Acute Renal Failure

PATHOPHYSIOLOGY, PREVENTION AND TREATMENT

EDITED BY
VITTORIO ANDREUCCI

MARTINUS NIJHOFF PUBLISHING

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Pathophysiology, Prevention, and Treatment

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Vittorio E. Andreucci

Martinus Nijhoff Publishing
a member of the Kluwer Academic Publishers Group

BOSTON THE HAGUE DORDRECHT LANCASTER

Distributors:

for North America

Kluwer Academic Publishers
190 Old Derby Street
Hingham, MA 02043

for all other countries

Kluwer Academic Publishers Group
Distribution Centre
P.O. Box 322
3300 AH Dordrecht
The Netherlands

Library of Congress Cataloging in Publication Data
Main entry under title:

Acute renal failure.

1. Renal insufficiency, Acute. I. Andreucci, Vittorio E. [DNLM: 1. Kidney failure, Acute. WJ 342 A1896]
RC918.R4A347 1984 616.6'14 83-23837
ISBN 0-89838-627-6

ACUTE RENAL FAILURE

To my dear wife Gabriella, *and to my beautiful children* Michele *and* Maria Vittoria, *who were patient enough to allow my editing work even during weekends and holidays.*

CONTRIBUTING AUTHORS

Vittorio E. Andreucci
Professor of Nephrology and Chairman
Department of Nephrology
Second Faculty of Medicine
University of Naples
80131 Naples
ITALY

Jean-Jacques Béraud
Praticien du Cadre Hospitalier
Division of Metabolic Diseases and Endocrinology
Montpellier University Hospital
34059 Montpellier Cedex
FRANCE

Gérard Bochereau
Service de Néphrologie et Réanimation Polyvalente
Centre Hospitalier
56 Boulevard de la Boissière
93105 Montreuil
FRANCE

J. Steward Cameron
Clinical Science Laboratories
Guy's Hospital Medical School
17th Floor Guy's Tower
London SE1 9RT
UNITED KINGDOM

Alfredo Capuano
Department of Nephrology
Second Faculty of Medicine
University of Naples
80131 Naples
ITALY

Paul Chauveau
Service de Néphrologie et Reanimation Polyvalente
Centre Hospitalier
56 Boulevard de la Boissière
93105 Montreuil
FRANCE

Bruno Cianciaruso
Department of Nephrology
Second Faculty of Medicine
University of Naples
80131 Naples
ITALY

Luigi Cirillo
Department of Radiology
Second Faculty of Medicine
University of Naples
80131 Naples
ITALY

Antonio Dal Canton
Department of Nephrology
Second Faculty of Medicine
University of Naples
80131 Naples
ITALY

Stefano Federico
Department of Nephrology
Second Faculty of Medicine
University of Naples
80131 Naples
ITALY

Carlos A. Gianantonio
Head, Department of Pediatrics
Hospital Italiano
Gascon 450
(1181) Buenos Aires
ARGENTINA

Joel A. Gordon
Assistant Professor of Medicine
Renal and Electrolyte Division
The Milton S. Hershey Medical Center
The Pennsylvania State University
P.O. Box 850
Hershey, Pennsylvania 17033
USA

George B. Haycock
Evelina Children's Department
Guy's Hospital
St. Thomas Street
London SE1 9RT
UNITED KINGDOM

Vittorio Iaccarino
Department of Radiology
Second Faculty of Medicine
University of Naples
80131 Naples
ITALY

Alain Kanfer
Service de Néphrologie
Hopital Bichat
Paris
FRANCE

Arthur Kennedy
Muirhead Professor of Medicine
University Department of Medicine
Royal Infirmary, Phase I
10, Alexandra Parade
Glasgow G31 2ER
UNITED KINGDOM

Dieter Kleinknecht
Service de Néphrologie et Réanimation Polyvalente
Centre Hospitalier
56 Boulevard de la Boissiére
93105 Montreuil
FRANCE

Franciszek Kokot
Department of Nephrology
Silesian School of Medicine
ul. Francuska 20
40-027 Katowice
POLAND

Joel D. Kopple
Professor of Medicine and Public Health Chief
Division of Nephrology and Hypertension
Harbor-UCLA Medical Center
1000 Carson Street
Torrance, California 90509
USA

Olivier Kourilsky
Centre Hospitalier Louise Michel
Quartier du Canal
Courcouronnes
91014 Évry Cedex
FRANCE

