Reversible Renal Insufficiency

DIAGNOSIS AND TREATMENT

Donald H. Atlas, M.D., Ph.D., F.A.C.P.
Associate Professor of Medicine,
Northwestern University School of Medicine;
Attending Physician, Cook County and
Mount Sinai Hospitals of Chicago.

Peter Gaberman, M.D.
Late Associate Professor of Medicine,
The Chicago Medical School;
Attending Physician, Cook County and
Mount Sinai Hospitals of Chicago.

BAILLIÈRE, TINDALL & COX, LTD. · London · 1958

Reversible Renal Insufficiency

Preface

For the past ten years we have been concerned and occupied with the problem of reversible renal insufficiency on the wards of the Cook County, Mount Sinai, and West Side Veterans' Administration Hospitals of Chicago. We studied several facets of the problem experimentally, and the results of our investigations have been published.

Although reversible renal insufficiency has been known for the past three decades as "extrarenal azotemia," it is only during the past fifteen years that a huge body of clinical and experimental literature dealing with the subject has appeared. During this period we have labored to keep abreast and digest the voluminous literature and its many conflicting and overlapping conclusions. The flood of published material is ever rising, and, like the Sorcerer's Apprentice, we are about to be submerged. We believe, therefore, that a survey of the entire field in the light of our own experience is a timely and worthwhile endeavor. As much material as possible is reviewed, including the several excellent monographs and volumes dealing with individual aspects of reversible renal insufficiency.

Our title has been chosen to emphasize the potential reversibility of both acute and chronic renal insufficiency associated with many diverse conditions. Although the term "acute renal failure" is widely used, we prefer the term acute (or chronic) renal insufficiency because "failure" implies bankruptcy of function, whereas "insufficiency" connotes, in truth, a more hopeful prognosis.

Our major objective is to enable the clinician to differentiate acute and chronic conditions associated with reversible renal insufficiency from primary renal disorders which progress inexorably to fatal uremia. Secondly, we make a decided effort to change the

all too hopeless attitude toward the patient with acute and chronic renal disease, and emphasize that with careful thought and patience, proper treatment often results in reversibility and prolongation of life.

To achieve our objective, we considered two divergent plans; first, to organize the material in a comprehensive, encyclopedic form which would be of value to nephrologists, physiologists, and internists; and second, to write a concise and simple monograph which would be of value to medical students, general practitioners, and specialists in surgical fields wherein this problem is most frequently encountered. As is often the case, we resolved our conflict by compromise, and we have included material of interest to all groups.

We wish to thank the staff members of the Cook County, Mount Sinai, and the West Side Veterans' Hospitals for their cooperation in granting us permission to study their cases, especially the following physicians: Drs. Arnold Black, Irving Dvore, Louis Feldman, Joseph Gault, Harry Isaacs, Herbert Lakin, Aaron Neiman, Irving Neims, Hans Popper, Henry Rappaport, Sidney Rosenberg, and Hyman Zimmerman.

We also wish to thank Dr. Harry F. Weisberg for his valuable suggestions, Mrs. Evelyn Palmer and Mr. Thomas Scanlan for photographs, and we are grateful to The Chicago Medical School for furnishing office facilities and secretarial help.

Introduction

That the function of the kidney may be vitally affected in a variety of disease states which are not primarily renal in origin has long been known. Kidney lesions were described as associated with burns, hemoglobinuria, shock, and acute infections as far back as 1823.[70] Such terms as acute Bright's disease, acute parenchymatous nephritis, and acute tubular nephritis were histologically descriptive terms applied to these lesions. When the modern classification of kidney disease by Volhard and Fahr[388] omitted these entities, the entire field was generally neglected.

In a comprehensive article in 1938, Jeghers and Bakst[167] categorized the knowledge to date. Under the term, "extrarenal azotemia," they described the basic mechanisms involved, and emphasized the comparatively minor nature of the histologic changes frequently observed. There seems then to have been a hiatus in investigative work in this area until curiosity was again stimulated by an appearance in the literature of a description of the "crush syndrome" by Bywaters[52] in England in 1941.

Following this, because of its wartime importance, the relation of shock to renal disturbance assumed general interest. Luecké,[213] in 1946, studied particularly the renal pathology of shock and introduced the term, "lower nephron syndrome."

Despite overwhelming evidence to the contrary, with histologic studies demonstrating that pathologic alterations range from complete absence to extensive damage involving the glomeruli, interstitial tissues, and all portions of the nephron structure, the appealing designation of Luecké,[213] "lower nephron nephrosis," is tenaciously entrenched as a "catch-all" loosely applied to all forms of acute potentially reversible azotemic, anuric, and oliguric states.

