

**DRUGS, SYSTEMIC DISEASES,  
AND THE KIDNEY**

# **DRUGS, SYSTEMIC DISEASES, AND THE KIDNEY**

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**DRUGS, SYSTEMIC  
DISEASES, AND  
THE KIDNEY**

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TO OUR WIVES

Pia Amerio  
Liliana Coratelli  
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Meira Massry

AND OUR CHILDREN

## PREFACE

We are pleased to present to our readers the proceedings of the Third Bari Seminars in Nephrology. The topic of these proceedings deals with effects of drugs and systemic diseases on the kidney.

The Bari Seminars in Nephrology are bi-annual meetings attended by a large international audience comprised of clinicians-scientists in the various disciplines of nephrology and related fields.

The next Bari Seminars of Nephrology will take place in April 1990 and the theme of the gathering will be Interstitial Nephritides and Obstructive Uropathy. We are indebted for the generous financial support of the Centro Nazionale delle Ricerche, Italy.

Alberto Amerio  
Pasquale Coratelli  
Vito M. Campese  
Shaul G. Massry

## CONTENTS

<b>Lupus Nephritis: Pathogenesis, Course and Management. . . . .</b>	<b>3</b>
James E. Balow	
<b>Prognostic Determinants in Lupus Nephritis. . . . .</b>	<b>17</b>
P. Coratelli, R. Rizzi, G. Pannarale, A. Ramunni M. Giannattasio, and G. Passavanti	
<b>Thrombotic Microangiopathy in Lupus Nephritis . . . . .</b>	<b>35</b>
M.T. Porri, M.I. Quarenghi, F. Ferrario G. Colasanti, R. Rossi, E. Schiaffino, G. Toia, and G. D'Amico	
<b>Vasculitis and the Kidney . . . . .</b>	<b>41</b>
Giovanni M. Frasca, Barbara Stagni, Concettina Raimondi, Alba Vangelista, and Vittorio Bonomini	
<b>Mixed Connective Tissue Disease and Renal Disease . . . . .</b>	<b>53</b>
Mohammad Akmal	
<b>Atheroembolic Renal Disease: Clinico-Pathologic Correlations. . . . .</b>	<b>59</b>
F. Antonucci, S. Pizzolitto, M. Travaglini, G.F. Marrocco, G. Boscutti, M. Messa, G.B. Fogazzi, E. Rivolta, and Servizio Nefrologia	
<b>Renal Involvement in Tuberous Sclerosis . . . . .</b>	<b>65</b>
F. Dossi, A.M. Marconi, P. Riegler, M. Brogginì, and D. Donati	
<b>Severe Renal Involvement in Primary Sjogren's Syndrome. . . . .</b>	<b>73</b>
A. Gentric, J.P. Herve, Y.L. Pennec, J.P. Leroy, and J. Clodes	
<b>IgA Nephropathy in Systemic Diseases. . . . .</b>	<b>83</b>
G. Piccoli, R. Coppo, D. Roccatallo, and A. Amore	
<b>Diabetic Nephropathy: New Pathogenetic Aspects. . . . .</b>	<b>95</b>
August Heidland, Markus Teschner, and Roland Schaefer	
<b>Uric Acid and Kidney. . . . .</b>	<b>107</b>
Giorgio Fuiano, Stefano Federico, Giuseppe Conte, and Vittorio E. Andreucci	
<b>Pre-Eclampsia as A Multi-System Disease . . . . .</b>	<b>119</b>
John M. Davison	
<b>Electrolyte Abnormalities in Cancer . . . . .</b>	<b>135</b>
Manuel Martinez-Maldonado, and Julio E. Benabe	