Bruno Memoli
Department of Nephrology
Second Faculty of Medicine
University of Naples
80131 Naples
ITALY

Charles M. Mion
Professor of Nephrology
Head, Division of Nephrology
Montpellier Medical School
University Hospital Saint-Charles
34059 Montpellier Cedex
FRANCE

Liliane Morel-Maroger
Hôpital Tenon and INSERM U64
4, rue de la Chine
75970 Paris Cedex 20
FRANCE

Steen Olsen
Professor of Pathology
University Institute of Pathology
DK-8000 Aarhus C
DENMARK

Solomon Papper
Distinguished Professor and Head
Department of Medicine
University of Oklahoma Health Sciences Center and
the Veterans Administration Medical Center
Oklahoma City, Oklahoma 73190
USA

Victor Parsons
Director, Renal Unit
King's College Hospital
Dulwich Hospital
East Dulwich Grove
London SE22 8PT
UNITED KINGDOM

Gabriel Richet
Hôpital Tenon and INSERM U64
4, rue de la Chine
75970 Paris Cedex 20
FRANCE

Brian H.B. Robinson
Consultant Physician and Director
Department of Renal Medicine
East Birmingham Hospital
Bordesley Green East
Birmingham B9 5ST
UNITED KINGDOM

Robert W. Schrier
Professor and Chairman
Department of Medicine, B-178
University of Colorado Health Sciences Center
Denver, Colorado 80262
USA

Visith Sitprija
Professor of Medicine and Associate Dean
Department of Medicine
Chulalongkorn Hospital Medical School
Bangkok
THAILAND

Jean-Daniel Sraer
Service de Néphrologie
Hôpital Tenon
4, rue de la Chine
75970 Paris Cedex 20
FRANCE

Mario Usberti
Department of Nephrology
Second Faculty of Medicine
University of Naples
80131 Naples
ITALY

PREFACE

Acute renal failure is undoubtedly one of the most interesting and frequent syndromes observed by clinicians. A great number of factors may acutely impair renal function, but the pathogenetic mechanism by which this occurs is frequently unknown. Even the pathophysiology of ischaemic/toxic forms of acute renal failure remains controversial despite the huge number of experimental and clinical studies.

Medical management of patients with acute renal failure has greatly improved in recent years, particularly with the use of different types of dialytic treatment. However mortality remains high. Further studies are necessary for improving our knowledge of the syndrome, for providing a better management of patients with acute impairment of renal function, for suggesting adequate prevention of renal shutdown, particularly with the increasing use of potentially nephrotoxic drugs.

It appears therefore evident why clinicians involved in the treatment of acute renal failure should be frequently updated on this important topic. For this reason I have accepted with enthusiasm to edit a book on acute renal failure. The aim was to summarize in one volume the recent advances on pathophysiology of acute renal failure, the clinical aspects of the various forms (even those which have been disregarded in other surveys), the diagnostic tests available today in our clinical practice, the general and specific therapeutic measures and (very important, indeed), some useful suggestions for prevention.

The contributors have provided clear, complete and up-to-date chapters. I am deeply grateful to them all.

I like to express my sincere thanks to Dr. A.J. Wing (St. Thomas' Hospital, London, U.K.), for his great help in editing the language in the chapters of non English-speaking authors (my chapters included). This arduous, very important task had to be performed, in my opinion, by an English nephrologist. Dr. Wing was so kind as to do it very quickly.

Special thanks to Martinus Nijhoff Publishing for their patience and for the excellent and rapid publication of this volume.

Napoli, Vittorio E. Andreucci

LIST OF ABBREVIATIONS USED IN THE BOOK

ACN: acute (bilateral) cortical necrosis
ACTH: adrenocorticotropin hormone
ADH: antidiuretic hormone; vasopressin
ADP: adenosine diphosphate
AI and AII: angiotensin I and angiotensin II
AIN: acute interstitial nephritis
ALG: antilymphocyte globulin
AMP: adenosine monophosphate
ARF: acute renal failure
ATN: acute tubular necrosis
ATP: adenosine triphosphate

BAL: mercaprol
β_2M: beta 2 microglobulin
BUN: blood urea nitrogen
BUO: bilateral ureteral obstruction

cAMP: cyclic 3′,5′-adenosine monophosphate
CAPD: continuous ambulatory peritoneal dialysis
CAVH: continuous arterio-venous hemofiltration
CEPD: continuous equilibration peritoneal dialysis
C_{H_2O}: positive free-water clearance
CMV: cytomegalovirus
CPK: creatine phosphokinase
CRF: chronic renal failure
CT: calcitonin
CT: computerized tomography
C_{UA}/C_{Cr}: uric acid clearance to creatinine clearance ratio
CVS: cardiovascular system
CyA: cyclosporin A

