The kidney in rheumatic heart disease

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SYNOPSIS Histological evidence of glomerulonephritis is reported in 95 (38.6%) of a series of 246 necropsies with concomitant rheumatic carditis. The details of these findings are given and their significance is discussed.

Although renal, and in particular glomerular, changes have long been recognized in the collagen diseases as a group, surprisingly little has been recorded of the kidney in rheumatic carditis. In 1932 Bell reported glomerulitis in 21% of a series of 104 cases with active rheumatic endocarditis, chronic changes being absent in 53. He described the glomerular lesion as diffuse, consisting of an increased number of endothelial cells, with occasional thickening of the basement membranes. In some examples the capillaries contained an excess of leucocytes. In three cases he found focal lesions of the tuft, described as being of embolic type; these, however, were unaccompanied by any terminal infection. On the other hand Baehr and Schiffrin (1932) found only three examples of glomerulonephritis amongst 235 cases in which death was due to rheumatic heart disease. Active carditis was present in 118. They excluded patients over 31 years of age to avoid confusion with atherosclerotic valvular deformities. Not surprisingly, they concluded that glomerulonephritis was not associated with rheumatic carditis. This view seems to have been tacitly accepted thereafter, and Allen (1951) dismisses the subject with a brief but somewhat equivocal statement.

A few chance observations suggested that the matter merited further investigation. To this end a series of 246 cases was selected for examination from material available from 1911 to 1959. Cases were rejected where intercurrent infection, especially bacterial endocarditis, extensive infarction of the kidneys, gross post-mortem change, or other factors were prejudicial to the analysis. Chronic heart failure was the cause of death in most instances but some patients died from a variety of intercurrent diseases. Elderly subjects with slight degrees of mitral-cusp thickening were excluded on the grounds that the rheumatic basis of this condition is question-

able. Cases over 40 years of age with solitary disease of the aortic valve were also excluded unless the condition was clearly rheumatic. The series in fact contained only four examples of solitary aortic valvulitis; two of these patients were 43 and 57 years old respectively.

Otherwise material was accepted from all decades whether the valvular changes were acute, chronic, or combined.

TECHNICAL NOTES

Paraffin-embedded sections stained with haematoxylin and eosin were principally used. Frozen sections stained with Sudan III and haematoxylin were frequently available after 1928. When more precise observation was required the blocks were re-cut, with special care to preserve a constant thickness, and stained with periodic acid-Schiff (P.A.S.) and with azan. Since the assessment of slight degrees of proliferative glomerulitis (numerical increase of endothelial cells with or without thickening of the basement membranes of the tuft) proved a major difficulty in analysis, photomicrographs at constant magnification were made from a graded series of selected glomeruli in P.A.S. preparations, including controls. These, mounted on a card, were useful for reference.

RESULTS

Of the 246 cases examined, 95 (38.6%) were judged to show some form of glomerulonephritis.

1 In 16 there was an advanced nephritis resembling that of Bright's disease. (a) In five the kidneys were contracted, the microscopical picture suggesting type 2 nephritis (Ellis) in three instances and type 1 in two. Death was due to uraemia in two cases of the former, and to chronic heart failure in the rest. (b) In the remaining 11 cases of this group the kidneys were of normal size or enlarged. Lipoid flecks were visible in the cortex in two instances; otherwise there was nothing to suggest more than back-pressure congestion. Two subjects, however

FIG. 1

FIG. 1. *Proliferative glomerulitis and capsulitis with increase of adjacent interstitial tissue. From male aged 49 with severe mitral stenosis and rheumatic vegetations. P.A.S. $\times 290$.*

FIG. 2

FIG. 2. *Proliferative glomerulitis with increase of interstitial tissue. Details in text. P.A.S. $\times 290$.*

were uraemic at the time of death. Microscopically a diffuse nephritis, suggestive of type 1, was found in three cases (Fig. 1), associated with polyarteritis nodosa in one; in two cases the picture resembled that of type 2 nephritis, but the remaining six cases could not be assigned to either category (Fig. 2).

