INTERNATIONAL YEARBOOK OF NEPHROLOGY 1989

INTERNATIONAL YEARBOOKS OF NEPHROLOGY

Editor

Vittorio E. Andreucci
University of Naples

Co-Editors

Leon G. Fine
UCLA School of Medicine

Michinobu Hatano
Nihon University

Carl M. Kjellstrand
Karolinska Hospital

INTERNATIONAL YEARBOOK OF NEPHROLOGY 1989

Editor
Vittorio E. Andreucci
University of Naples
Naples, Italy

Co-editors

Leon G. Fine
University of California, Los Angeles
School of Medicine
California, USA

Michinobu Hatano
Nihon University
Tokyo, Japan

Carl M. Kjellstrand
Karolinska Hospital
Stockholm, Sweden

Kluwer Academic Publishers
Boston/Dordrecht/London

Distributors for North America:
Kluwer Academic Publishers
101 Philip Drive
Assinippi Park
Norwell, Massachusetts 02061 USA

Distributors for the UK and Ireland:
Kluwer Academic Publishers
Falcon House, Queen Square
Lancaster LA1 1RN, UNITED KINGDOM

Distributors for all other countries:
Kluwer Academic Publishers Group
Distribution Centre
Post Office Box 322
3300 AH Dordrecht, THE NETHERLANDS

Library of Congress Cataloging-in-Publication Data

ISBN-13:978-1-4612-8934-0 e-ISBN-13:978-1-4613-1673-2
DOI:10.1007/978-1-4613-1673-2

CONTENTS

Contributing Authors vii
Preface xi

RENAL PHYSIOLOGY AND PATHOPHYSIOLOGY

1. Diagnostic and Prognostic Implications of Renal Hypertrophy
   Aaron Knecht and Leon G. Fine 3

GLOMERULONEPHRITIS

2. IgA Nephropathy: Current Views on Pathogenesis and Treatment
   Hideto Sakai 23

INFECTIONS

3. Single-Dose Antibiotic Therapy in Urinary Tract Infection
   William Brumfitt and J.M.T. Hamilton-Miller 49

RENAL STONE DISEASE

4. Prevention of Calcium Oxalate Renal Stones
   Charles Y.C. Pak 67

HYPERTENSION

5. Calcium Channel Blocking Drugs as Antihypertensive Agents
   Austin E. Doyle 89

6. Angiotensin Converting Enzyme Inhibitors as Antihypertensive Therapy
   A. Steiner, D. Edmonds, P. Greminger, and W. Vetter 115

THE KIDNEY IN PREGNANCY

7. Prevention of Preeclampsia
   Antonio Dal Canton, Giulio Romano, and Patrizia Veniero 131

PEDIATRIC NEPHROLOGY

8. Cyclosporin in the Therapy of Idiopathic Nephrotic Syndrome in Children
   Patrick Niaudet and Michel Broyer 155

DRUG NEPHROTOXICITY

9. Cyclosporine A Nephrotoxicity
Vittorio E. Andreucci and Giorgio Fuiano 171

ACUTE RENAL FAILURE

10. The Changing Epidemiology of Acute Renal Failure: Patterns in Economically Advanced and Developing Countries
Kirpal S. Chugh and Carl M. Kjellstrand 207

11. Acute Renal Failure and Continuous Renal Replacement Therapy
F. Cosentino and E. P. Paganini 227

CHRONIC RENAL FAILURE

12. Erythropoietin in the Treatment of the Anaemia of Chronic Renal Failure
Christopher G. Winearls 263

DIALYSIS

13. New Strategies for High Efficiency Hemodialysis
Prakash R. Keshaviah and Allan J. Collins 281

14. Has CPD Been as Effective as Hemodialysis?
Allen R. Nissenson 301

RENAL TRANSPLANTATION

15. Monoclonal Antibodies in the Treatment of Transplant Rejection
David J. Cohen 325

DIAGNOSTIC METHODS IN NEPHROLOGY

16. Magnetic Resonance Imaging of the Kidneys
Zoran L. Barbaric 347

INDEX 367

CONTRIBUTING AUTHORS

Vittorio E. Andreucci,
Department of Nephrology, Second Faculty of Medicine,
University of Naples, Nuovo Policlinico
Via S. Pansini,
80131 Naples, Italy