A voluminous literature has accumulated under various titles;

i.e., extrarenal azotemia, prerenal azotemia, traumatic kidney, shock kidney, crush syndrome, hemoglobinuric nephrosis, reversible uremia, acute renal insufficiency, toxic nephrosis, lower nephron syndrome, traumatic uremia, acute tubular necrosis, and necrotizing nephrosis. This list is by no means complete, but the multiplicity is indicative of the need for nosologic reorganization.

It is unfortunate that each author in this field, in a well-meaning attempt to clarify pathogenesis, chose to coin new terminology; i.e., "burn nephritis" (Marchand,[225] 1908); "crush syndrome" (Dunn,[89] Bywaters,[52] 1941); "renal anoxia" (Maegraith,[217] 1945; the authors,[121] 1951); "hemoglobinuric nephrosis" (Mallory,[220] 1947); "the ischemuric and nephrotoxic kidney" (Oliver,[275] 1951); and "acute renal failure" (Swan and Merrill,[370] 1953; Grollman,[138] 1954; and Strauss and Raisz,[368] 1956).

Previously we preferred to use the term, "renal anoxia," suggested by Maegraith[217] since anoxia seems to be the common denominator in these conditions. However, we have since adopted the all-inclusive term, acute renal insufficiency.

In 1947, Trueta and his group[381] added to the understanding of the pathologic physiology involved by demonstrating the importance of neurogenic factors in animals subjected to shock.

Van Slyke[384] and others[194] enhanced our knowledge of renal physiology by renal clearance studies following shock in dogs and human subjects.

In 1951, Oliver's[275] microdissection of nephrons contributed enormously to the understanding of the morphology of these conditions, and most recently, Swan and Merrill[370] published extensive studies on the clinical course.

The importance of acute reversible renal insufficiency is evident in its ubiquity, for it has been observed by physicians in every phase of medicine and its specialties. Indeed, there is no phase or specialty of medicine in which this syndrome may not be encountered, wherefore a knowledge of this subject is necessary for every practicing physician.

In military medicine, post-traumatic acute renal insufficiency

has been a major problem. In World War II, 40 per cent of one group of severely wounded patients developed acute post-traumatic renal insufficiency with a fatality rate of 90 per cent among the severely oliguric.[161]

With such a diversity of conditions, a common pathogenesis is probably non-existent. More than one mechanism is commonly involved. Certain mechanisms, such as renal ischemia, however, occur so frequently that they may be considered fundamental. A thorough understanding of the pathogenesis and an awareness of the various disease states in which acute renal insufficiency can occur will lead to earlier diagnosis and more effective treatment. When detected early, this condition may be reversible, whereas later, the mortality rate is high.

While this work deals primarily with potentially reversible acute renal insufficiency, we believe that a more complete purpose will be served by including a survey of potentially reversible chronic renal insufficiency. The common denominator in many of these conditions is a disturbance of calcium metabolism resulting in nephrocalcinosis. Although most patients afflicted with chronic renal insufficiency slowly deteriorate and ultimately expire, occasionally chronic renal disease is caused by a condition which can be arrested or improved if not completely reversed. It is not our intention to review the diagnosis and treatment of those inexorably fatal cases although with proper management life can be prolonged for months or even years as illustrated by Merrill[370] in his recent volume. Rather, it is our purpose here to review those conditions associated with chronic renal insufficiency which are amenable to arrest, amelioration, or cure.

TABLE OF CONTENTS

Part I—Reversible Acute Renal Insufficiency

Part II—Reversible Chronic Renal Insufficiency

Part I

Reversible Acute Renal Insufficiency

I

Pathology of Acute Renal Insufficiency

Historic Background

Histologic findings in acute renal insufficiency have been controversial, both with respect to microscopic details and the portions of the nephrons principally involved. In 1946, Luecke[213] suggested that the pathologic changes in all cases are localized in the distal segment of the nephron, and coined the term "lower nephron nephrosis." Such precise localization has seemed to us[121] and others[52, 53, 73, 115, 131, 152, 217, 231] incompatible with the known physiologic, histologic, and experimental facts.

Histologic changes within the lower segment of the nephron, as described by Luecké,[213] consist of focal degeneration or necrosis of the tubular epithelium, heme casts, secondary inflammatory reactions of the adjacent stroma, and thrombosis of the thin-walled veins. Luecké[213] described this picture not only in conditions associated with shock but also those associated with sulfonamide intoxication, mushroom poisoning, acidosis, alkalosis, and dehydration. This concept, of damage localized specifically at the distal segment, directed Luecké[213] to the term "lower nephron nephrosis" which immediately became a medical cliché.

Prior to Luecké's concept,[213] pathologic alterations of the kidney in shock or burn cases were described as involving all areas of the kidney grossly, and the entire nephron histologically. Some reports designated the proximal convolution[231] as the portion of the nephron most damaged; but alterations were also observed in the distal convolution,[220] the glomerulus,[115] the interstitial tissue, and the blood vessels.

Early Pathologic Descriptions

Moon,[253, 254, 255] in a description of renal insufficiency associated with shock, confirmed the histologic findings of previous investigators[18, 406] in his statement:

The microscopic picture presents varying degrees of changes within a regular pattern. Usually, hyperemia of the glomerular tufts and of the intertubular vessels is conspicuous. Sometimes, capillary hemorrhages are present. Frequently, amorphous material is seen in the capsular spaces. The epithelium of the convoluted tubules shows acute degeneration ranging to necrosis. When death occurs after several days, the cells are low or cuboidal in shape and the lumens are wide. The cytoplasm is granular; more advanced degeneration is indicated by vacuolization of the cytoplasm or by disintegration of the cells. Nuclear changes, especially karyolysis and hyperchromatism, are conspicuous. Usually, these changes are more pronounced in the upper segment, sometimes in the lower, but in general all portions of the convoluted tubules are affected. Plugs of debris often form in the lumens of the lower segments because such debris, originating in the upper portion of the nephron, collects in the narrow lumen of the lower portion. Hyaline droplets may form in the cytoplasm when degeneration is advanced; the lumens may contain masses of this deep red material when the cells containing it have disintegrated. Hyaline, granular, and sometimes pigmented casts, debris, erythrocytes, nuclei, and masses of desquamated epithelial cells occur in the collecting tubules. Edema is a varying feature, more pronounced in the medullary than in the cortical zones.

In 164 experimentally burned dogs, Christophe[59] described manifestations of an "acute glomerular nephritis" characterized by oliguria, albuminuria, casts, and a rise in non-protein nitrogen. He described changes identical to those of acute glomerular nephritis, consisting of extensive glomerular congestion and tubular degeneration.

Sevitt[337] studied renal tissues obtained from 86 fatally burned patients of all ages, and concluded that fifty to sixty per cent of such patients have some form of tubular necrosis. He reported that necrosis of the proximal convoluted tubules is more common in elderly persons, while distal tubular necrosis is more frequent in children and young adults.

Martineau and Hartman,[231] in a description of renal damage associated with extensive burns, reported changes in the tubules (particularly in the proximal convoluted tubules, less frequently in the distal convoluted tubules), the blood vessels, the glomeruli, and the interstitial tissue.

Bell and Knutson,[26] in a study of 84 patients who were preterminal and had azotemia (urea nitrogen 50 or more) from a variety of causes, found histologic changes in the kidney in only 20. In these 20, mild to severe hydropic degeneration of the *proximal* convoluted tubules was observed. There was no correlation between the histologic findings and the level of the blood urea nitrogen, or the severity of the oliguria.

Acute Renal Insufficiency without Apparent Histologic Changes

Acute renal insufficiency may occur without gross or histologic evidence of kidney damage as in the cases of "low salt syndrome" reported by Schroeder[333] or in the preterminal cases of Bell and Knutson.[26]

Failure of tubular function often develops before pathologic changes become apparent. Mallory[220] found no visible changes until eighteen hours after the onset of shock and oliguria in wounded soldiers, and concluded that at this stage, "The initial renal insufficiency is, therefore, functional rather than anatomical in basis." There appears to be no correlation between the degree of kidney dysfunction and the histologic picture. However, in renal insufficiency resulting from hemorrhage, shock, or nephrotoxic damage to the tubules, a more constant morphological pattern is discernible.

Microdissection of Individual Nephrons

A major contribution toward an understanding of the pathology of acute renal insufficiency was made by Oliver and his group[275, 276] by the use of microdissection technique. They demonstrated two general types of morphologic change confined to the tubules which could be correlated with two main etiologic factors, shock and nephrotoxins.

The "Ischemuric Kidney"

In the first group, kidney damage is due primarily to shock (ischemuric episode), and the insult is considered predominantly circulatory. Here the histologic picture is characterized by "disruptive tubular damage" or "tubulorrhexis." These lesions occur at *random areas* of the nephron and in *random nephrons*. In Oliver's[275] dissections:

> As one follows the course of the intact tubules, quite suddenly, a place is found where the basement membrane is broken, frayed, or disintegrated, and the epithelial lining disrupted and necrotic. The result is a solution of continuity which may include only a part of the wall of the tubule or which completely interrupts its course so that the fragmented remnants lie between a still intact and well preserved proximal portion and its distal prolongation. The lumen thus lies open to the intertubular, interstitial tissue and its capillaries and veins.

Oliver[275, 276] stated that the histologic picture will vary in accordance with the extent of damage, the presence or absence of casts in the lumen, and the possible reaction of the interstitial tissues in the vicinity of the rupture. Evidence of reparative processes may be visible even in the most severely damaged segments of the nephrons. Thus, disruption of the basement membrane of the tubule is the dominant and characteristic pathologic development in nephrons damaged as a result of shock (fig. 1).

The "Nephrotoxic Kidney"

In the second group of cases described by Oliver,[275, 276] insult to the kidney results from the presence of nephrotoxic substances, which are (in his cases): mercuric chloride, potassium chlorate, diethylene glycol, carbon tetrachloride, sulfonamides, and mushroom poisoning (fig. 2).

With this type of renal injury, necrosis of the tubular epithelium is found evenly distributed throughout all the nephrons with predominance at the proximal convolutions. A characteristic feature is the intact basement membrane despite severe damage to the renal tubular epithelium. In addition, the tubulorrhexia of the "shock kidney" is scattered at random throughout the nephrons.

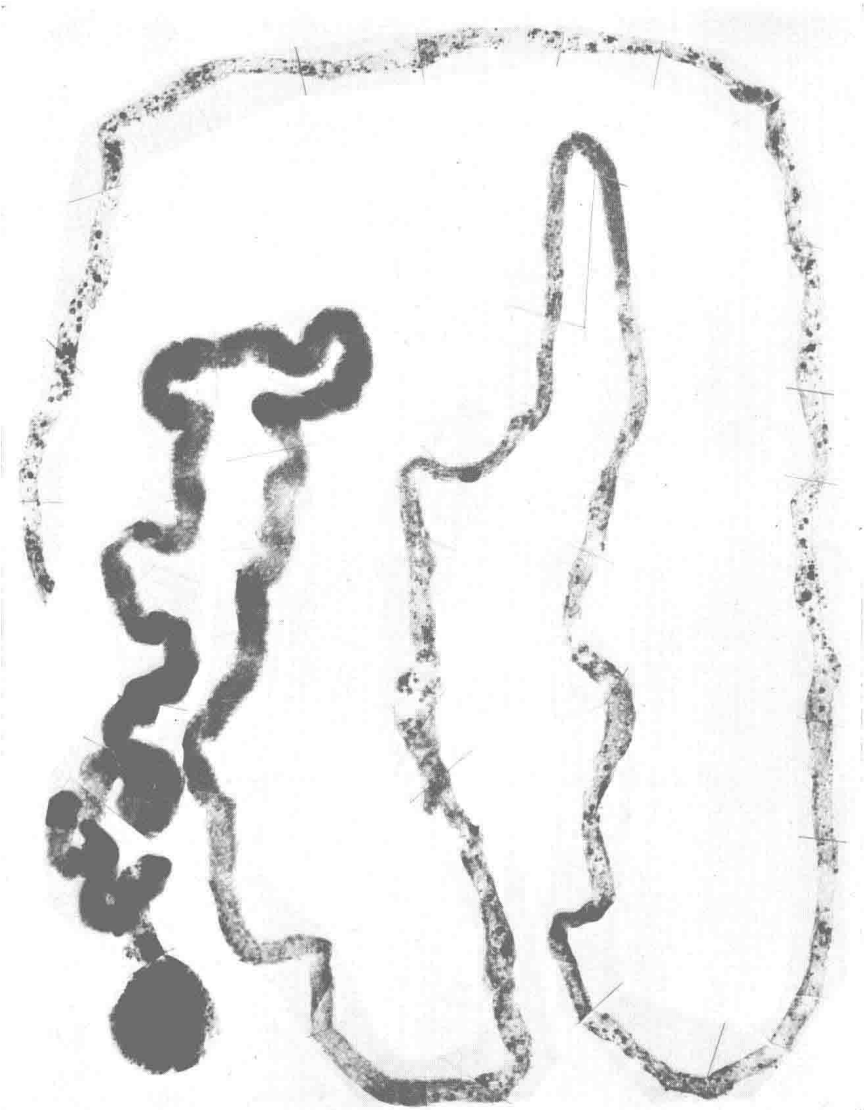

Figure 1. Complete proximal convolution from acute tubular necrosis following fatal burns. Death on ninth day. In its first loop (right), the tubule is fairly well preserved; from there on extensive tubulorrhexic damage. (OLIVER, J.: Correlations of structure and function and mechanism of recovery in acute tubular necrosis. Am. J. Med., **15:** 535–557, 1953.)