

THE FIRST K. PRATHAP MEMORIAL LECTURE

THE CONTRIBUTION OF PATHOLOGY IN RENAL DISEASE

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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 countries^{2, 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

R E P O R T S
O F
M E D I C A L C A S E S ,
S E L E C T E D
W I T H A V I E W O F I L L U S T R A T I N G
T H E S Y M P T O M S A N D C U R E O F D I S E A S E S
B Y A R E F E R E K C E T O
M O R B I D A N A T O M Y .

B Y R I C H A R D B R I G H T , M . D . F . R . S . & c .

L E C T U R E R O N T H E P R A C T I C E O F M E D I C I N E .

A N D O N E O F T H E P H Y S I C I A N S T O

G U Y ' S H O S P I T A L .

L O N D O N :

P R I N T E D B Y R I C H A R D T A Y L O R , R E D L I O N C O U R T , F L E E T S T R E E T .

P U B L I S H E D B Y L O N G M A N , R E E S , O R M E , B R O W N , A N D G R E E N .

1827.

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

PLATE II.

KIDNEY IN DROPSY.

FIG. 1. External appearance of one of the kidneys of SALLAWAY (page 12, 67, 75, &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. 4. A portion of one of the kidneys of CADMORE (page 14, 111, 119, 115) in a state of degeneration after long suffering from chronic disease. The state of the urine was not particularly ascertained, and no material dropsical effusion had taken place.



Fig. 1



Fig. 2



Fig. 3



Fig. 4

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.¹⁰ In 1942 **Ellis**¹¹ 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**.¹² 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 **glomeru-**

lonephritis, 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**.^{13,14} The localization of the complexes may be determined by its size; small complexes passing through the glomerular basement membrane and deposit in the **subepithelium**; larger size immune complexes through the subendothelium-mesangial system.¹⁵ 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**.^{16,17,18} 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.^{19,20} Immune complex **glomerulonephritis** accounted for most of the human **glomerulonephritis**.⁵ Antibodies may be produced against GBM, as in the experimental **Masugi type nephritis**²¹ or **anti-GBM antibody nephritis**, with continuous linear deposits of **IgG and C3** along the glomerular basement membrane (Fig. 4). Goodpasture's syndrome

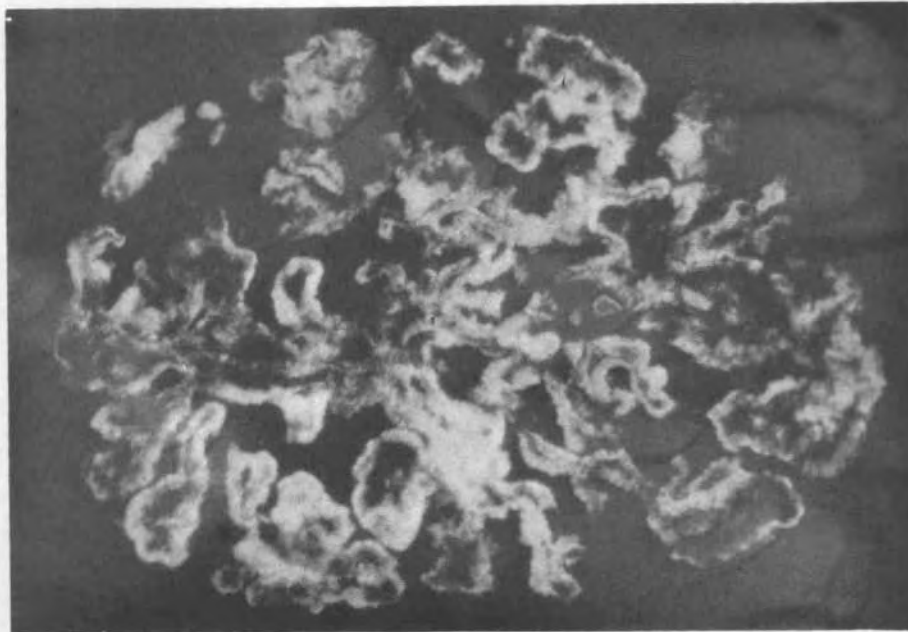


FIG. 3 : Immunofluorescence pattern of granular deposits in the glomerulus, which denotes an immune complex type glomerulonephritis, with IgG deposits along the glomerular basement membrane. (Immunofluorescence microscopy x 350)

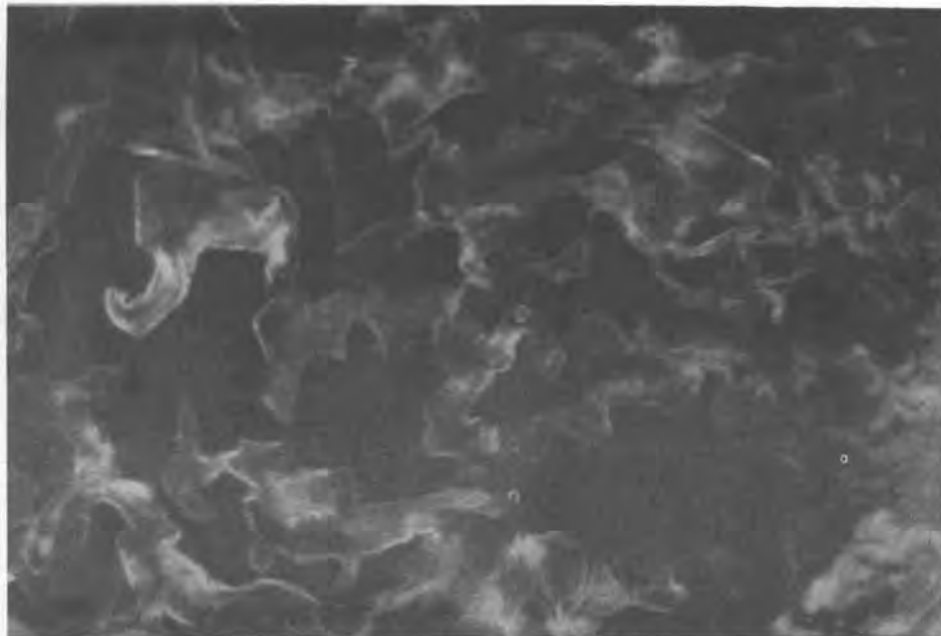


FIG. 4 : Continuous linear deposits of IgG along the glomerular basement membrane (GBM) which denotes anti-GBM-antibody induced glomerulonephritis. (Immunofluorescence microscopy x 500)

with anti-GBM glomerulonephritis shows a uniformly linear fluorescence.^{22, 23, 24} This type of glomerulonephritis is infrequent in Western and temperate countries, and rare in tropical countries of Southeast Asia.^{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.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.^{15, 20, 29} The alternative pathway of complement activation utilizes factor A, factor B or C3 proactivator and properdin. Aggregated IgA will fix complement *in vitro* by the alternative pathway.³⁰ This feature of alternative pathway of C3 activation

has been well demonstrated in IgA nephropathy of Berger and the Henoch Schonlein syndrome.^{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.

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.^{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.³⁶ The subdivision of diffuse *mesangiocapillary glomerulonephritis*, membranoproliferative glomeru-

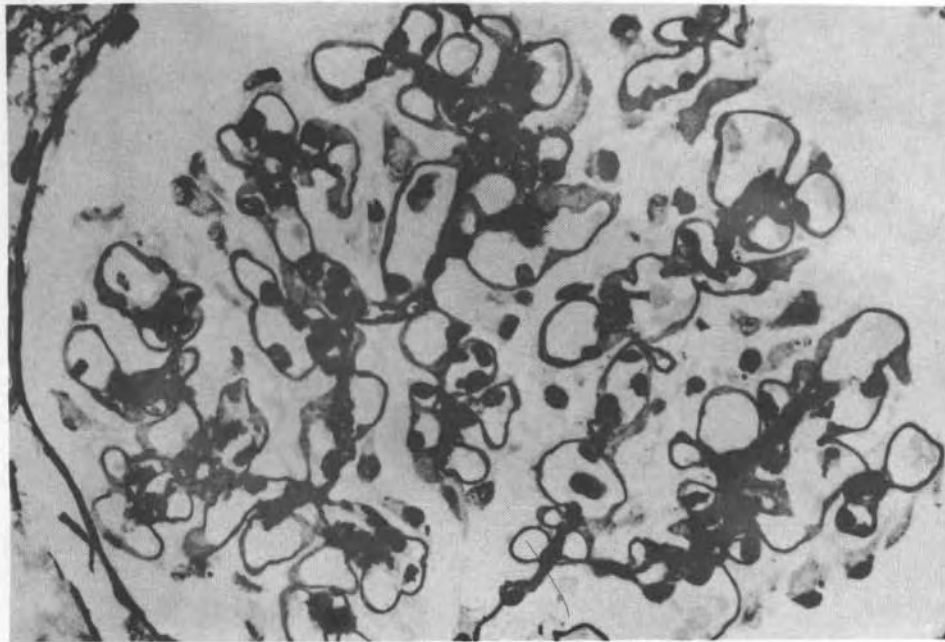


FIG. 5 : Light microscopy of early stage 1, membranous nephropathy which is indistinguishable from minor change lesion. The capillary loops are thin and there are no spikes. (PAS-silver stain x 640)

lonephritis types 1 and 3 was based on the additional presence of subepithelial dense deposits in the latter.^{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.^{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.^{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 glomerulus.

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," with concomitant 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.⁴⁶ The nephropathy in various *dysproteinemias* also show characteristic fibrils or tubules which may be formed in the subendothelium or epithelium.^{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."⁵² 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*.^{53, 54}

THE W.H.O. CLASSIFICATIONS OF RENAL DISEASES

The study of percutaneous or open renal biopsies over the last three decades has contri-