DDP: cis-diammine dichloroplatinum
DIC: disseminated intravascular coagulation
DIP: drip infusion pyelography
DNA: desoxyribonucleic acid
DPN: diphosphopyridine nucleotide
DSA: digital subtraction angiography

ECV: extracellular fluid volume
EFP: effective glomerular filtration pressure

FDP: fibrin/fibrinogen degradation products
FE_{Na}: fractional excretion of sodium
FSH: follicle-stimulating hormone
FT_4I: free T_4 index

GBM: glomerular basement membrane
GCP: glomerular capillary hydrostatic pressure
GFR: glomerular filtration rate
GOT: glutamic oxaloacetic transaminase

HCG: human chorionic gonadotropin
HD: haemodialysis
HGH: growth hormone
HRS: hepatorenal syndrome
HUS: Haemolytic uraemic syndrome

IC: intravascular coagulation
IPD: intermittent (periodic) peritoneal dialysis
IRI: immunoreactive insulin
ITP: intratubular hydrostatic pressure
IVP: intravenous pyelography

JGA: juxtaglomerular apparatus

K_f: glomerular capillary ultrafiltration coefficient

LDH: lactic dehydrogenase
LH: luteinizing hormone
LH-RH: luliberin
LtH: lactogenic hormone, prolactin
LVEDP: left ventricular end diastolic pressure
LVFP: left ventricular filling pressure

NE: norepinephrine
NSAID: nonsteroidal anti-inflammatory drugs

P_{cr}: plasma concentration of creatinine
PD: peritoneal dialysis
PG: prostaglandin
P_G: glomerular capillary hydrostatic pressure
PGI_2: prostacyclin
P_{Na}: plasma sodium concentration
PP: pancreatin polypeptide
PRA: Plasma renin activity
PTH: parathyroid hormone
PVS: peritoneal jugular venous shunt

RAS: renin-angiotensin system
RBC: red blood cells
RBF: renal blood flow
RCN: renal cortical necrosis
RDT: regular dialysis treatment
RES: reticulo-endothelial system
RFI: renal failure index
RNA: ribonucleic acid

RPF: renal plasma flow
rT_3: reverse T_3

SA: body surface area
S_{Cr}: serum concentration of creatinine
SLE: systemic lupus erythematosus
SNGFR: glomerular filtration rate in single nephron
SUN: serum urea nitrogen
SW: stroke work

TBG: throxine-binding globulin
TBM: tubular basement membrane
TBW: total body water
TGF: tubuloglomerular feedback
$T^c_{H_2O}$: negative free-water clearance
TPN: total parenteral nitrogen
TRH: thyroliberin
TSH: thyrotropin
TxA_2: thromboxane A_2
T_3: triiodothyronine
T_3I: T_3 binding index
T_4: thyroxine

UA: uranyl acetate
UAN: uric acid nephropathy
U_{Cr}: urinary concentration of creatinine
UN: uranyl nitrate
UNA: urea nitrogen appearance
U_{Na}: urinary sodium concentration
U_{Osm}: urine osmolality
U/P_{Cr}: urine to plasma creatinine ratio
U/P_{Osm}: urine to plasma osmolality ratio
U/P UN: urine to plasma urea nitrogen ratio
UUO: unilateral ureteral obstruction