Zoran L. Barbaric,
Department of Radiological Sciences, UCLA School of Medicine,
Los Angeles, California 90024, USA

Michel Broyer,
Service de Nephrologie Pediatrique and INSERM U 192,
Hopital Necker-Enfants Malades, 149 Rue de Sevres,
75015 Paris, France

William Brumfitt,
Department of Medical Microbiology,
The Royal Free Hospital and School of Medicine,
London NW3 2QG, England

Kirpal S. Chugh,
Department of Nephrology,
Postgraduate Institute of Medical Education and Research,
Chandigarh, 160012 India

David J. Cohen,
Department of Medicine,
Columbia University College of Physicians and Surgeons,
New York, New York 10032, USA

Allan J. Collins,
Regional Kidney Disease Program, Hennepin County Medical Center,
Minneapolis, Minnesota 55415, USA

Frank A. Cosentino,
The Section of Dialysis and Extracorporeal Therapy,
Cleveland Clinic Foundation,
Cleveland, Ohio 44106, USA

Antonio Dal Canton,
Division of Nephrology, University of Reggio Calabria,
Faculty of Medicine at Catanzaro,
Via T. Campanella,
88100 Catanzaro, Italy

Austin E. Doyle,
Department of Physiology, University of Melbourne,
Parkville 3052, Australia

Dorothea Edmonds,
Department of Internal Medicine, University Hospital,
8091 Zurich, Switzerland

Leon G. Fine,
Division of Nephrology, Department of Medicine,
UCLA School of Medicine,
Los Angeles, California 90025, USA

Giorgio Fuiano,
Department of Nephrology, Second Faculty of Medicine,
University of Naples, Nuovo Policlinico,
Via S. Pansini,
80131 Naples, Italy

Peter Greminger,
Department of Internal Medicine, University Hospital,
8091 Zurich, Switzerland

Jeremy M.T. Hamilton-Miller,
Department of Medical Microbiology,
The Royal Free Hospital and School of Medicine,
London NW3 2QG, England

Prakash R. Keshaviah,
Regional Kidney Disease Program, Hennepin County Medical Center,
Minneapolis, Minnesota 55415, USA

Carl M. Kjellstrand,
Department of Medicine, Division of Nephrology,
Karolinska Hospital,
104 01 Stockholm, Sweden

Aaron Knecht,
Division of Nephrology, Department of Medicine,
UCLA School of Medicine,
Los Angeles, California 90025, USA

Patrick Niaudet,
Service de Nephrologie Pediatrique and INSERM U 192,
Hopital Necker-Enfants Malades, 149 Rue de Sevres,
75015 Paris, France

Allen R. Nissenson,
Division of Nephrology, Department of Medicine,
UCLA School of Medicine,
Los Angeles, California 90024, USA

Charles Y.C. Pak,
Center on Mineral Metabolism and Clinical Research,
Department of Internal Medicine,
Southwestern Medical School at Dallas,
Dallas, Texas 75235, USA

Emil P. Paganini,
The Section of Dialysis and Extracorporeal Therapy,
Cleveland Clinic Foundation,
Cleveland, Ohio 44106, USA

Giulio Romano,
Department of Nephrology, Second Faculty of Medicine,
University of Naples, Nuovo Policlinico
Via S. Pansini,
80131 Naples, Italy

Hideto Sakai,
Division of Nephrology and Metabolism,
Department of Internal Medicine,
School of Medicine, Tokai University,
Isehara City, Kanagawa-ken 259-11, Japan

Albert Steiner,
Department of Internal Medicine, University Hospital,
8091 Zurich, Switzerland

Patrizia Veniero,
Department of Nephrology, Second Faculty of Medicine,
University of Naples, Nuovo Policlinico
Via S. Pansini,
80131 Naples, Italy

Wilhelm Vetter,
Department of Internal Medicine, University Hospital,
8091 Zurich, Switzerland

Christopher G. Winearls
Renal Unit, Department of Medicine,
Royal Postgraduate Medical School, Hammersmith Hospital,
London W12 OHS, England

PREFACE

The aim of the INTERNATIONAL YEARBOOKS OF NEPHROLOGY is to publish every year a volume to keep nephrologists up to date on all the rapidly changing areas of nephrology. Each volume will be published by the end of each calendar year which corresponds with the annual meeting of the American Society of Nephrology.

