A CLINICO-PATHOLOGIC STUDY OF SOME FORMS OF GLOMERULONEPHRITIS IN EGYPT WITH THE TRIAL OF IMMUNOSUPPRESSIVE THERAPY IN SOME OF THESE FORMS

M.D. Thesis

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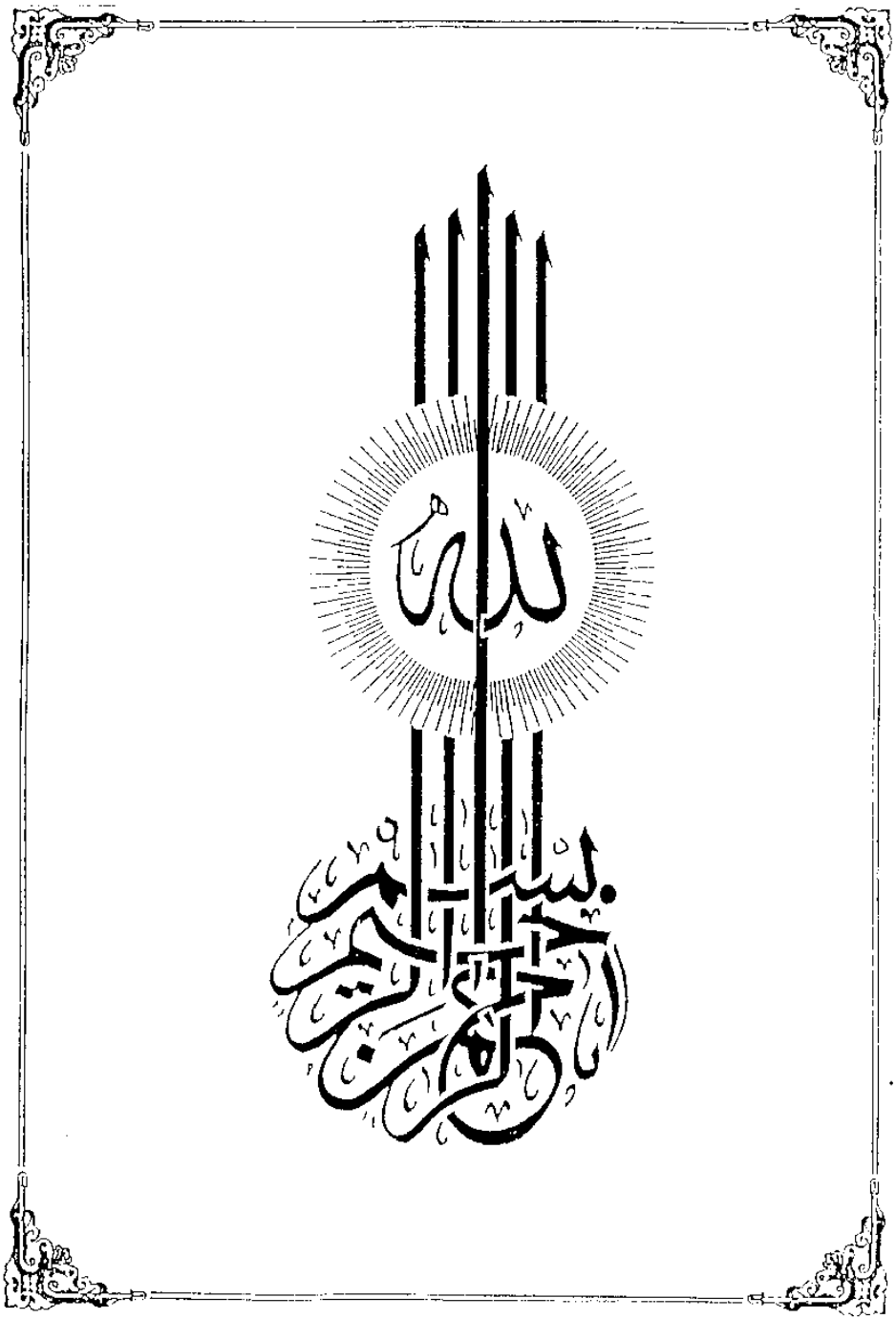

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C O N T E N T

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INTRODUCTION AND HISTORICAL OUTLINE

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The association between scarlatina and the subsequent appearance of dropsy was noted as early as 1641 by Sennert. But Bright in 1827 was the first to point the relation between scarlatina and renal disease (Peters and Freedman 1959).
Bright described many patients with generalized oedema or dropsy who had well marked lesions of the kidney and in these cases the urine was coagulated by heat. Although some of the kidneys were large and pale, whilest others were small and contracted, other organs as the heart were abnormal (Boyd, 1963).

Since the days of Bright large number of classifications have been proposed. Volhard and Fahr (1914) outlined the various entities making up the general conditions of Brights disease , and out of this emerged the various forms of nephritis. Other degenerative conditions as amyloidosis and mercuric choloride poisoning were treated separately as there was no inflammatory element. From the clinical stand point nephritis was classified to diffuse and focal entities. The diffuse, glomerulonephritis (with obligatory hypertension) was further subdivided into: Acute stage , chronic stage and end stage with renal insufficiency, while the focal form was subdivided into focal

glomerulonephritis without hypertension, interstitial focal nephritis and Embolic focal nephritis.