Hypercalcemia and the Kidney. . . . .	147
Wadi N. Suki	
Hypokalemia . . . . .	155
Neil A. Kurtzman	
The Renal Response to Infection . . . . .	163
Richard J. Glasscock, Cynthia C. Nast, and Arthur H. Cohen	
Renal Involvement in Hantavirus Disease . . . . .	173
B. Cizman, D. Ferluga, S. Kaplan-Pavlovic, M. Koselj, J. Drinovec, and T. Avsic	
Glomerular Lesions and Opportunistic Infections of the Kidney In Aids: An autopsy study of 47 cases. . . . .	181
H.J. van der Reijden, M.E.I. Schipper, S.A. Danner, and L. Arisz	
Selected Aspects of Drug Use in Renal Failure . . . . .	191
William M. Bennett, and Lawrence W. Elzinga	
The Analgesic Agents and Renal Disease. . . . .	199
Sandra Sabatini	
Lithium Induced Polyuria and Polydipsia . . . . .	215
Giuseppe Passavanti, Erasmo Buongiorno, Giuseppina De Fino, Giulio Rutigliano, Michele Giannattasio, and Pasquale Coratelli	
Aminoglycoside Nephrotoxicity: Mechanism and Prevention . . . . .	233
Marc E. De Broe, Ruben A. Giuliano and Gert A. Verpoeten	
The Natural Course of Gold and Penicillamine Nephropathy: A Longterm Study of 54 Patients . . . . .	247
Clive L. Hall	
Effects of Contrast Media on Renal Hemodynamics and Tubular Function: Comparison Between Diatrizoate and Iopamidol. . . . .	257
Carlo Donadio, Gianfranco Tramonti, Roberto Giordani, Amalia Lucchetti, Andrea Calderazzi, Paola Sbragia, and Claudio Bianchi	
Nephrotoxicity of Fumaric Acid Monoethylester (FA ME) . . . . .	265
M. Hohenegger, M. Vermes, A. Sadjak, G. Egger, S. Supanz, and U. Erhart	
Cyclosporin and Renal Injury. . . . .	273
R. Maiorca, F. Scolari, S. Savoldi, S. Sandrini, P. Scaini, and L. Cristinelli	
Cyclosporin A and Drug Interaction. . . . .	285
R. Menta, S. David, and V. Cambi	
Magnesium after Renal Transplantation - Comparison between Cyclosporine A and Conventional Immunosuppression . . . . .	297

<b>A Case of Relapsing Renal Micropolyarteritis: A Possible Association with Assumption of Non Steroidal Antiinflammatory Drugs (NSAID).</b>	303
P. Stanziale, G. Fuiano, M.M. Balletta, V. Sepe, G.C. Marinelli, G. Colucci, and V.E. Andreucci	
<b>Randomized Multi Center Study Comparing Nephrotoxicity of Ceftazidime Versus The Combination of Piperacillin and Netilmicin with and without Furosemide.</b>	307
A. Werner Mondorf, Christina Bonsiepe, and Wolfgang Mondorf	
<b>Mechanism of the Mitochondrial Respiratory Toxicity of Cephalosporin Antibiotics</b>	313
Bruce M. Tune	
<b>Drugs-Induced Renal Diseases: Personal Contribution</b>	319
E. Lusvardi, M. Leonelli, L. Furci, and A. Baraldi	
<b>The Effect of Parathyroid Hormone on Cisplatin Nephrotoxicity.</b>	325
Giovambattista Capasso, Dario R. Giordano, Natale G. De Santo, and Shaul G. Massry	
<b>Effect of Antihypertensive Agents on Renal Function and on Sodium-Volume Status</b>	331
Vito M. Campese	
<b>Characterization of Bilateral Renal Response to Atrial Natriuretic Peptide in 2-Kidney, 1 Clip Hypertensive Rats</b>	349
Wann-Chu Huang and Jian-Nan Wu	
<b>The Effects of Hydrocortisone on the Mesonephros Proximal Tubule Cells.</b>	357
Mirella Bertossi, Beatrice Nico, Luisa Roncali, Daniela Virgintino, Lucia Mancini, Domenico Ribatti, and Pasquale Coratelli	
<b>Oxalate Deposits in the Kidney of 5/6 Nephrectomized Rats Supplemented by Large Doses of Vitamin C</b>	365
Keiji Ono, Hiroko Ono, Yohko Hisasue, Kazuhiko Kikawa, and Yukinori Oh	
<b>Effects of Canrenone on Na<sup>+</sup>, K<sup>+</sup> ATPase Activity, Arterial Pressure and Plasma Potassium Concentration in Uremic Hemodialyzed Patients</b>	371
F. Quarello, R. Boero, C. Guarena, C. Rosati, G. Beltrame, P. Colombo, I.M. Berto, M. Aimino, M. Formica and G. Piccoli	
<b>Renal Excretion of Arginine-Vasopressin in Microalbuminuric Diabetic Patients</b>	377
Giovanni Maria Nardelli, Mauro Cignarelli, Adriano Paternostro, Vittoria Romanazzi, Giuseppe Passavanti, Rosaria Cospite, Giovanni De Pergola, Pasquale Coratelli, and Riccardo Giorgino	
<b>CAH in Myorenal Syndrome</b>	385
Bernd Winterber, Werner Tenschert, Norbert Rolf, Katrin Ramme, Gisela Winterberg, Michael Wendt, Konrad Teerling, Arno Lison, and Heinz Zunkley	

Effect of Imidazole 2-Hydroxybenzoate on Erythrocyte Charge: A Possible Explanation of Its Hypoalbuminuric Action. . . . .	393
G. Gambaro, E. Ciccerello, S. Mastrosimone, D. Del Prete, T. Lavagnini, G. Briani, and B. Baggio	
INDEX . . . . .	395