Each issue of the INTERNATIONAL YEARBOOKS OF NEPHROLOGY will be divided into sections; each section will have different primary focus every year, depending upon what area is of greatest interest at the time. In other words, each annual volume will deal with what is truly current in nephrology.

All the authors appointed for the chapters of the INTERNATIONAL YEARBOOKS OF NEPHROLOGY are known experts in the field who will give an objective review of the topic up-dating the readers on the world-wide literature.

A crucial point for the success of the INTERNATIONAL YEARBOOKS OF NEPHROLOGY is the list of the references at the end of each chapter. We have asked all authors to provide a complete, accurate and up-to-date list of important references.

In order to guarantee the most up-to-date yearbook, very rapid production is mandatory. Rapid publication can be obtained only with camera-ready manuscripts for direct photo-offset reproduction. Thus we have agreed to use photo-offset printing for the series.

For the first issue of the series, the INTERNATIONAL YEARBOOK OF NEPHROLOGY 1989, the Editorial Board has focused attention on the latest and most important scientific and clinical advances in nephrology.

The editor and Co-editors are deeply grateful to all authors for their clear, complete and up-to-date reviews and for having fulfilled the deadline in forwarding their manuscripts. Special thanks are due to Kluwer Academic Publisher for the rapid publication of this volume.

Vittorio E. Andreucci
Leon G. Fine
Michinobu Hatano
Carl M. Kjellstrand

INTERNATIONAL YEARBOOK OF NEPHROLOGY 1989

RENAL PHYSIOLOGY AND PATHOPHYSIOLOGY

1

DIAGNOSTIC AND PROGNOSTIC IMPLICATIONS OF RENAL HYPERTROPHY

Aaron Knecht M.D. and Leon G. Fine M.D.

Division of Nephrology, Department of Medicine, UCLA School of Medicine, Los Angeles, CA 90025

INTRODUCTION

Knowledge of cell growth control has increased with great rapidity within the last decade due to the discovery and purification of specific growth factors, the identification of genes which are expressed in a cell-cycle-dependent fashion and an improved understanding of the roles of various oncogenes in control of growth in non-transformed cells. Only recently has the understanding of renal growth control started to advance apace with these discoveries, but the clinical approach to predicting adaptive growth responses or their manipulation is in its infancy. This review attempts to summarize current knowledge of mechanisms of renal hypertrophy and regeneration and to apply the emerging principles to human renal disease. The picture that emerges indicates that, whereas growth in the size of nephrons provides an obvious advantage in prolonging the function of the diseased kidney, in certain cases it may be the harbinger of progressive injury and its control may have important prognostic implications.

OVERVIEW OF BASIC MECHANISMS OF RENAL HYPERTROPHY

Causes of Hypertrophy

This topic has recently been summarized in detail (1). In essence, a vast body of research has been devoted to identifying pathophysiologic states which promote renal growth, to determining structure-function correlates in

the hypertrophied kidney, to elucidating initiating events in cell hypertrophy and to isolating one or more kidney-specific growth factors.

Despite a prolonged search for a kidney-specific growth factor or "renotropin" (2-7) no such factor has been identified or purified. Indeed, it is conceptually difficult to imagine that production of a growth factor at a site distant from the kidney is stimulated when renal mass is reduced. Thus, until such a factor is identified, it seems reasonable to focus on other elements which control kidney growth including vasoactive substances and intrarenal hormones which act in a paracrine or autocrine fashion but without necessarily being "kidney-specific".

