Edited by
JOSÉ STRAUSS

PEDIATRIC NEPHROLOGY

VOLUME 3
Current Concepts in Diagnosis and Management

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J. Strauss

Introduction

This volume is based on the 1976 Pediatric Nephrology Seminar, the third of an annual international exchange sponsored by the Division of Pediatric Nephrology, Department of Pediatrics, University of Miami School of Medicine in cooperation with the Division of Continuing Education. These seminars expose all registrants to new ideas and data in pediatric nephrology and involve all in discussion of new and old questions. This series makes the seminar content available to those interested in pediatric nephrology but unable to attend, and permanently records the material presented. Volumes I and II have been well received and proven to be valuable references for decisions about simple and complex problems.

The focus is on current concepts in diagnosis and management with emphasis on certain parts of the field. Volume I attempts to define terms such as "hematuria," "proteinuria," and syndromes such as "nephrotic" and "nephritic." Volume II and III focus on diseases such as "Henoch-Schönlein nephritis," "vasculitis," and attempt a more refined characterization of these entities.

Volume III includes workshop discussions, but unlike I and II excludes general discussions. The time and cost for recording, transcribing, editing, securing releases, and printing general discussions negate the value of this effort. Workshops have been kept because they are especially rich in detail and technically manageable. However, to expedite publication, participants names were omitted since their inclusion requires written speaker approval of all editing. An additional change is our beginning association with Plenum Press to gain earlier publication and lose editorial headaches since each author's paper will be printed exactly as submitted.

The Seminar faculty-authors are chosen on the basis of the contribution each can make to the subjects selected. All are well known and highly respected for their steady interest and dedication to discovering and documenting new ways of understanding pediatric nephrology and related problems.

José Strauss, M.D.
July 1976

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Immunohistologic, Hematologic, and Psychologic Aspects of Renal Disease

IMMUNOLOGIC ASPECTS OF RENAL FAILURE

Rawle M. McIntosh, M.D., Dennis Durante, M.D. and Nisan Gilboa, M.D.

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Immunologic mechanisms play a significant role in patients with renal failure. Several diseases which result in chronic irreversible renal failure leading ultimately to dialysis and/or transplant are the result of immune tissue injury. In addition, the uremic state is known to be associated with abnormalities of the immune system. Furthermore, immunologic considerations are of major importance in donor selection, graft rejection and modification and prevention of graft rejection. The immune mechanisms involved in renal disease may be an important consideration in recurrent disease in grafts or development of disease in grafts.

IMMUNOLOGIC ASPECTS OF UREMIA

There have been conflicting reports regarding humoral antibody responses in uremic patients. Although some investigators have suggested abnormal antibody production in renal failure (1,2) immunoglobulin levels are usually normal and antibody response to specific antigens have been demonstrated to be normal. A subnormal antibody response to typhoid vaccine and decreased cutaneous hypersensitivity have been demonstrated in some patients with renal failure. The discrepancies in reports on antibody response in renal failure may be related to the antigenic stimulus and dependent on time sequence of the investigations. However, the presence of cytotoxic antibodies in patients with chronic renal failure and the observation of hyperacute rejection in the absence of preformed antibodies suggest intact humoral immunity at least to certain antigens in some patients.

Acute and chronic renal failure are generally associated with a marked blood lymphopenia (3). This lymphopenia is rapid and in

the experimental animal may occur as early as one day after induction of uremia. The early onset tends to rule out decreased production as a causative factor. Adrenalectomy does not diminish the severity of the lymphocytopenia eliminating elevated corticosteroids as a cause. An increased destruction or shortened half-life of lymphocytes has been suggested. Uremic serum and quanidosuccinic acid, a toxic metabolite of uremia, destroy incubated lymphocytes in vitro. However, recent studies on incubation of ^{51}Cr-labelled lymphocytes with uremic serum or GSA and electron microscopic studies suggested that the lymphocytopenia of uremia is not due to increased destruction of cells but may be due to redistribution to other body compartments (3).

Depression in cell-mediated immunity has been well recognized in uremia. Delayed hypersensitivity and homograft rejection are impaired and lymphocytes in uremic serum show an impairment in blast transformation in the presence of PHA (4-6). Skin test sensitivity is decreased with the severity of uremia. Skin test sensitivity may be decreased in the presence of normal blast response. The uremic state inhibits previously established skin test reactivity but does not prevent sensitized T lymphocytes from transferring cellular immunity (7). Patients with renal failure may have a circulating factor which interferes with the mixed leukocyte culture. When this corresponds to the presence of preformed antibodies the prognosis is bad. When no correlation with lymphocytotoxic antibody is present the prognosis is usually good.

Normal T-cell population and T-cell rosette have been observed in chronic renal failure.

Studies on the effect of hemodialysis and transplantation on inhibition of lymphocyte transformation by sera from uremic patients suggest that uremic serum has a depressive effect on PHA-induced lymphocyte transformation--an effect attributable to a maromoleculure (nondialyzable factor) which is lost after renal transplantation (8).

Impairment of phagocytic activity has been reported in uremia (9,10).

The defects in immunity and phagocytosis in uremia pose several clinical problems. Interference with tests of donor matching and susceptibility to infection especially in the patient on antimetabolites are of great concern.

DONOR SELECTION AND REJECTION

Immunologic tests used in donor selection and in attempts to predict and diagnose rejection have been detailed in previous volumes and elsewhere in this book (11,12). The presence of preformed anti-

bodies is of serious concern. There has been some suggestion that antibodies may be either toxic or protective. Presensitization by transfusions, previous transplants, pregnancy, etc. represent major causes of preformed antibodies. There is still controversy as to withholding transfusions, the efficacy of special preparations and graft survival. However, most workers in the field agree that the presence of antibodies is a contraindication to transplantation.

RECURRENT DISEASE

Recurrent disease in the graft has been a subject of great concern. However, recently it has been realized that disease may develop in grafts without relationship to the original process. Lesions secondary to vascular change, HLA antigens, TBM antigens, etc. may simulate processes which suggest recurrence as well as rejection. Immune injury from organ preservation has recently been recognized as a potential cause of hyperacute rejection in human cadaver kidney transplants (13).

TREATMENT OF REJECTION

Several modalities have been used, clinically and experimentally in the treatment of rejection. Several of these are dangerous, unpractical or not presently feasible. Antimetabolites (Cytoxan^{R} or Imuran^{R}) and corticosteroids remain the agents of choice. Radiation, splenectomy, and thymectomy have been used without continuing benefit.

Table 1 outlines some of the clinical and experimental modalities used in the treatment of rejection.

Table 1. Modification of Graft Rejection

Antimetabolites
Corticosteroids
ALG
ALG-FAB_2
Modification of coagulation system

Enhancement

Active

Passive

L Asparginase ?

Concavalin A ?

Blocking: Immune complexes ?

RE Blockage

AMS

Glutaminase

Thymectomy

Thoracic duct drainage

Ionizing radiation

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VALUE OF RENAL BIOPSY IN DIAGNOSIS, PROGNOSIS AND MANAGEMENT OF GLOMERULAR DISEASES

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Renal biopsies have proven of greatest theoretical value in the understanding of glomerular nephropathies. However, in light of the poor prognosis of many glomerular disorders, the lack of effective therapy in most cases and the inconvenience of the procedure, the practical value of obtaining renal biopsies may be questioned.

Before discussing the problem of the value of renal biopsy we would like to emphasize the conditions that must be fulfilled in order to provide maximal information from examination of a renal biopsy specimen.

1. No definite conclusion can be expected if the specimens contain less than ten glomeruli.
2. Only pathologists who are knowledgeable in the problems of clinical pediatric nephrology should be consulted.
3. Specimens must be processed with special attention to all technical aspects to ensure proper interpretation.
4. Each specimen should be examined by light, electron and fluorescent microscopic techniques. These three techniques complement each other by providing specific information unique to each: all three should be utilized whenever possible.

Analysis of the information provided by the routine use of renal biopsy during the past 20 years reveals that this procedure has two main applications. Examination of renal tissue is useful for the diagnosis and indispensable for the establishment of the prognosis of the various types of morphologic abnormalities responsible for the clinical presentation of the patients affected with a glomerular disorder.