VDM: vasodilator material
VIP: vasoactive intestinal polypeptide

ACUTE RENAL FAILURE

CONTENTS

1. PATHOPHYSIOLOGY OF ISCHEMIC/ TOXIC ACUTE RENAL FAILURE

Vittorio E. Andreucci

1 Introduction

An adequate blood flow through the renal cortex and sufficient hemodynamic pressure in the glomerular capillaries are both critical prerequisites for normal glomerular filtration. If either a fall in systemic blood pressure or circulatory failure (due to acute myocardial infarction or other heart disease) or reduction of blood volume (due to volume depletion secondary to hemorrhage or fluid loss from burns, vomiting, diarrhea, excessive sweating, etc.) occurs, renal perfusion is reduced and glomerular filtration decreased. Homeostatic mechanisms of body fluid conservation are then activated with an increase in antidiuretic hormone and aldosterone secretion and enhancement of reabsorptive activity of renal tubular epithelium. Reduction in urine output results, while the fall in the urinary excretion of nitrogenous end products increases plasma concentrations of urea and creatinine. In this "functional" phase of acute renal failure (ARF) [1] or extrarenal failure or renal functional insufficiency [2] (the so-called "prerenal azotemia" or "prerenal ARF"), the kidney is not damaged and tubular integrity is preserved: tubules, in fact, retain sodium avidly and concentrate urine; thus, urine becomes hypertonic, with low sodium concentration and with a markedly reduced fractional excretion of sodium (FE_{Na}). If volume depletion or blood pressure or cardiac output is restored to normal values, renal function rapidly returns to normal. If the reduction in renal perfusion (due to hypotension, sustained circulatory failure, or hypovolemia) is maintained or even worsened, an "organic" damage in the kidney ensues (the so-called "acute tubular necrosis," ATN, or "intrinsic ARF") in which oligo-anuria is associated with a reduction in the reabsorptive ability of tubular epithelium, resulting in isoosmotic urine and increased fractional excretion of filtered sodium ($FE_{Na} > 1\%$). If the patient survives (with the help of dialysis) despite the loss of renal function, a recovery phase ensues with an increase in urine volume, which usually occurs within 10 to 15 days, but sometimes 30 days or even more after the onset of oligo-anuria [3].

Hence, on the basis of our clinical experience, ARF may be considered a three-phase disease: (a) the initial functional phase ("functional ARF," improperly called "prerenal azotemia"), which is readily reversible; (b) the following irreversible phase of organic damage ("organic ARF", improperly defined as ATN); and (c) a phase of recovery of renal function. Nephrotoxic drugs (such as aminoglycoside antibiotics) may cause immediate organic damage (ATN) through a direct toxic effect on renal tubular epithelium.

In contrast with agreement on the above clinical observations, there is still controversy on the pathophysiology of ARF. Many theories in recent years have been usually seen as mutually exclusive. Even the terminology has been a matter of debate. Scientists who believe that tubular mechanisms play a primary role in the pathogenesis of ARF define the ARF due to ischemic or toxic factors as "acute tubular necrosis" (ATN); those who believe that vascular mechanisms are predominant define ARF as

V.E. Andreucci (ed.). ACUTE RENAL FAILURE.

Martinus Nijhoff Publishing, Boston/The Hague/Dordrecht/Lancaster.

"vasomotor nephropathy" [4]. Actually, as we will describe later, vascular and tubular mechanisms are both involved in the pathogenesis of ARF.

Most of our knowledge of ARF derives from experimental studies in animals. Clinical studies of ARF are inadequate for understanding the fine mechanisms involved in the pathogenesis of the renal function shutdown. It is impossible, in fact, to follow in humans in a prospective trial the predisposing factors and the initiating stage of ARF, since usually physicians will face the problem when the failure is already established. Furthermore, many studies cannot be performed because they are unsuitable for human beings (e.g., micropuncture techniques, radioactive microsphere methods) or because for ethical reasons the patients cannot be exposed to unnecessary risks.

Thus, the experimental models of ARF appear to be very important because they reproduce the human forms and can be adequately studied.

Unfortunately, conflicting results have been obtained quite frequently not only from different models, but even from the same experimental model of ARF. Many reasons may account for this discrepancy in experimental data [5]:

a. Too many different nephrotoxins or ischemic methods have been employed, and the observation of similar renal abnormalities obtained by different means does not necessarily imply a similar pathogenetic mechanism.
b. The doses of nephrotoxin or the durations of the ischemic insult were frequently different so that resulting renal damage might differ.
c. The observation time intervals following the toxic or ischemic challenge were quite variable, while it is well known that factors responsible for the initiation stage of ARF are usually different from those responsible for the maintenance stage and for recovery.
d. The route of nephrotoxin administration was not always the same, the same toxin having been given intravenously, intramuscularly, or subcutaneously; this might make the time course of the renal insult very different.
e. Different techniques, which are not always comparable, have been used to measure total and regional renal blood flow (RBF).
f. Changes in renal hemodynamics may be either the cause or the consequence of the renal insult, or may even be unrelated to the fall in glomerular filtration rate (GFR).
g. Species difference may exist as far as the sensitivity to nephrotoxins is concerned.

2 *Heavy Metal-Induced ARF*

Three major experimental models of ARF have been induced in animals by the use of heavy metals.