TABLE I: CAUSES OF RENAL HYPERTROPHY

1.	With elevation of Glomerular Filtration Rate
(a).	"Adaptive"
	Ablation of renal mass or nephron destruction
	High protein diet/total parenteral nutrition
	Pregnancy
	Hormone administration (thyroid, ACTH, growth hormone, testosterone, vasopressin)
	Chronic volume expansion with mineralocorticoid and sodium chloride
(b).	Pathological
	Insulin-dependent diabetes mellitus
2.	Without elevation of glomerular filtration rate
	Potassium depletion
	Ammonium chloride loading (metabolic acidosis)
3.	With associated hyperplasia
	Renal ablation in neonatal period
	Extensive renal ablation in adults
	Potassium depletion

Table I lists the conditions which lead to renal hypertrophy. The seemingly-disparate set of initiating causes has led to confusion in attempts to find a common

pathogenesis. It should be emphasized that "hypertrophy" implies growth in the size of existing elements in the kidney with only minimal hyperplasia or cell proliferation. Hypertrophy is defined as an increase in protein/cell or protein/DNA. This term is not always applicable, however, since growth of the neonatal kidney occurs both by hypertrophy (8-11) and hyperplasia and in extensive renal ablation an increase in kidney DNA content has been shown to occur.

Common Pathogenetic Events

Glomerular Filtration. It has been proposed that, rather than considering the process of renal hypertrophy to be under the control of a specific renal growth factor, it is more feasible to suggest that initiation of growth is due to a set of early events which sensitizes the kidney to normally-occurring local growth factors (including epidermal growth factor, insulin-like growth factors, transforming growth factor β, etc) (1). Alternatively, initiation of cell enlargement may occur independently of growth factors by a unique process of growth. These initiating events could include changes in hemodynamic or neurogenic function (1). The singlemost important early event which correlates with an increase in kidney size is a rise in glomerular filtration rate (12,13). This occurs in response to protein loading (14), amino acid infusion (15), pregnancy (16), renal ablation and early insulin-dependent diabetes mellitus (17, 18) (Table I). Other than in diabetes, when the initiating stimulus is reversed, the GFR returns toward normal and kidney size diminishes. Thus an elevated GFR seems to be necessary for most forms of renal hypertrophy. A clinical correlate of this, is that in the absence of infiltrative disease or diabetes, (which is discussed below) a large kidney signifies an elevated GFR.

Perhaps the best test of whether an elevated GFR is required for nephron hypertrophy is provided by the

heterogeneously damaged nephron population of the kidney with chronic glomerulonephritis (19). In this disease there are varying levels of glomerular damage and a wide dispersion of single nephron filtration rates. Those glomeruli that escape injury undergo enlargement which is reflected by an increase in single nephron GFR (1). The elegant microdissection studies by Oliver of the human kidney with chronic nephritis showed that large, hyperfiltering glomeruli are attached to large tubules, whereas normal-sized glomeruli are attached to normal-sized tubules and small glomeruli to small tubules, thus reinforcing the concept that tubular hypertrophy accompanies glomerular hypertrophy (20,21).

Since a rise in GFR is one of the earliest events to occur following renal ablation (within minutes to hours) (12,13), it is not unreasonable to suppose that this may be the earliest signalling event in initiating renal growth. What remains to be explained is how this signal is transduced into a growth response at the level of the tubular epithelial cell.

Two experimental models (not studied in man) provide examples of hypertrophy which are unassociated with a rise in GFR (Table I). These are chronic ammonium chloride loading and chronic potassium depletion (22). In both models an increase in Na^+/H^+ and increased ammoniagenesis have been documented (see below) suggesting that a common mechanism may exist for initiating cell enlargement in these models which circumvents the need for a rise in GFR.

Conversely there is also a model of increased GFR in which hypertrophy does not occur, i.e. unilateral diversion of urine into the peritoneal cavity (23,24). While this model has been used to argue against a strong link between growth and GFR, the possibility exists that inhibitory growth factors accumulate to high levels to inhibit a normal growth response in this model. Clearly the isolated exceptions should not obscure the large body

of literature which supports the link between GFR and hypertrophy.

$\underline{Na^+/H^+ \text{ Exchange}}$. If a hemodynanic or neurogenic event sensitizes tubular cells to local growth factors one way in which this could occur is via alteration of a membrane transport event. Alkalinization of the cell interior has been shown to be an early event in the proliferative response of different cell types to growth factors (25). This is mediated by an increase in Na^+/H^+ exchange activity which increases Na^+ entry into, and H^+ exit from the cell and can be documented only if alternative mechanisms for maintaining cell pH are paralyzed. A similar increase in Na^+/H^+ exchange has been demonstrated in cells which are induced to undergo hypertrophy without hyperplasia (26,27). In models of renal ablation, an early and sustained increase in the maximum rate of Na^+/H^+ exchange has been demonstrated in brush border membrane vesicles (28-30). Since this transport system is localized to the luminal membrane and is the principle mode of transport of Na from the lumen into the cell, the increase in proximal tubular fluid transport which occurs in experimental models with increased GFR is probably mediated largely by this transport mode.