The kidneys represented by Fig. 2 were of normal size and finely flecked with lipoid. The principal glomerular change was an uneven proliferative glomerulitis. In a few glomeruli the capsular epithelium was heaped up, and occasionally fusion of the tuft to the capsule had led to disorganization through invasion by fibroblasts. The interstitial tissue was diffusely increased, sparsely cellular and oedematous. The lumina of the tubules contained many red corpuscles. The patient, aged 50 at death, was known to have rheumatic endocarditis at 45, his urine then being reported as normal. Ten weeks before death the urine became dark and three weeks later he was admitted to hospital with heart failure, albuminuria, and haematuria. Following this he had a phase of uraemia, but his blood urea returned to normal and death was ultimately due to heart failure.

2 PROLIFERATIVE GLOMERULITIS In 76 cases the glomeruli principally showed proliferative glomerulitis. This change, when advanced, caused enlargement of the tuft (Fig. 3) in excess of any that could be attributed to simple back-pressure congestion (Fig. 4). Both the endothelial proliferation and thickening of basement membranes varied in degree and distribution. Although widespread when present, a number of the glomeruli, or part of an affected tuft, might appear normal. Thickening of basement membranes can only be correctly assessed by special stains, the appearances in haematoxylin-and-eosin preparations being frequently deceptive. The P.A.S. method proved the most reliable, demonstrating that the thickening is due to an increase of fine, interwoven fibrils between the capillary loops and not of the 'wire-loop' character seen in disseminated lupus erythematosus. In one case only was this picture equivocal (Fig. 5). The centres of lobules were more affected than the periphery and, when the hilar region was involved, there was sometimes in continuity a peri-adventitial increase of fibrils and cells about the glomerular arterioles. Figs. 6 to 9 inclusive illustrate moderate or lesser degrees of proliferative

FIG. 3

FIG. 4

FIG. 5

FIG. 3. Enlargement of tuft from proliferative glomerulonephritis. From male aged 52 with severe mitral stenosis; death due to mesenteric embolus. Haematoxylin and eosin $\times 290$.

FIG. 4. Congested, otherwise normal glomerulus. From female aged 56 with mitral stenosis. P.A.S. $\times 290$.

FIG. 5. Basement-membrane changes of 'wire loop' type, not fibrinoid. From male aged 56 with mitral stenosis; no evidence of active carditis. P.A.S. $\times 290$.

FIG. 6

FIG. 6. Proliferative glomerulitis. From male aged 39; chronic heart failure from mitral stenosis and chronic aortic valvulitis. P.A.S. $\times 290$.

FIG. 7

FIG. 7. Proliferative glomerulitis with 'lobulation' of tuft. From female aged 52 with chronic pancarditis; no evidence of active lesions. P.A.S. $\times 290$.

FIG. 8

FIG. 8. Proliferative glomerulitis; predominantly thickening of basement membranes. From female aged 39 with chronic mitral and aortic valvulitis. P.A.S. $\times 290$.

FIG. 9

FIG. 9. Proliferative glomerulitis. From female aged 37 with chronic mitral valvulitis. P.A.S. $\times 290$.

FIG. 10

FIG. 10. *Proliferative glomerulitis with adhesions. Hyaline droplet degeneration was found in capsular epithelium. From female aged 46; chronic heart failure from mitral stenosis. P.A.S. $\times 290$.*

FIG. 11

FIG. 11. *Proliferative glomerulitis with adhesions. From male aged 40 with rheumatic aortitis and endocarditis. P.A.S. $\times 290$.*

glomerulitis in this group: all are from cases in which this was the sole change observed.

ADDITIONAL GLOMERULAR CHANGES In 39 examples of this group the glomeruli also showed adhesions of the tuft to the capsule (Figs. 10 to 12), often with localized degeneration ('focal necrosis') of the tuft. In 13 cases the altered tuft contained aggregates of foam cells. In eight cases the adhesions were associated with hyaline-droplet degeneration of the capsular epithelium, and in these it was remarkable that the proximal convoluted tubules were not similarly affected though the distal segment sometimes contained rather sparse droplets.