KIDNEY IN SYSTEMIC ABNORMALITIES AND DISEASES



## LUPUS NEPHRITIS: PATHOGENESIS, COURSE AND MANAGEMENT

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### INTRODUCTION

Lupus nephritis contributes notably to the morbidity and mortality of systemic lupus erythematosus. Improved medical therapies have increased the median survival of patients with lupus to more than 15 years over the past several decades. Uremia was a rare cause of death in the era before steroids, anti-hypertensives and antibiotics. As longevity of patients with lupus improved in the second half of the twentieth century, renal disease became a key factor in the clinical expression and management of this disease. Today, renal involvement is expected in the majority of patients with systemic lupus erythematosus.

### PATHOGENESIS

Lupus nephritis represents a complex illness with a broad spectrum of immunopathology. The deposition of immune complexes appears to be the inciting step in the pathogenesis of this disease. DNA and anti-DNA antibodies are among the most nephritogenic of circulating immune complexes and they are amassed in glomerular deposits (Koffler et al, 1969).

The factors which promote the deposition of immune reactants in different sites along the nephron are incompletely understood (Couser, 1985). Immune complexes appear earliest in the mesangium (Michael et al, 1980). Localization in the mesangium may not be governed by specific immunologic factors (such as complement or immunoglobulin receptors); experimental studies show that the mesangium is a clearing site for a host of macromolecules many of which have limited nephritogenicity. On the other hand, certain attributes of immune complexes appear to enhance their accumulation in the subendothelial region of glomerular capillaries. DNA antigen has been shown to have an affinity for the glomerular basement membrane (Izui et al, 1977). This characteristic of DNA could account for the deposition of preformed DNA/anti-DNA circulating immune

complexes or cause in situ formation of complexes following the "planting" of DNA in the glomerulus.

The glomerular capillary is comprised of proteoglycans which confer an distinctively high density of anion charges (Stow et al, 1985). Nephritogenicity of immune complexes appears to be substantially augmented if there is a dominance of cationic charge groups on either the antigen (Border et al, 1982) or antibody (Gauthier et al, 1982). Immune complexes with a high isoelectric point have been reported to be concentrated in glomerular deposits in murine lupus nephritis (Ebling and Hahn, 1980).

The composition of subepithelial immune deposits in membranous lupus nephropathy is unknown; it is doubtful that DNA is a relevant antigen in these lesions. The prospect that the subepithelial deposits are formed in situ by reaction of an autoantibody with constituents of the basement membrane or of the epithelial cell podocytes has not been determined (Madaio et al, 1983).

#### COURSE AND PROGNOSIS

In a multicenter study of over 1000 patients, the mortality rate was 10% at one year and 29% at 10 years after diagnosis of lupus (Ginzler et al, 1982). Patients with evidence of lupus nephritis had a nominally worse death rate. In a study of over 600 patients at a single center (Wallace et al, 1981), 10 year patient mortality was 21% (11% without and 35% with nephritis). In a group of over 100 patients with lupus nephritis followed at the National Institutes of Health, the risk within 10 years of dying was 25%, of end stage renal failure 28%, and of doubling serum creatinine 38%.

Lupus nephritis is the cause of approximately 3% of cases of end stage renal failure requiring maintenance dialysis or transplantation. These patients experience a higher mortality rate than properly matched dialysis patients (Kramer et al, 1982; Jarratt et al, 1983); the subset of patients with rapid escalation of their renal disease and persistently active extra-renal lupus are at particular risk (Cheigh et al, 1983; Correia et al, 1985).

The course of lupus nephritis is intricate and cannot be easily defined for several reasons. Among others, the clinical characteristics of the patients are extremely heterogeneous, the onset of the disease (systemic lupus erythematosus, lupus nephritis, or the specific class of glomerulonephritis) is often difficult to pinpoint, transitions among several types of renal pathology are common, and several different outcomes of the renal disease must be considered. Thus, determination of the probable clinical course of the individual patient with lupus nephritis is usually based on crude estimations at best.

Prognosis undoubtedly depends on a large number of factors specific to each patient with lupus nephritis. It is difficult to define the single most important variable in estimating the prognosis of lupus nephritis. It is judicious to develop a composite of demographic, clinical, laboratory and pathologic parameters in estimating prognosis and in planning management.

## Demographic features

Young age at onset of lupus and male gender are associated with an increased risk of renal failure (Austin et al, 1983; Cameron et al, 1979). Race has been thought to have an influence on the severity of lupus; but recent analyses suggest that when race is adjusted for socioeconomic factors, it does not appear to have a major influence on the clinical course of systemic lupus or lupus nephritis (Ginzler et al, 1982).