The mechanism whereby an increase in transport of Na^+ into the cell, or transport of H^+ out of the cell could mediate a growth response is still not known but an elevation of intracellular pH seems to be a likely signal. It should be emphasized however, that a causal relationship between an increase Na^+/H^+ exchange and hypertrophy has never been established. Indeed mutant cells which lack the exchanger (31) will grow in a bicarbonate-containing medium, thus indicating that other regulatory systems (especially Cl^-/HCO_3^- exchange) are effective in maintaining pH.

An intriguing fact is that in the few models of hypertrophy which are not associated with an increase in GFR (see below), Na^+/H^+ exchange is increased in the

proximal tubule.

Increased Ammoniagenesis. An increase in ammonia production per nephron characterizes renal hypertrophy following a number of different stimuli. Ammonium chloride loading, per se, causes hypertrophy in vivo (32) and this has been ascribed to intracellular acidosis which could activate Na^+/H^+ exchange. However, Golchini, Norman and Kurtz have recently shown that ammonium chloride at low concentrations (<5 mM) induces pure hypertrophy and an increase in Na^+/H^+ exchange in a proximal tubular cell line in vitro with only minimal changes in internal pH (33). Thus the possibility exists that increased cellular ammonia availability and/or increase ammoniagenesis may be an initiating signal for hypertrophy.

Functional Response to Renal Ablation in Humans

Removal of renal mass for surgical diseases (i.e. tumors, unilateral pyelonephritis, etc), donation of one kidney for renal transplantation and chronic total parenteral nutrition are the commonest causes of sustained renal hypertrophy in patients (34-37). The fact that compensatory glomerular hyperfiltration occurs in transplant donors is attested to by the rapid normalization of serum creatinine concentration which occurs. Of critical importance is the issue of whether the existence of hypertrophy portends a bad prognosis in terms of progressive deterioration of renal function since data accumulated from rat studies have linked glomerular hypertension and hyperfiltration to progressive glomerular sclerosis. Based upon the studies described below there is, thus far, no evidence that the same loss of renal mass which leads to "hyperfiltration injury" in rats (38,39), occurs in humans (40).

Unilateral nephrectomy in transplant donors. Following donation of one kidney, the remaining kidney undergoes an increase in GFR and renal plasma flow within 24 hours, and 70% of the original two-kidney function is

attained by 7 days (41). Since studies conducted 2-4 years after donation show increases in GFR and para-aminohippurate clearances of 71% and 66%, respectively, it is evident that most of the compensation is complete within the first few weeks (36-38,41,42). In parallel with the increases in GFR and renal plasma flow, increases in tubular reabsorption and secretory capacity occur, including those for glucose, phosphate, urate, potassium and sodium (43,44), in accordance with the need to maintain balance for these solutes.

In the late 1970's, long-term follow-up studies of renal donors began to emerge. In subjects studied 14-18 years after unilateral nephrectomy, creatinine clearance was 78% of prenephrectomy levels (45). No trend has been demonstrated for a decline in GFR nor has a consistent correlation been found between the age of the donor and the level of renal function (46,47). There are studies, however, which suggest that the degree of compensation is less in older patients (41,48-50).

Given that there is no evidence for long-term deterioration of renal function over 10-20 years, does hypertrophy of the remaining kidney have an adverse prognosis in any other context? Here the two issues of importance are hypertension and proteinuria. While the literature contains isolated reports which describe an increase in the incidence of hypertension (51,52), the majority of the studies show little or no tendency for blood pressure to increase above the levels expected for age and sex (45,50,53-58).

Where an increase in proteinuria has been described, it is generally less than 500 mg/day (59) and includes non-albumin protein (56,57). Thus, most patients with proteinuria of greater than 1 g/day should be considered to have renal disease of independent origin (59).