Ellis (1942) divided glomerulonephritis into two main types (I) and (II), although he described a number of cases which he considered to be focal nephritis. Type (I) was characterized by a sudden abrupt onset with the clinical features of hematuria, proteinuria, oedema of moderate degree and transient hypertension, the general tendency in this category was towards recovery. Ellis type II nephritis, on the other hand, differed in many respects from his type (I) nephritis. The onset was inciduous , general symptoms and hematuria were absent or slight, oedema was severe and persistent, history of previous infection was found in less than 5% of patients, proteinuria was severe and the blood pressure was frequently normal in the early stages.

Glomerulonephritis in man has been suspected to be the result of immune mechanisms since Schick's (1907) suggestion that the lapse of time between symptomatic streptococcal infection and the onset of acute nephritis might represent the period required for the development of hypersensitivity of the host to remaining organisms. However the concept of immunologically induced renal disease was first seriously

considered when it was shown that antikidney serum made in one species of laboratory animal could produce glomerulonephritis in others. Masugi (1934). The labeled antibody techniques originally developed by Coon's et al. (1941) has provided an excellent procedure where by specific agents under investigation can be localized and identified.

The pathologic classification of glomerulonephritis is subjected to considerable disagreement among pathologists. Much of the recent data about glomerulonephritis have been obtained by percutaneous renal biopsy, also immunofluorescence studies and electron microscopy can be performed affording a valuable clue to the cause particulary in the differentiation of antiglomerular basement membrane disease and immune complex disease in human (Kincaid Smith, 1973).

REVIEW OF LITERATURE

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REVIEW OF LITERATURE

Pathogenesis of Glomerulonephritis

Thomas (1971) refers to kidney transplantation and haemodialysis as "half way technology" by this he means a technology that compensates for established disease or postpones death in such states. It is evidint now that the end stages of glomerulonephritis are responsible for renal failure and for the necessity for dialysis and transplantation in approximately two thirds of the cases treated by these modalites.

The prevention or at least arrest of glomerulonephritis before it reaches the renal failure seems appropriate, this can be done by understanding the pathophysiologic - immunologic mechanisms underlying glomerulonephritis.

The immune process is clearly responsible for almost all forms of glomerulonephritis (G.N.) based on animal experiments done in the past 70 years, it is realized that immune precesses are a major cause of the disease in man (McCluskey, 1973).

There are two major humoral mechanism involved in the immune pathogenesis of G.N.:

In the first mechanism, antibodies having specificity for renal structural constituents are involved; mainly the glomerular basement membrane (G.B.M.), also the tubular B.M. (T.B.M), antibodies with special affinity for the mesangium, vessels or tubular cytoplasmic material (Dixon 1971).

In the second mechanism, antibodies combine with nonglomerular antigens to form immune complexes that circulate and deposite primarily in the glomeruli, in the G.B.M. and the mesangium as well as in the vessel wall and interstitium. (Wilson and Dixon 1973).

Once antibodies combine with antigen and deposite in the kidney or other tissue, they initiate inflammatory processes after which mediators are released, these mediators function equally well for anti-basement membrane antibody or immune complexes promoting the progression of this glomerular injury. The highly sophisticated glomerular capillary filter composed of the ferusteated endothelium, the basement membrane and epithelial cells with its foot processes is particularly vulnerable to the effect of these mediators (Graham - 1966 and Dixon and Wilson 1973).

These mediators (effector mechanisms) include complement and possibly non-complement pathways such as the haegman factor systems (Kinin forming and coagulation systems). The precise contribution of the various mediation pathways in human G.N. is not clear (Wilson and Dixon 1976).

In experimental nephritis neutrophils attracted by activation of the complement system play a major role in the production of tissue damage (Wilson and Dixon 1976).
Platelets and mast cells may be involved also by releasing mediators, such as the vasoactive amines, histamine and serotonin, which can enhance capillary permeabelity. Fibrin deposition in Bowman's space is thought to contribute to the development of glomerular crescents. Currently there is little evidince for a direct role of cell mediated immunity in human G.N. (Wilson and Dixon 1976).

Glomerular injury is sometimes observed in the absence of obvious immunoglobulin (Ig) deposition but with striking glomerular complement (C) accumulation, and the glomerular lesion is also accompanied by depression of senum (C) level. This observation has led to the suggestion that non immune (Non Ig) induced activation of (C) may sometimes play an important role in the initiation and perpetuation of glomerular injury (Verrotust 1974).

Antiglomerular basement membrane Antibody induced glomerular injury

(A) Experimental Modles:

1. Anti glomerular basement membrane nephritis (Nephrotoxic serum or Masugi nephritis):

Lindemann in 1900 first demonstrated that injection of an antiserum against the rabbit kidney raised in guinea pigs would cause rabbits to develop proteinuria and uremia .

The pathology of nephrotoxic nephritis was studied in the 1930's by Masugi (1934), so extensively that the condition is often refered to as Masugi nephritis.

Anti G.B.M. antibodies can be prepared by immunizing animal of a different species with glomerular basement membrane. The antibody can then be used to induce antiglomerular basement membrane nephritis in normal recepients. The resulting glomerular injury occurs in 2 phases:

(i) The heterogenous phase: develops only when sufficient quantities of anti BGBM antibodies are given (75 ug. of kidney fixing antibody pergram of kidney in the rat), immediate injury and proteinuria occur (Lerner 1966).