## Clinical features

Numerous clinical and laboratory measurements have been assessed for their prognostic value in lupus nephritis. The presence of nephrotic syndrome at onset of proliferative lupus nephritis (especially refractory nephrotic syndrome) seems to signal an adverse prognosis (Baldwin et al, 1977; Wallace et al, 1982; Ginzler et al, 1982).

There is no doubt that renal function tests are useful in the overall assessment of the patient with lupus nephritis. It is also important to recognize their limitations. Renal function is affected by reversible perfusional and structural lesions, as well as by fixed scarring and atrophic processes. Furthermore, hemodynamic and hypertrophic compensatory mechanisms can result in an underestimation of the degree of permanent renal damage based on standard renal function tests (Shemesh et al, 1985). Analyzing renal function tests over time yields a better correlation of structure and function as well as a more reliable estimate of renal prognosis. Insidious progression of azotemia heralds the development of chronic irreversible disease, while rapid swings in renal function often indicate the presence of active, treatable and potentially reversible lupus nephritis.

## Pathology

The prognostic usefulness of the World Health Organization classification of lupus nephritis is controversial (Churg et al, 1982; Appel et al, 1978). It is apparent that there are smaller differences in renal outcomes among these classes of lupus nephritis in recent times (Appel et al, 1987; Austin et al, 1986; Cameron et al, 1979; Platt et al, 1982; Wallace et al, 1982) than there were a few decades ago (Baldwin et al, 1970; Pollak et al, 1964).

Assessment of lupus nephritis has been facilitated by defining the types and degrees of reversible and permanent renal lesions (Austin et al, 1984; Balow and Austin, 1988). The activity index encompasses the following: glomerular cellularity, leucocyte exudation, fibrinoid necrosis, hyaline thrombi, cellular crescents, and interstitial inflammation. The chronicity index encompasses the following: glomerular sclerosis, fibrous crescents, tubular atrophy, and interstitial fibrosis. The chronicity index has been found to have a graded relationship to the risk of end-stage renal failure (Austin et al, 1984; Morel-Maroger et al, 1976). Glomerular sclerosis, fibrous crescents, interstitial fibrosis and/or tubular atrophy



are attended by reduction of renal reserve capacity or ineffective compensatory mechanisms; the presence of these lesions appears to increase the risk of renal functional deterioration as a consequence of superimposed active glomerular disease. The risk of renal failure is highest in patients with nephritic and/or nephrotic syndrome associated with extreme histologic activity (i.e., crescents, necrosis) or with less severe glomerular lesions superimposed on a background of chronic irreversible disease (i.e., tubular atrophy, interstitial fibrosis). Although suggested from observations in certain experimental models, there is little evidence that sclerosing or atrophic lesions themselves perpetuate renal failure in the absence of concomitant immunological disease.

The activity index was found to be a relatively weak predictor of renal failure outcome (Austin et al, 1984). Mild to moderate elevations of this index usually represent reversible disease (under the influence of effective treatment). Marked elevations of the activity index usually reflect structural disruption of the glomerular capillaries which heal by scarring rather than by regression. Thus, extreme elevations of the activity index predict an increased risk of renal failure. Subendothelial electron dense deposits are considered to be evidence of active lupus nephritis. However, their occurrence in a renal biopsy need not portend an unfavorable outcome since they can be mobilized and reduced in patients who are receiving effective immunosuppressive therapy (Austin et al, 1984).

### Serologic Parameters

The obvious limitations on repeated sampling of renal histology have prompted studies of the utility of serologic tests to predict the activity of the lupus nephritis, to guide therapy and to judge prognosis. The level of serum complement (CH50, as well as C3 and C4 components) have been found to correlate with the degree of activity of glomerular disease on renal biopsy (Feldman et al, 1982). Falling levels of complement components are felt to be rather strong predictors of a flare of lupus nephritis. Some have advocated that therapy should be adjusted according to the level of C3 complement (Garin et al, 1979). Our group has found a relatively weak correlation between the duration of abnormal C3 levels and the acquisition of chronic sclerosing lesions on serial renal biopsies (Pillemer et al, 1988). Immunosuppressive drugs often produce an improvement in levels of C3 components which seems to be associated with reduction of disease activity. In particular, cytotoxic drugs are effective in this process. However, it should be underscored that one risks serious overtreatment of some patients by attempting to increase persistently abnormal levels of complement components. Supporting evidence of disease activity should be present if one utilizes these serologic tests as therapeutic guidelines.

Other tests have been advocated by some for monitoring lupus nephritis, including anti-DNA antibodies, circulating immune complexes, immunoglobulin levels, cryoglobulins, C-reactive protein, and erythrocyte sedimentation rate. However, none of these tests alone have sufficient power in terms of