Another convincing demonstration of the functional integrity of filtration in the remaining kidney is the demonstration that 6 months to 20 years after donation

the "functional reserve" of the kidney (60) is entirely normal; i.e., the increase in GFR following a protein meal is within the normal range (61,62).

Unilateral Renal Agenesis

Unilateral renal agenesis has been shown to be associated with hypertrophy of the solitary kidney which is greater than that which is observed in uninephrectomized children of the same age (63,64). Since there is an increased incidence of renal "complications" in these patients, including glomerulosclerosis (64-67), nephrosclerosis (68) and chronic tubulo-interstitial nephritis (68), the question arises as to whether the renal hypertrophy implies an adverse prognosis. An important consideration in this regard is whether hyperfiltration in the remaining glomeruli leads to hemodynamically-mediated glomerular injury (69).

It is important to realize that most patients with unilateral renal agenesis show no evidence of renal disease of any sort. Furthermore, this syndrome is associated with other organ malformations, including involvement of the urinary tract, with up to 50% of the cases demonstrating either hydronephrosis or vesicoureteric reflux (70). Since reflux nephropathy is itself associated with proteinuria and focal sclerosis (71) it is inappropriate to attribute such findings to hyperfiltration in a supposedly-normal solitary kidney.

Nephrectomy for Renal Disease. Most cases of unilateral nephrectomy for disease of one kidney are complicated by an uncertainty about whether the same disease exists in the remaining kidney. (Long-term studies of uninephrectomy for unilateral traumatic injury are, unfortunately, not available.) Following removal of a Wilm's tumor in children, most of the compensatory growth of the remaining kidney takes place during the first few months (72) and probably continues for up to 4 years (63,72,73). The final size of the kidney is inversely related to the age at which nephrectomy is performed

(73).

Robitaille et al have reported on the long-term outcome of 27 patients who underwent unilateral nephrectomy in childhood for tumor, dysplasia, hydronephrosis or trauma at a mean age of 2.1 years. After a mean follow up of 23 years, there was no evidence of an increased incidence of hypertension or renal disease when compared with age-matched controls (74).

Is Glomerular Hypertrophy A Predictor of Glomerular Damage?

As pointed out above, glomeruli which escape injury undergo hypertrophy. While the emphasis on the cause for progression has been glomerular capillary hypertension in studies of the rat, it is not at all clear that this applies to man. Furthermore recent information in the rat is beginning to show that glomerular hypertrophy rather than pressure is correlated with sclerosis (75). If this is the case, it is not unreasonable to propose that growth factors which cause the glomeruli to enlarge could be the very factors which cause the laying down of collagen and cell proliferation which lead to the progressive destruction of capillary loops. Whether this applies to humans is not clear.

It is also not clear whether glomerular hypertrophy in uninvolved nephrons has long-term adverse effects in man. Low protein diets decrease GFR and kidney size but a clear-cut protective effect of low protein diets on progression of disease has not been demonstrated unequivocally in man. Well-controlled prospective clinical studies are urgently needed in this area. It is thus reasonable to consider the compensatory hypertrophy of uninvolved nephrons to be a "positive" adaptation which augments renal function in the face of disease.

Renal Hypertrophy in Diabetes Mellitus

One condition which seems to deviate from the normal pattern described above is insulin-dependent diabetes mellitus. This condition is associated with an early

rise in GFR and an increase in kidney size (76). However, the anticipated return of kidney size toward normal does not invariably occur when GFR is reduced by strict metabolic control. This has led to the assumption that GFR and hypertrophy are unrelated in this disease. However a careful scrutiny of the data shows that, when GFR is reduced early in the course of diabetes, kidney size reverts to normal whereas it does not if the treatment is instituted later (77). What is more, even when progressive diabetic glomerulosclerosis supervenes and a fall in GFR occurs, kidney size remains larger than it would be in other glomerular diseases with similar levels of function. This has led us to propose that diabetes may be associated with the intrarenal production of one or more growth factors and that the production of such factor(s) is "switched on" at some point in the evolution of the disease and continues to operate autonomously once the disease has progressed beyond a critical point. Such factors could contribute to the progressive microvascular disease of the diabetic kidney (77). These speculations require further investigation.

