.¹⁵¹ This drug has some effect on the "minimal change" lesion, but preliminary results from the collaborative controlled trial of the M.R.C.¹⁵² suggest that there is little or no effect on either proteinuria or renal function in proliferative glomerulonephritis taken as a whole over one to two years. Indomethacin, however, reliably reduces excretion of fibrin degradation products in many forms of proliferative glomerulonephritis,¹⁵⁰⁻¹⁵² as does prednisolone. Aspirin does not yet appear to have been used but has several attractive pharmacological properties; again, it appears to reduce excretion of fibrin degradation products in proliferative glomerulonephritis.¹⁵³ Unfortunately agents specifically acting against the inflammatory agents released by the action of cytophilic IgE antibody—for example, cromoglycate—are not yet a practical proposition for parenteral administration.

Arrest of Damage

A major problem is that by the time the situation signals its clinical presence it may be too late to alter the course of events by tackling the early pathogenetic mechanisms. For this reason inhibiting the secondary responses, such as complement activation, coagulation, and inflammation, may have more to offer in the short term. Nevertheless, the inhibition of progressive glomerular scarring may be very difficult indeed and beyond a certain point arrest of damage may prove impossible.

The agents suggested for arrest of these processes have great potential for harm. Apart from the obvious dangers of immuno-suppression and anticoagulation (such as facilitation of infection or haemorrhage or induction of neoplasia or genetic damage) there are more subtle dangers. Manipulation of antigen replication, antibody production, cell-mediated responses, or tolerance in situations where balance between antigen and antibody may be critical or induction of tolerance desirable or undesirable may lead to disaster as easily as to cure. We do not know enough about the events taking place in many diseases to use immuno-suppression with precision. We may smile now at the way Bright used metallic mercury as a diuretic; are our efforts less risible or less dangerous?

Conclusion

Viewed with the perspective of a century our achievement as physicians has undoubtedly been smaller in this area than might have been hoped. Yet despite this primary failure we can achieve a surprising amount by palliation, the obvious example of this being regular dialysis treatment and transplantation. We still have much to learn about the conditions at present called "glomerulonephritis." We have as yet practically no specific therapeutic agents to postpone or avert the chronic renal damage which is the fate of most adults affected by these conditions.

What we and our patients need urgently now is the application of data already available in the laboratory to the field of clinical studies. We must also search for mechanisms of injury and disease production in those actually suffering from glomerulonephritis. Substantially, over the past 140 years we have employed refinements of tools already available in Bright's day. Clearly if we are to proceed further towards precision and primary cure we must change from descriptive to investigative modes of thought.

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How Many Acute Beds Do We Really Need?

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Summary

At the end of 1972 two new "best-buy" district general hospitals should open at Bury St. Edmunds and Frimley, eventually serving their catchment areas at a ratio of two acute beds per 1,000 population. This study shows that one of these areas is already operating below this projected target as a result of a considerable decline in the bed ratio over the past decade. Drastic shortening of the average length of stay has permitted an increase in admission rates from 60 to 79 per 1,000 population over the decade, while costs per case measured at constant prices have fallen. These changes have taken place more rapidly than in the U.K. generally. The evidence points to the pattern of clinical management as the main reason for this and suggests that similar gains could be achieved on a national scale, even without waiting for new buildings and expanded community services.

Introduction

The opening later this year of new district general hospitals at Bury St. Edmunds and Frimley will mark one of the most

significant policy innovations in the history of the National Health Service—the implementation of a standard of two acute beds per 1,000 population, thereby shifting the emphasis between institutional and community care. If this standard were adopted nationally clinicians would lose 50,000 of the 150,000 beds now allocated to acute specialties, and the Liverpool and North-West Metropolitan hospital regions would have their existing acute beds cut by half. The reduction of bed norms would curb the soaring costs of building and running acute hospitals and free resources for the competing claims of advances in medical technology and the neglected areas of long-stay care.

The full impact of the hospitals now being commissioned will not be apparent for many years. Nevertheless a situation of declining bed ratio accessible to investigation was found in Bury itself, where one of the new hospitals will replace the existing West Suffolk General. Preliminary examination suggested that there had already been a substantial reduction in the acute bed ratio. It was therefore decided to review the development of the West Suffolk General over the previous decade from the available documentary sources in the hope that it would yield useful pointers to the future effects of the "best-buy" scheme on patterns of clinical management and patient care.

Nationally, there has been a slow decline in the provision of acute beds, from 3.9 per 1,000 population in 1949 to 3.6 in 1959 and 3.2 in 1971. The number required has been the subject of continual debate. During the 1950s a number of

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