The tuft in the region of an adhesion sometimes had a smudged appearance resembling that often seen in disseminated lupus (Fig. 11), but the haematoxyphil deposits so characteristic of the latter were

never observed. Slight degrees of proliferation of the capsular epithelium were found in nine examples and an excess of leucocytes in the tufts in five.

INTERSTITIAL TISSUE In 12 cases this was increased, being generalized through the cortex in five and focal, mainly periglomerular, in seven. This change was not the collagenous sclerosis of the ischaemic kidney, but a finely fibrillated and sparsely cellular tissue, the cells being fibrocytes, occasional large mononuclear cells, and lymphocytes; polymorphonuclear leucocytes and plasma cells were rare.

3 In three cases there was no obvious proliferative glomerulitis, but scattered tufts showed adhesions and focal necroses. In one there was slight epithelial proliferation in a few other glomeruli. In addition two of these examples showed focal, periglomerular increase of interstitial tissue.

FIG. 12. Focal thickening of basement membranes and adhesion of tuft to capsule. From female aged 59 with chronic aortic and mitral endocarditis. Death under anaesthesia (appendicectomy). P.A.S. $\times$ 290.

The findings in groups 2 and 3 (79 cases) are summarized:—

	No. of Cases
Proliferative glomerulitis alone	33
Proliferative glomerulitis with increase of interstitial tissue	4
Proliferative glomerulitis with increase of interstitial tissue and focal necroses	8
Proliferative glomerulitis with focal necroses	31
Focal necroses alone	1
Focal necroses with increase of interstitial tissue	2

DISCUSSION

SIGNIFICANCE OF RESULTS The incidence of glomerular disease in a total of 38.6% of this series suggests more than coincidence. It might, however, be agreed that coincidence accounts for the five examples of contracted kidney, for this small group seems to lie apart from the rest of the series. The ages of these five patients ranged from 24 to 52 years and in none could the duration of the rheumatic carditis be clinically assessed. In three, however, the degree of

chronic valvulitis found at necropsy was only slight or moderate. In one case there had been an attack of acute haemorrhagic nephritis seven years before death and the terminal picture resembled type 1 (Ellis). The question of coincidence might be clarified by estimating the natural incidence of chronic nephritis in adult necropsy material over the period of this investigation. This has not been attempted owing to the obvious inflation in the number of such cases at the London Hospital from the activity of the Nephritis Clinic.

The 11 cases classified as 1*b* fall into a different clinico-pathological category. Cardiac disease was dominant during life except in one case where polyarteritis nodosa posed a diagnostic problem. In this small group the nephritis was clinically submerged in nine cases and was not detected at necropsy except in the two instances in which the kidneys were lipid-flecked. Microscopically this group includes cases that so closely approximate to the more florid examples in group 2 that they may reasonably be regarded as transitional.

In this second and largest group (76 cases) the total number hinges on the identification of proliferative glomerulitis as objective evidence of disease when this was the sole change found. Minor degrees are obviously difficult to detect, even with the help of the P.A.S. stain. Therefore examples that appeared marginal were repeatedly examined, at intervals of weeks or months, and those that seemed doubtful were ultimately rejected. A different observer might increase or reduce the number of cases in this group; therefore the total assessed must be regarded as the fairest approximation that can be reached in the circumstances.

However, as already shown, solitary proliferative glomerulitis was restricted to 33 cases; in the remainder this finding was reinforced by other significant changes: focal necroses and adhesions, or an inflammatory increase of interstitial tissue, or both. If the 33 cases were totally removed from the series the percentage showing evidence of nephritis would be reduced to 25, still a considerable proportion of the whole.

It might also appropriately be asked whether the changes recorded could be interpreted as terminal; this applies particularly to examples in which no increase of interstitial tissue was found. This suggestion is poorly supported by the circumstances responsible for death. Although chronic heart failure was the principal cause of death, in five patients it was due to severe haemorrhage from different sources, two died as the direct result of valvulotomy, one from carcinoma of the stomach, and one during anaesthesia for appendicectomy (Fig. 12). Focal necroses in addition to proliferative glomerulitis were

found in three of these cases, and in two there was an increase of interstitial tissue.

ACTIVITY OF THE RHEUMATIC CARDITIS Evidence of activity was provided by the macroscopic description of the characteristic vegetations and, when available, the examination of histological preparations. The latter were not always satisfactory and, indeed, an exhaustive examination of the heart would be necessary if evidence of rheumatic activity were to be positively excluded. But such an examination has not been feasible in an enquiry of this kind. Subject to these limitations it can only be stated that 30% of the group with glomerular changes had positive evidence of active inflammation in the heart, whereas activity was found in 19% in the group with no renal inflammation.

AGE INCIDENCE All decades, from the first to the eighth, are represented in both the nephritic and non-nephritic groups. On analysis there appears to be little difference between them: the second and third decades are better represented in the former than in the latter, but in both the greatest number of cases falls in the fourth to sixth decades. The actual figures for consecutive decades are: (a) nephritic, 1, 12, 15, 21, 16, 22, 6, 1, 1; (b) non-nephritic, 5, 8, 9, 22, 41, 39, 21, 6.

EVIDENCE OF NEPHRITIS The renal implications of rheumatic carditis were not detected clinically, with the exception of those patients, already mentioned, who died in uraemia. Cardiac failure dominated the picture; albuminuria and oedema were naturally attributed to this and haematuria, if present, could be explained by infarction. Blood-urea estimations were available in only 14 cases, seven of these being in group 1. In the seven of group 2 the figures ranged from normal to 78 mg. % except in one case where 300 mg. was recorded two months before death.

This man, aged 45, was admitted with chronic mitral and aortic endocarditis. The urine contained 9/10 albumin and a deposit of leucocytes, red corpuscles, granular and hyaline casts. He was discharged, one month before death, with gross anasarca and pleural effusions. At necropsy death was attributed to serofibrinous pericarditis. There was chronic endocarditis of the aortic and mitral valves, with slight stenosis of the latter and microscopic evidence of active inflammation. In the kidneys a uniform diffuse fibrosis pervaded the

cortex and extended into the upper medulla. This tissue appeared oedematous and contained scanty fibroblasts mixed with an uneven, rather sparse infiltration of lymphocytes, plasma cells, occasional large mononuclear cells and neutrophil leucocytes. Proliferative glomerulitis was slight and focal. Hyaline-droplet degeneration of the capsular epithelium was associated with slight focal cellular proliferation, adhesions, and focal necroses. Isotropic fatty droplets occupied the epithelium of the convoluted tubules and hyaline droplets were found in the ascending loops of Henle. Bulky eosinophilic hyaline casts were numerous.

These details illustrate the kind of case in which nephritis might well be suspected clinically. In this instance a nephrotic syndrome (though information about the plasma proteins is lacking) was associated with raising of the blood urea and renal changes that have points in common with Bright's disease but do not lend themselves to any existing classification. The case also demonstrates the artificiality of separating the small group of 11 cases (1b) from group 2: it is clearly transitional.

In conclusion, the findings in the present investigation support those of Bell (1932), and suggest the desirability of further investigation of this problem both clinically and in the laboratory. The surprising negative results reported by Baehr and Schiffrin (1932) may be partly accounted for by their exclusion of cases over 31 years old for, in the present series, most of the glomerular changes were found in older subjects. This in itself suggests that successive attacks of carditis may generate an immunological state in which the kidneys become vulnerable, by analogy with disseminated lupus. On the other hand, the incidence of glomerulonephritis in any series investigated might depend in its turn upon the incidence of infection with nephritogenic strains of group A streptococci (Rammelkamp and Weaver, 1953). Further speculation is unprofitable until the background of combined renal and cardiac disease in rheumatism is more fully investigated.

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