"Physiological" Renal Hypertrophy. There are clinical situations in which renal growth is observed without there being any intrinsic loss of kidney function. The important situations are pregnancy and total parenteral nutrition (TPN). In pregnancy the kidneys increase in size in parallel with the increased renal blood flow and GFR which occur during the second trimester. It is still not clear whether this represents true hypertrophy or vascular engorgement of the kidney, since data in experimental animals are conflicting.

Nephromegaly is a consequence of total parenteral nutrition (TPN) and is presumably mediated by the constant amino acid infusion (78). The longer the TPN is continued, the larger the kidneys become. When TPN is discontinued, kidney size reverts to normal. Prognostically, there is no evidence that either repetitive

pregnancy or chronic TPN, which presumably cause sustained elevations of GFR, lead to progressive renal disease in man.

CONCLUSIONS

Renal hypertrophy in humans is an adaptive phenomenon which augments renal function either in response to a reduction of functioning renal mass or in response to reversible factors which cause GFR to increase. In experimental animals there is correlative data to suggest that hypertrophy may be the forerunner of progressive disease but currently there is no evidence that this applies to humans. The one exception to this may be diabetes mellitus but there is not enough information available to analyze this adequately. Thus, at this point, renal hypertrophy must be recognized as an index of increased GFR and tubular function and viewed as a important mechanism of prolonging life in patients with loss of renal mass or with chronic renal diseases.

REFERENCES

1. Fine, L.G. The biology of renal hypertrophy. Kidney Int. 29:619-634, 1986.
2. Braun-Menendez, E. Evidence for renotropin as a causal factor in renal hypertension. Circulation 17:696-701, 1958.
3. Austin III, H., Goldin, H. and Preuss, H.G. Humoral regulation of growth. Nephron 27:163-170, 1981.
4. Gaydos, D.S., Goldin, H., Jenson, B., Gerten, D., Boedeker, B., Baitz C., and Preuss, H.G. Partial characterization of a renotropic factor. Renal Physiol. 6:1139-1144, 1983.
5. Harris, R.H., Hise, M.K. and Best, C.F. Renotropic factors in urine. Kidney Int. 23:616-623, 1983.
6. Yamamoto N., Kanetake H. and Yamada, J. In vitro evidence from tissue cultures to prove the existence of rabbit and human renotropic growth factor. Kidney Int. 23:624-631, 1983.
7. Nomura, K., Puett, D., Nicholson, W.F. and Liddle, G.W. Partial purification and characterization of a renotropic fraction from ovine pituitaries. Proc. Nat. Acad. Sci. U.S.A. 79:6675-6679, 1982.
8. Enesco, M. and Leblond, C.P. Increase in cell

number as a factor in the growth of the organs and the tissues of the young male rat. J. Embryol. Exp. Morph. 10:530-562, 1962.
9. Dicker, S.E. and Shirley, D.G. Compensatory renal growth after unilateral nephrectomy in the newborn rat. J. Physiol. 228:193-202, 1973.
10. Celsi, G., Jakobssen, B. and Aperia, A. Influence of age on compensatory renal growth in rats. Ped. Res. 20:347-350, 1986.
11. Miskell, C.A. and Simpson, D.P. The effects of dietary protein on DNA and protein synthesis after sham, unilateral and 5/6 nephrectomy. Kidney Int. 33:380, 1988 (abstr).
12. Diezi, J., Michoud, P., Grandchamp, A. and Giebisch, G. Effects of nephrectomy on renal salt and water transport in the remaining kidney. Kidney Int. 10:450-462, 1976.
13. Tabei, K., Levenson, D.J. and Brenner, B.M. Early enhancement of fluid transport in rabbit proximal straight tubules after loss of contralateral renal excretory function. J. Clin. Invest. 72:871-881, 1983.
14. Johnston, J.R., Brenner, B.M. and Hebert, S.C. Uninephrectomy and dietary protein affect fluid absorption in rabbit proximal straight tubule. Am. J. Physiol. 253:F222-F223, 1987.
15 Castellino, P., Coda, B. and DeFronzo, R.A. Effect of ammino acid infusion on renal hemodynamic in humans. Am. J. Physiol. 251:F132-F140, 1986.
16. Garland, H.O., Green, R. and Moriatry, R.J. Changes in body weight, kidney weight and proximal tubular length during pregnancy in the rat. Renal Physiol. 1:42-47, 1978.
17. Wiseman, M.J., Viberti, G.C. and Keen, H. Threshold effect of plasma glucose in the glomerular hyperfiltration of diabetes. Nephron 38:257-260, 1984.
18. Mogenson C.E., Steffes, M.W., Deckert, T. and Christiansen, J.S. Functional and morphological renal manifestation in diabetes. Diabetologia 21:89-93, 1981.
19. Allison, M.E., Wilson, C.B. and Gottschalk, C.W. Pathophysiology of experimental glomerulonephritis in rats. J. Clin. Invest. 53:1402-1423, 1974.
20. Oliver, J. Architecture of the Kidney in Chronic Bright's Disease. Paul B. Hoeber Inc., London/New York, 1939.
21. Oliver, J. New directions in renal morphology: a method, its results and it future. Harvey Lectures 40:102-155, 1944, 1945.
22. Fine, L.G., Nord, E.P., Danovitch, G.M., Kurtz, I. and Bacallao, R. Pathophysiology and nephron adaptation in chronic renal failure. In Diseases of the Kidney (eds. R.W. Shrier and C.W. Got-

tschalk), Little Brown and Co., Boston, 1988, pp.2985-3018.
23. Weinman, E.J., Renquist, K., Stroup, R., Kashgarian, M. and Hayslett, J.P. Increased tubular reabsorption of sodium in compensatory renal growth. Am. J. Physiol. 224:565-571, 1973.
24. Royce, P.C. Inhibition of renal growth following unilateral nephrectomy in the rat. Proc. Soc. Exp. Biol. Med. 113:1046-1049, 1963.
25. Moolenaar, W.H. Effects of growth factors on intracellular pH regulation. Ann. Rev. Physiol. 48:363-376, 1986.
26. Fine, L.G., Badie-Dezfooly, B., Lowe, A.G., Hamzeh, A., Wells, J. and, Salehmoghaddam, S. Stimulation of Na^+/H^+ antiport is an early event in hypertrophy of renal proximal tubular cells. Proc. Nat. Acad. Sci. U.S.A. 82:1736-1740, 1985.
27. Fine, L.G., Holley, R.W., Nasri, H. and Badie-Dezfooley, B. BSC, growth inhibitor transforms a mitogenic stimulus into a hypertrophic stimulus for renal proximal tubular cells: relationship to Na^+/H^+ antiport activity. Proc. Nat. Acad. Sci. U.S.A. 82:6163-6166, 1985.
28. Cohn, D.E., Hruska, K.A., Klahr, S. and Hammerman, M.R. Increased Na^+-H^+ exchange in brush border vesicles from dogs with renal failure. Am. J. Physiol. 243:F293-F299, 1982.
29. Harris, R.C., Seifter, J.L. and Brenner, B.M. J. Adaptation of Na^+- exchange in renal microvillus membrane vesicles. Role of dietary protein and nephrectomy. Clin. Invest. 74:1979-1987, 1984.
30. Nord, E.P., Hafezi, A., Kaunitz, J., Trizna, W. and Fine, L.G. pH gradient-dependent increased Na^+-H^+ antiport capacity of the rabbit remnant kidney. Am. J. Physiol. 249:F90-F98, 1985.
31. Pouyssegur, J., Sardet, C., Franchi, A., L'Allemain, G. and Paris, S. A specific mutation abolishing Na^+/H^+ antiport activity in hamster fibroblasts precludes growth at neutral and acidic pH. Proc. Nat. Acad. Sci. U.S.A. 81:4833-4837, 1984.
32. Lotspeich,. W.D. Metabolic aspects of acid-base change. Science 155:1066-1075, 1967.
33. Golchini, K., Norman, J. and Kurtz, I. NH_4Cl in the absence of extracellular acidemia induces hypertrophy and increased Na^+/H^+ antiport activity in monkey proximal tubule cells (JTC cells). Kidney Int. 33:157, 1988 (abstr).
34. Krohn, A.G., