THE FIRST K. PRATHAP MEMORIAL LECTURE

THE CONTRIBUTION OF PATHOLOGY IN RENAL DISEASE

RAJA SINNIAH, MA, MBBC, BAO, MD, PHD, FRCP, FRCPA, FRCPATH

Professor of Pathology, Department of Pathology, Faculty of Medicine, National University of Singapore, Singapore 0511

INTRODUCTION

Mr. Chairman and Learned Members of the Malaysian Society of Pathologists. I wish to thank you for bestowing on me the honour of delivering the First K. Prathap Memorial Lecture. The late Professor Prathap had a great interest in the study of renal disease, and had contributed to its literature. Therefore it is fitting that I have chosen as the theme of my lecture "The Contribution of Pathology in Renal Disease".

Nephrology has gained much prominence and importance, not because it is a major cause of death but the advent of dialysis and transplantation have prolonged the lives of end-stage renal disease patients. Diseases of the genitourinary tract rank 12th among the causes of deaths in Japan and many Western countries2, 3, 4 and the 9th major cause of deaths by broad groups of causes in Singapore per 100,000 population.5 Dialysis treatment is in its fifth decade of clinical application, and the number of living patients undergoing such treatment is nearly 0.5 million.6 The true incidence of dialysis treatable end-stage renal failure has been estimated at 50 to 100 patients per million population each year.7 Though dialysis and transplantation treatment have made remarkable progress in medicine, the cost is prohibitive, and only a few countries will be able to afford it. The United States of America is spending over US$3 billion. Few countries have these resources, and the problems are most acute in the "Third World Countries". The only solution out of this quandary is for us to obtain a better understanding of the renal diseases with identification of aetiological agents which should lead to more cost-effective therapy and prevention.

Glomerulonephritis is the most common kidney disease leading to dialysis and transplantation treatment, followed by pyelonephritis and tubulo-interstitial nephritis, congenital renal cystic disease and multisystem diseases. The pathological study of these lesions lies at the heart of the solution.

HISTORICAL PERSPECTIVE

Since ancient times man has believed in impurities in the body as the cause of disease. The historical Greeks and Romans based their diagnosis on six criteria: patient's behaviour, the excreta, other effluvia from the body, swellings, character and location of the pain, and qualities of the pulse. The Arabic contribution to medicine through the Arabist practitioners (8th to 12th Century) was in the development of efficient hospitals and pharmacy as a science. Their emphasis on examining the urine for its colour, consistency, sediment, smell and taste helped to determine what was wrong with a patient, to predict his prognosis and to guide treatment. These concepts were taken to Europe by the returning Crusaders, and became part of the medical teaching in the Universities to be established.8

Contribution of Morbid Anatomy

The systematic study of organ pathology was pioneered by Carl Rokitansky (1804-78) and Rudolf Virchow (1821-1902) in Austria and Germany. They strove to integrate clinical medicine, morbid anatomy and physiology, with classification of the anatomical changes produced by disease. These revolutionary approaches radically altered the direction of medicine toward the concept that disease was produced by disturbances in the structure and function of the body cells.

The masterful reports from Guy's Hospital, London, by Richard Bright (1789-1855) on the clinical and pathological nature of diseases of the kidneys (Fig. 1) led to the beginning of our present knowledge of renal diseases. The condition named "Bright's Disease" was based on observations after death with symptoms during life, with close correlation which exists both between functional and organic disease as determined by the examination of autopsy materials (Fig. 2). From this time on many methods were devised to predict the renal pathology and prognosis from clinical parameters, without the opportunity of seeing the...
Reports
of
Medical Cases,
Selected
With a view of illustrating
The Symptoms and Cure of Diseases
By a reference to
Morbid Anatomy.

By Richard Bright, M.D. F.R.S. &c.
Lecturer on the Practice of Medicine.
And one of the Physicians to
Guy's Hospital.

London:
Printed by Richard Taylor, Red Lion Court, Fleet Street.
Published by Longman, Rees, Orme, Brown, and Green.
1827.

FIG. 1 The profoundly influential "Reports of Medical Cases" by Richard Bright (1827), which correlated clinical syndromes to morbid anatomy.
PLATE III.

KIDNEY IN DROPSY.

Fig. 1. External appearances of one of the kidneys of Sallaway (page 19, &c.). Part of the tunic is removed to show more plainly the tuberculated and motley appearance of the surface. The secretion of this kidney was albuminous, and general dropsical effusion was a prominent symptom.

Fig. 2. A longitudinal section of the same kidney, showing its internal texture greatly altered: the general colour yellow, the lighter parts were more opaque than the rest, while the coloured broken lines, proceeding in a direction perpendicular to the external surface, corresponded nearly with the more vascular parts of the structure.

Fig. 3. A portion of a longitudinal section of one of the same kidney, which had been injected with fine red size by the arteries, showing a large portion of the kidney nearly impermeable.

FIG. 2: Richard Bright described and illustrated the morphological changes in the kidneys, and correlated them to the clinical symptoms, leading to nephritis being referred as Bright's disease.
tissues during life, but none were satisfactory. The first attempt at a clinicopathological correlation was made by Volhard and Fahr (1914), who subdivided glomerulonephritis into diffuse and focal lesions, with acute, chronic and end stage. In 1942 Ellis attempted to improve this classification basing the criteria on the time of onset of clinical disease. It did not prove helpful to use clinical symptoms to diagnose pathological lesions.

In 1950 Perez reported percutaneous renal biopsy was a safe and relatively simple clinical procedure, which was confirmed by Iversen and Brun. The examination of renal biopsies during life led to the present understanding of renal disease.

Contribution of Immunopathology

Immunology as a science developed in association with the study of infectious diseases. The pioneering works of Pasteur, Koch, Behring, Kitasato and Ehrlich in the latter part of the 19th century laid the principles of immunological response to injury and infections. The use of immunological and electron microscopical techniques have been utilized extensively in the study of human renal biopsy specimens, and in experimental animals. Studies on serum sickness in man and experimental animals implicated immune reactions in the development of associated glomerulonephritis.

From the observations of extensive experience from human and experimental glomerulonephritis, there appeared to be four major mechanisms of glomerular injury. Many human glomerulonephritides were due to the localization of circulating immune complexes, involving the formation of small, soluble antigen-antibody complexes in the presence of an excess of antigen. The localization of the complexes may be determined by its size: small complexes passing through the glomerular basement membrane and deposit in the subependymal; larger size immune complexes through the subendothelial system. It has been demonstrated that the glomerular capillary wall contains negatively charged molecules, which may influence the deposition of charged immune complexes, in the subendothelial and subepithelial regions. With immunofluorescent microscopy, it is now accepted that granular deposits of immunoglobulins along the GBM indicate immune complex glomerulonephritis (Fig. 3) e.g. in acute post-streptococcal glomerulonephritis, and other types of glomerulonephritis i.e. systemic lupus erythematosus with renal involvement. Immune complex glomerulonephritis accounted for most of the human glomerulonephritis. Antibodies may be produced against GBM, as in the experimental Masugi type nephritis or anti-GBM antibody nephritis, with continuous linear deposits of IgG and C3 along the glomerular basement membrane (Fig. 4). Goodpasture's syndrome.

![FIG. 3: Immunofluorescence pattern of granular deposits in the glomerulus, which denotes an immune complex type glomerulonephritis, with IgG deposits along the glomerular basement membrane. (Immunofluorescence microscopy x 350)](image-url)
with anti-GBM glomerulonephritis shows a uniformly linear fluorescence.\textsuperscript{22, 23, 24} This type of glomerulonephritis is infrequent in Western and temperate countries, and rare in tropical countries of Southeast Asia.\textsuperscript{25, 26, 27}

In-situ immune complex formation involving nonrenal antigens can occur. The principal factor that leads to this is the relation between the antigen or antibody charge and the charge of the glomerular capillary wall or of proteins localized on it.\textsuperscript{28} With immunofluorescence and electron microscopy, granular deposits are localized along the GBM. Therefore, the absence of circulating immune complexes in an immune complex glomerulonephritis may be suggestive of in-situ complex formation. Many cases of idiopathic membranous nephropathy may be due to this mode of injury.

The Pathway of Complement Activation can be helpful in classifying the types of glomerulonephritis. Circulating immune complexes activate the classical pathway, utilizing C1, C4, and C2 which react to elaborate C3-convertase. The activated C3 sets in motion the cascade phenomenon of C5 to C9 utilisation. This is the pathway of activation in poststreptococcal and lupus glomerulonephritis.\textsuperscript{15, 20, 29} The alternative pathway of complement activation utilizes factor A, factor B or C3 proactivator and properdin. Aggregated IgA will fix complement \textit{in vitro} by the alternative pathway.\textsuperscript{30} This feature of alternative pathway of C3 activation has been well demonstrated in IgA nephropathy of Berger and the Henoch Schonlein syndrome.\textsuperscript{31, 32} Despite our inability to identify the responsible antigen in most cases of human disease, a good deal of knowledge has been gained in understanding the pathogenesis of the various forms of human glomerulonephritis.

\textbf{Contribution of Electron Microscopy}

The electron microscope invented in the 1930's has been used extensively over the past three decades to study in great detail various glomerular and other renal diseases. It was responsible for proving definitively the existence of the mesangial cell in the glomerulus. It is especially useful in the study of patients with asymptomatic proteinuria, or the nephrotic syndrome with minimal change on light microscopy.\textsuperscript{33, 34, 35} It has now been well documented in lipoid nephrosis, the only changes are effacement or obliteration of the podocytes, with the formation of microvilli. In the absence of immunofluorescence microscopy, and light microscopy showing only minor changes (Fig. 5), electron microscopy will reveal the subepithelial deposits of early, Stage 1, membranous nephropathy (Fig. 6). The progression through four stages of membranous nephropathy (Fig. 7) was also determined by ultrastructural analysis.\textsuperscript{36} The subdivision of diffuse \textit{mesangiocapillary glomerulonephritis}, membranoproliferative glomerulo-
lonephritis types 1 and 3 was based on the additional presence of subepithelial dense deposits in the latter.\textsuperscript{37,38} Electron microscopy also shows the very striking change in the presence of electron dense deposits in the lamina densa of the capillary basement membrane in dense deposit glomerulonephritis, membranoproliferative glomerulonephritis type 2 with intramembranous deposits.\textsuperscript{39,40,41}

Ultrastructural studies of lupus nephritis have shown a good correlation between the sites of the deposits and the pattern of glomerulonephritis, and the severity of clinical manifestation. In the groups of patients with subendothelial deposits, the renal involvement was the most severe, while pure mesangial deposits do not lead to severe glomerulonephritis. The electron microscopical examination of membranous lupus nephritis and idiopathic membranous nephropathy will show additional mesangial deposits in the former (Fig. 8), which feature is important in distinguishing these lesions.\textsuperscript{29,42,43,44} The presence of heavy intraendothelial cytoplasmic inclusions of tubuloreticular structures seen in over 95% of lupus nephritis may be an aid in its diagnosis, where dense deposits are seen at various sites in the glomeruli.

Electron microscopy has also contributed to the better understanding, and diagnosis of metabolic diseases with renal involvement. In diabetes mellitus thickening of the glomerular basement membrane is a very early sign,\textsuperscript{\textsuperscript{\textdagger}} with concomittant increase in mesangial matrix. Amyloid may also be identified by electron microscopy, with fine non-branching fibrils, 7–10 nm in diameter, arranged in criss-crossing bundles.\textsuperscript{46} The nephropathy in various dysproteinemias also show characteristic fibrils or tubules which may be formed in the subendothelium or epithelium.\textsuperscript{47,48,49,50} Many of the hereditary nephropathies show characteristic ultrastructural changes. In Alport's syndrome there is segmental thickening and splitting of the glomerular basement membrane and small dense particles between the parallel layers.\textsuperscript{\textsuperscript{\textdagger},51} In benign recurrent haematuria, thin basement membrane disease, there may be segmental thinning of the basement membrane, with the lamina densa reduced to less than half its normal thickness (Fig. 9), to measure as little as 60–80 nm. This lesion can be diagnosed only by electron microscopy. Characteristic ultrastructural changes are also seen in the Nail-Patella syndrome, Fabry's disease and Familial Lecithin-cholesterol Acyl Transferase Deficiency.\textsuperscript{51,52}

THE W.H.O. CLASSIFICATIONS OF RENAL DISEASES

The study of percutaneous or open renal biopsies over the last three decades has contri-
FIG. 6. Electron microscopy of the case in Fig. 5 shows subepithelial electron dense deposits scattered along the glomerular basement membrane (BM). There is obliteration of the podocytes, indicative of proteinuria. Epi = epithelial II. (Electron microscopy x 8,100).
FIG. 7: Electron micrograph of stage 2, membranous nephropathy, with subepithelial dense deposits (D), and in areas BM extensions or "spikes" (arrows). End = endothelial cell; Epi = epithelial cell. (Electron microscopy x 12,600).
FIG. 8: Lupus nephritis. Electron micrograph of segment of the glomerulus shows dense deposits (D) at various sites along the glomerular basement membrane (BM) and in the mesangium (MM). Inset shows clump of tubulo-vascular particles in the endothelial cytoplasm. Mes = mesangial cell; Epi = epithelial cell. (Electron microscopy x 6,300).
FIG. 9  Electron micrograph of segment of glomerulus shows marked thinning of the glomerular basement membrane (BM) in a patient with "Benign recurrent haematuria". Epi = epithelial cell; MM = mesangial matrix. (Electron microscopy x 6,300).
buted to the great progress in nephrology. With accumulation of knowledge, we begin to classify diseases and lesions as it is the logical road to scientific analysis. Several recent efforts were made by international groups to provide a systematic classification.** With the large numbers of papers published from many centres from around the World, it was imperative that international agreement was reached on the criteria for diagnosis, a standardized nomenclature, and a uniform system of classification. Renal diseases can present in a limited number of clinical syndromes, and it has been shown that almost any type of glomerular pathology can be found in any of the syndromes, and vice versa.** The renal biopsy provides a more exact diagnosis if correlated with clinical and laboratory data.

The classification should reflect the present state of knowledge, and by using the internationally agreed criteria for diagnosis, the studies by nephrologists, pathologists and epidemiologists in one country can be compared with another. To achieve these objectives, the World Health Organization in 1974 established a Collaborating Center for the Histological Classification of Renal Diseases at the Department of Pathology, Mount Sinai School of Medicine in New York, under the leadership of Dr. J. Churg. The Center worked with pathologists and nephrologists from 14 countries to produce the First Volume, Renal Disease: Classification and Atlas of Glomerular Diseases.59

The Book consists of two sections:— the first gives a complete listing of glomerular lesions and their definitions. The main clinical and morphological features including light, electron and immunofluorescence microscopy are described. The second section describes in detail and illustrates the various glomerular lesions. This standardized classification is being used extensively, and a shortened version of

### Table 1

<table>
<thead>
<tr>
<th>W.H.O. CLASSIFICATION OF GLOMERULAR DISEASES</th>
</tr>
</thead>
</table>

1. Primary Glomerular Diseases (Glomerulonephritis and Related Conditions)
   A. Minor Glomerular Abnormalities
   B. Focal/Segmental Lesions (with only minor abnormalities in other glomeruli)
   C. Diffuse Glomerulonephritis
      a. Membranous Glomerulonephritis (Membranous Nephropathy)
      b. Proliferative Glomerulonephritis
         Mesangial Proliferative Glomerulonephritis
         Endocapillary Proliferative Glomerulonephritis
         Mesangiocapillary Glomerulonephritis (Membranoproliferative *Glomerulonephritis* Types 1 and 3)
         Dense Deposit Glomerulonephritis (Dense Deposit Disease)
         (Membranoproliferative Glomerulonephritis Type 2)
      c. Crescentic (Extracapillary) Glomerulonephritis
      c. Sclerosing Glomerulonephritis
   D. Unclassified Glomerulonephritis

2. Glomerulonephritis of Systemic Diseases

3. Glomerular Lesions in Vascular Diseases

4. Glomerular Lesions in Metabolic Diseases

5. Hereditary Nephropathies

6. Miscellaneous Glomerular Diseases

7. End Stage Kidney

8. Glomerular Lesions Following Transplantation
Table 2

W.H.O. MORPHOLOGICAL CLASSIFICATION OF LUPUS NEPHRITIS (MODIFIED)

I. Normal Glomeruli
   a) Nil (by all techniques)
   b) Normal by light microscopy, but deposits by electron or immunofluorescence microscopy

II. Pure Mesangial Alterations (Mesangiopathy)
   a) Mesangial widening and/or mild hypercellularity (+)
   b) Moderate hypercellularity (++)

III. Focal Segmental Glomerulonephritis (associated with mild or moderate mesangial alterations)
   a) "Active" necrotizing lesions
   b) "Active" and sclerosing lesions
   c) Sclerosing lesions

IV. Diffuse Glomerulonephritis (severe mesangial, endocapillary or mesangio-capillary proliferation and/or extensive subendothelial deposits)
   a) Without segmental lesions
   b) With "active" necrotizing lesions
   c) With "active" and sclerosing lesions
   d) With sclerosing lesions

V. Diffuse Membranous Glomerulonephritis
   a) Pure membranous glomerulonephritis
   b) Associated with lesions of Category II (a or b)
   c) Associated with lesions of Category III (a – c)
   d) Associated with lesions of Category IV (a – d)

VI. Advanced Sclerosing Glomerulonephritis

The classification is shown in Table 1. The W.H.O. Morphologic Classification of Lupus Nephritis (see modified Table 2) is now being used almost universally to grade the severity of the lesions, and prognosis.

The second volume, Classification and Atlas of Tubulo-Interstitial Diseases again represents a collaborative effort of pathologists and nephrologists from many countries of the World. A great variety of aetiological agents and several pathogenetic mechanisms lead to tubulo-interstitial damage with similar histological changes. Therefore, this classification takes into account aetiological, pathogenetic and clinical features. The format of the book is similar to volume I.

The third volume, now in publication, will deal with Vascular Diseases of the Kidney and Development and Hereditary Diseases. The fourth volume, now in preparation will deal with Infectious and Tropical Diseases of the Kidney.

These four volumes should, hopefully, classify all the known renal diseases, excluding tumours, and enable pathologists, nephrologists and epidemiologists to diagnose the various diseases seen in their countries using the same criteria, and therefore compare their data. This should lead us to a better understanding of renal diseases, and hopefully towards better treatment and prevention.

IDENTIFICATION OF MAJOR RENAL LESIONS IN SOME CLINICAL SYNDROMES

Nephrotic Syndrome

It is the knowledge gained from the study of renal biopsies which has helped us to better understand this disease(s). Though the aetiological agent(s) may not be known in the majority of cases, it is now well established that Minimal change (lipoid nephrosis) is more common in children than in adults. The majority respond well to steroid therapy with complete remission of the proteinuria. When they do not respond, renal biopsy often reveals focal segmental sclerosis and hyalinosis. The information gained
from studies from many centres, and especially the Reports from the International Study of Kidney Diseases in Children have revolutionized the treatment of childhood nephrotic syndrome.\textsuperscript{55, 58, 61, 62, 63, 64} Membranous nephropathy is a common cause of nephrotic syndrome in adults, and usually do not respond to corticosteroid therapy.\textsuperscript{36} In Singapore 10\% of patients with IgA nephropathy present with nephrotic syndrome.\textsuperscript{65}

Haematuria

The major causes of haematuria, either gross or microscopical, have included tumours of the kidney, renal pelvis, ureter, prostate and urethra: renal and vesicle stones, infections, analgesic nephropathy with papillary necrosis, vascular malformations, infections and coagulation abnormalities and polycystic kidney disease. With the advent of renal biopsy studies, several glomerular lesions of major importance as causes of haematuria have been discovered. Thin basement membrane disease and Alport's syndrome have already been described.

The primary glomerulonephritis of major importance as a cause of haematuria is IgA Nephropathy, (Berger's disease), first described in Paris in 1968--69.\textsuperscript{55, 66} Due to its great geographical importance in this region, we should discuss the problem in some detail. Initially it was not accepted as an entity, but is now recognized to be the most common primary glomerulonephritis in many parts of the world.\textsuperscript{**} The first cases in Southeast Asia were reported from Singapore in 1974.\textsuperscript{31, 68} The diagnosis of this disease is made by immunopathology, with the finding of the characteristic mesangial deposition of IgA (Fig. 10), which may be associated with IgG and/or IgM in approximately 50\% of the cases. The activation of complement C3 is via the alternative pathway\textsuperscript{69} and properdin may be utilized. This and the predominance of IgA helps to distinguish this from mesangial lupus nephritis with IgA/IgG deposits.

Epidemiological studies done in Singapore showed IgA nephropathy to occur in >50\% of young, male army recruits with asymptomatic microscopical haematuria-proteinuria.\textsuperscript{31, 66} IgA deposits in 4\% of a "normal" autopsy population.\textsuperscript{31} The disease most commonly presents as haematuria, which usually follows an upper respiratory infection. Other clinical manifestations are nephrotic syndrome, acute nephritis, hypertension or acute renal failure: with a large proportion being asymptomatic and detected on routine medical examination. A number of biopsy studies have shown that proteinuria > 1 gm/day, glomerular sclerosis, arterial hypertension, severe intra- and extracapillary proliferation and peripheral extension of IgA deposits as determined by immunofluo-

FIG. 10: The characteristic distribution of IgA deposits along the centrilobular stalks of the glomerular mesangium in IgA nephropathy of Berger. (Immunofluorescence microscopy x 350).
rescence (Fig. 11) and electron microscopy, denote a poor prognosis.\textsuperscript{72,73,74} The IgA deposits cause mesangiolysis and also stimulate the cells to proliferative and ultimately lead to glomerular sclerosis.\textsuperscript{75}

IgA nephropathy has immunopathological features similar to the glomerulonephritis in the Henoch Schonlein syndrome,\textsuperscript{76,77,78} and is considered by many to be a forme fruste of Berger's disease with systemic manifestations. The aetiology of the disease(s) is as yet ill understood. Figure 12\textsuperscript{67} shows the possible mechanisms for the IgA mesangial deposits, which also can be seen in cases of liver cirrhosis,\textsuperscript{79,80} cancers, especially mucin secreting adenocarcinomas,\textsuperscript{81} and ankylosing spondylitis.\textsuperscript{82} Both human and experimental studies\textsuperscript{73} indicate the mesangial IgA deposits are probably derived from mucosally-presented antigen(s). There is increased production of IgA and its polymers by both mucosal and peripheral blood lymphocytes. Mediators other than IgA alone are involved in the glomerular injury. The role of the phagocytic reticuloendothelial system in the catabolism of IgA associated-immune complexes has also to be studied. Though the enigma of IgA nephropathy has not been solved, it is likely that with increasing knowledge of pathogenesis and mediation, this widespread disease will ultimately lend itself to more effective treatment and hopefully its prevention.

**Acute Glomerulonephritis**

The clinical features of Bright's disease or acute nephritis have been well documented to occur either sporadically or in epidemics especially after streptococcal infections. It has been known that the majority of patients recover, with a proportion going into chronic renal failure or dying in the acute phase.\textsuperscript{84} Though the disease has been recognised since Richard Bright's descriptions in 1827,\textsuperscript{9} it is the study of sequential biopsies that have given us an insight into its behaviour.\textsuperscript{85,86} In the acute phase, there is diffuse endocapillary proliferation with exudative lesions of polymorphonuclear infiltrates. There are subepithelial granular deposits of immune complexes with IgG and C3, with subepithelial humps seen on electron microscopy. These changes disappear or resolve within 2 to 3 months. In some cases, the mesangial hypercellularity may persist for years, with these mesangial changes corresponding to the chronic latent phase of the disease. In the patients with rapid progression and poor prognosis, the underlying pathology is usually the development of superimposed extracapillary proliferation with crescents formation.\textsuperscript{57}

**IgA nephropathy** is now also known to present as acute nephritis in approximately 10% of cases.\textsuperscript{69}
Renal Lesions in Systemic ("Collagen") Diseases

Renal biopsy has contributed greatly to the understanding of the multisystem, "collagen" diseases. It has been shown that SLE patients with no clinical or laboratory evidence of renal involvement will show a glomerulonephritis or tubulo-interstitial nephritis by either light microscopy or more commonly by immuno-fluorescent and electron microscopy. The sites of immune complex deposits give a good index of the severity of disease; most severe with subendothelial and intramembranous deposits. Disease activity can be determined by the finding of fibrinoid changes, karyorrhexis and interstitial inflammation.
mation. In Scleroderma, the vascular damage can be determined by biopsy even in the absence of hypertension. Wegener's syndrome and Goodpasture's syndrome can be diagnosed accurately only by biopsy. These conditions may lead to rapidly progressive glomerulonephritis, and a renal biopsy may show a diffuse crescentic glomerulonephritis (Fig. 13), with linear fluorescence along the glomerular basement membrane of IgG and C3 in Goodpasture's syndrome (Fig. 14). This finding of anti-GBM antibodies may be indicative for instituting immunosuppressive treatment and plasmapheresis.

Biopsy In Renal Transplantation

Dialysis and renal transplantation were instituted widely in the second half of the 20th Century. Failures in transplantation were identified to be rejection only when renal biopsies and nephrectomies were examined under the microscope. The stages and the pathological features of transplant rejection have been well documented by Porter.89

(i) Hyperacute rejection which occurs some 10 to 20 minutes after blood flow is re-established in the kidney. The glomerular and intertubular capillaries show platelet aggregates, followed by polymorphonuclear neutrophils along the capillary wall, with fibrin in the lumen soon after, and subsequently the intrarenal capillaries and arterioles are occluded by microthrombi. After a few days there is renal cortical necrosis.

(ii) Acute rejection may occur at any time during the life of the graft, but are uncommon after one year. There is a wide spectrum of changes with combinations of predominantly cellular rejection and antibody-mediated vascular damage. In early stages the rejection is often of the cellular type and is amenable to immunosuppressive therapy. The biopsy shows the interstitium and intertubular capillaries to contain mononuclear cells, lymphocytes and lymphoblasts (Fig. 15). The glomeruli, arterioles and arteries are usually normal, and there are no significant immunoglobulin or complement deposits. With predominantly humoral (vascular) rejection there is interstitial oedema and focal haemorrhages. There is only slight to moderate mononuclear cell infiltration. The vessels show severe vasculitis and contain fibrin thrombi, and there are foci of fibrinoid necrosis in the walls of small arteries and arterioles (Fig. 16). With immunofluorescence microscopy, IgG, IgM, C1, C3 and fibrinogen are commonly present in the wall of arteries and arterioles and glomeruli. If uncontrolled it leads to cortical necrosis.

FIG. 13: Crescentic (extracapillary) glomerulonephritis with circumferential involvement in a patient with rapidly progressive glomerulonephritis (PAS silver stain x 350).
FIG. 14: Immunofluorescence microscopy of renal biopsy from the case in Fig. 13 showing IgG and C3 linear deposits along the glomerular basement membrane. Patient was diagnosed Goodpasture's syndrome. (Immunofluorescence microscopy x 300).

FIG. 15: Acute rejection of human renal allograft showing predominantly cellular rejection with massive mononuclear cell infiltration. Lymphocytes-lymphoblasts are found within peritubular capillaries and interstitium, and some of the tubules show necrosis. (PAS silver stain x 250).
Acute rejection of human renal allograft predominantly humoral vascular type. There is a vasculitis with fibrinoid necrosis, and infiltration of the small artery by polymorphonuclear neutrophils. There is lymphocytic cellular infiltrate of the surrounding interstitium. (H & E x 250).

High dosage steroids are needed, and in resistant cases, the outlook is poor.

(iii) Chronic rejection
This may occur after one or more episodes of acute rejection that are partially responsive to high-dose steroids. The biopsy shows arterial narrowing and glomerulopathy, with tubular atrophy and interstitial fibrosis.

Therefore the renal biopsy can establish the accurate diagnosis in the recipient as to the condition of the allograft. In the early post-transplant period, the biopsy can diagnose whether hyperacute rejection or acute tubular necrosis is the cause of the renal disorder. It is now also well recognized that a number of renal disease processes are likely to recur in transplanted kidney. The recurrence has been reported in anti-GBM-mediated glomerulonephritis, Berger's IgA nephropathy, dense deposit disease, type 2 mesangiocapillary glomerulonephritis, membranous nephropathy, focal segmental glomerulosclerosis, and Henoch Schönlein purpura. Recurrence of other metabolic diseases have also been reported.

Tubulo-Interstitial Diseases

Diseases affecting the tubulo-interstitium may mimic many of the clinical syndromes due to lesions in the glomerulus. Tubulo-interstitial nephropathies represent a heterogeneous group of disorders with diverse aetiologies. This group of disorders includes pyelonephritis and drug-induced kidney disease. These various conditions may mimic the clinical syndromes of acute nephritis, acute renal failure, massive proteinuria leading to nephrotic syndrome, gross haematuria and chronic renal failure. Biopsy will show a variety of tubular changes, interstitial
oedema, and cellular infiltrates of lymphocytes, eosinophils, plasma cells, histiocytes and less commonly polymorphonuclear neutrophils, in acute tubulo-interstitial nephritis, which will help to distinguish from the above clinical syndromes due to glomerular diseases.

Renal pathology including gross and microscopical examination, immunofluorescence microscopy and in some cases electron microscopy, when taken into account with the clinical, radiological, aetiological and pathogenetic mechanisms have helped in a better understanding of the pathogenesis and treatment of many of these tubulo-interstitial disorders. The pathological features of tubulo-interstitial diseases, aetiologies and pathogenetic mechanisms have been well documented in several books, and time does not allow us to go into the details in this area of renal pathology.

Vascular, Congenital and Hereditary Renal Diseases

These areas of kidney disease are too vast for any meaningful discussion in the time allotted for this lecture, except to comment that the renal pathologist has, and continues to contribute to a better understanding of these diseases.

THE FUTURE ROLE OF RENAL PATHOLOGY

In this brief lecture, I have outlined the contribution of pathology in the better understanding of renal diseases. Biopsy is now widely used for diagnosis, management, classification and investigation of kidney diseases. At present it is the only method of making a precise morphological diagnosis, on which the treatment and prognosis are based. Much information gained from the correlation between structure and function in health and disease has led to a better understanding of the various diseases that affect the kidney, and which present in a limited number of clinical syndromes.

The classification and examination of the kidney along conventional lines by observing the changes in the glomerulus, tubules, interstitium and blood vessels is artificial as the various structural elements of the kidney are closely inter-related anatomically and functionally. These inter-relationships are now being better understood, largely due to the morphological studies correlated with physiological and clinical diseases, and biochemical functions of the kidney.

Molecular biology has made impressive strides in the last decade, and attempts are being made to define the molecular basis of disease. We may be on the threshold of studying the cell components and products of cells which may enable us to better understand the modes of renal injury and the pathogenetic mechanisms involved. These new investigative approaches should prove invaluable in the understanding, better care of the patient with renal disease, and finally its prevention. It appears new and exciting horizons are opening for our young renal pathologists, and our discipline will continue to be a major contributor to renal medicine.

ACKNOWLEDGEMENTS

This work was supported by grants from the National University of Singapore, The Singapore Turf Club, and the P.B. Davar Memorial Fund. I wish to thank the Technicians and Secretarial staff of the University Department of Pathology.

REFERENCES


47. Faragiana T, Parolini C, Previtali G, Lupo A. Light and electron microscopic findings in five cases of cryoglobulinaemic glomerulonephritis. Virchows Arch Path h a t 1979; 384: 29–44.