2.1 URANYL NITRATE-INDUCED ARF

The administration of uranyl nitrate (UN) in experimental animals (usually rats and dogs) intravenously, intraperitoneally, or subcutaneously, in doses ranging from 5 to 25 mg/kg b.w., usually leads to a polyuric ARF. A non-oliguric ARF has been similarly induced in rabbits by i.v. injection of uranyl acetate (UA) [6].

The fall in GFR and the increase in urine output and salt excretion observed both after UN [7] and UA [6] clearly demonstrate a depression in tubular reabsorption caused by uranyl ions, suggesting a functional impairment of tubular epithelium soon after uranium salt administration. The increase in urine output and in salt excretion occurred in association with a reduction in PAH extraction and was observed much earlier than the occurrence of tubular necrosis [6].

The uranyl cation of the uranium salts is responsible for renal injury at the tubular epithelial cell level. It seems that uranyl ions complex with phosphoryl, carboxyl, and sulphydryl groups of surface cell membranes without penetrating the cells.

Early after UN administration, minimal epithelial lesions are observed in proximal tubules in the form of cell swelling, vacuolation and mitochondrial degeneration. Only after 48 hours the proximal tubules exhibit, almost uniformly, a cell necrosis in the "pars recta"

with shedding of epithelial cell cytoplasm into the tubular lumen [8, 9]. The convoluted portion of proximal tubules shows, at this stage, degenerative changes with swelling and granularity of the epithelial cytoplasm [9]. Many casts are seen in the proximal and distal tubules. In a similar fashion, when ARF was induced in rabbits by i.v. UA (mg/kg b.w.), minor lesions were observed in tubular cells even 24 hours following UA; only after three days were tubular necrosis and intratubular casts and debris seen by light and electron microscopy [6].

2.1.1 Renal Blood Flow (RBF) and Glomerular Filtration Rate (GFR) Experiments in rats [10] and in dogs [8, 11, 12] have demonstrated that early (i.e., already in the first hour and throughout the first six hours) after the administration of UN, parallel falls in RBF and in GFR occur. Subsequently, 48 hours after UN, further decrements both in RBF and in GFR have been observed in rats [10] but not in dogs [12].

When the distribution of renal blood flow was studied in UN-treated dogs by Xenon 133 washout or Strontium 85-labeled microsphere techniques, a preferential cortical ischemia appeared to be the main contributor to the fall in RBF [8, 9, 13].

Since the course of ARF in dogs was not modified by the intrarenal infusion of PGE_2 (a vasodilator prostaglandin) and the fall in GFR occurred despite normalization of RBF [14], renal vasoconstriction has not been regarded as the main factor in initiating the impairment of renal function in this model of ARF [15]. In the experiments with PGE_2 [14], however, a low dose of UN (5 mg/kg b.w.) was used, so that the RBF even in the control (non-PGE_2-injected) kidney was not significantly decreased, as observed with greater doses (10 mg/kg b.w.) [8, 11]; but GFR fell anyhow, and this fall may be accounted for by factors other than changes in renal hemodynamics.

When renal vasodilation was induced in dogs treated with greater doses of UN (10 mg/kg b.w.), by the association dopamine + furosemide, an attenuation of the fall in GFR was obtained [16].

2.1.2 The Glomerular Capillary Ultrafiltration Coefficient (K_f) The glomerular capillary ultrafiltration coefficient (K_f) is given by the product of glomerular permeability and the effective filtering surface area. Thus, a reduction in glomerular permeability and/or in the filtering area may decrease K_f. In rats with ARF secondary to UN administration (15 and 25 mg/kg b.w. i.v.), K_f is reduced within two hours of UN administration; and this reduction is proportional to the dose of administered UN [17].

A reduction in both diameter and density of endothelial fenestrae was observed, by scanning electron microscopy, within two hours of UN administration in rats [18]; this observation may well account for the decrease in K_f. A further progressive reduction in the endothelial fenestrae was detected with time (up to 17 hours after UN) and directly correlated with the progressive fall in GFR [18]. Loss of endothelial fenestrae associated with a decrease in K_f has also been observed in rats in vitro, in isolated glomeruli, 36 to 48 hours after UN administration [19].

Glomerular epithelial cells were normal two to six hours following UN (i.e., when ARF was already established). Changes of podocytes (swelling of foot processes; wide areas with primary, secondary, and foot processes no longer distinguishable) were initially observed 7 hours following UN and appeared more marked after 17 hours [18] and after 48 hours [9, 12]. It is possible that alteration in both endothelial and epithelial cells may lead to a greater reduction in the glomerular filtration area [18], thus contributing to the decrease in K_f in the maintenance stage of this model of ARF.

The demonstrated increase in intrarenal angiotensin II (AII) early (six hours) after UN administration [7, 20] may well account for the fall in K_f; possibly through the reduction in the endothelial fenestrae area. AII, in fact, is known to reduce K_f [21]. In favor of this hypothesis is the observation that salt-loaded rats (in which renal renin is suppressed) were protected against renal function impairment following UN administration; in these rats, the endothelial cell morphology was normal with a normal area of endothelial fenestrae. In salt-depleted rats (in which the renin-angiotensin sys-

tem is markedly activated), GFR was greatly reduced; in these rats, a severe reduction in the area of endothelial fenestrae was observed [18].

2.1.3 Role of Tubular Obstruction in the Pathogenesis of UN-Induced ARF Early (six hours) in the course of UN-induced ARF, intratubular hydrostatic pressure (ITP) was not increased [10] (as expected behind a tubular obstruction), and no intratubular casts (obstructing tubular lumina) have been observed in histopathologic specimens [8, 22]. These observations argue against an early tubular obstruction in this model.

Obstruction of proximal and distal tubules by eosinophilic casts occurred 24 hours after UN administration, when widespread damage of tubular epithelium was present, with cell necrosis, mainly in the "pars recta" of the proximal tubules; these observations suggest an important role of tubular obstruction in maintaining rather than initiating UN-induced ARF [15].

It should be noted that values of ITP significantly lower than control, 8 to 24 hours after 10 mg/kg b.w. of UN, and not different from control 24 to 33 hours after 15 mg/kg b.w. of UN have been observed in rats [23]. Similarly, near normal values of ITP in the maintenance stage of UN-induced ARF have been reported in dogs [9]. These observations, however, do not rule out the possibility of an important role of tubular obstruction in maintaining ARF, since the concomitant fall in GFR may well account for normalization of ITP despite obstruction [24].

2.1.4 Role of the Backleak of Filtrate in the Pathogenesis of UN-Induced ARF Microinjection studies in rats with UN-induced ARF have given conflicting results. Thus, the microinjection of radioactive inulin into proximal convoluted tubules of superficial nephrons two to six hours after subcutaneous injection of 10 mg/kg b.w. of UN was followed by a complete recovery of the inulin from the urine of the microinjected kidney, exactly as it occurred in control normal animals [25]. A substantial recovery of microinjected radioactive inulin and mannitol from the urine of the contralateral kidney has been reported, instead, at similar intervals but with 25 mg/kg b.w. of UN administered intravenously, suggesting an important leak of tubular fluid from the microinjected nephrons [17]. The site of the leak of inulin and tubular fluid was located beyond the superficial portion of the proximal tubules (pars recta?) since values of GFR measured in single nephrons (SNGFR) by micropuncture of early and late loops of proximal convoluted tubules were identical [17]. Since the tubular cell damage after UN administration has been shown to be proportionally increased with increasing doses [22], the described discrepancy in the microinjection studies is presumably related to the different severity of tubular damage [25]. Since ARF occurred with a relatively low dose of UN (10 mg/kg b.w.) and leak of inulin was not observed at this dosage, backleak of filtrate cannot be regarded as one of the predominant factors in promoting the ARF, as suggested by some authors [15]. Backleak may be important in the maintenance stage of ARF; thus 48 hours after UN administration (5 to 10 mg/kg b.w.) in dogs, only an average of 14% (against 97% observed in normal dogs) of microinjected inulin was recovered from the urine of the microinjected kidney [12].

2.1.5 Role of the Renin-Angiotensin System (RAS) in UN-Induced ARF Early (six hours) after UN administration in rats, significant increases in (a) plasma renin activity (PRA) [7, 20, 25, 26], (b) renin activity in the juxtaglomerular apparatus (JGA) of single superficial nephrons associated with a greater sodium chloride concentration in the distal tubule at the macula densa level [20, 25, 26], and (c) intrarenal AII [7, 20] have been demonstrated, reflecting activation of the RAS. When salt depletion secondary to the UN-induced natriuresis was prevented by oral sodium chloride replacement, PRA and intrarenal renin were not different from control values, and the animals were protected against ARF (i.e., creatinine clearance remained normal) despite a minor but still significant increase in intrarenal AII (attributed either to a direct effect of UN or to minor degrees of volume depletion) [7].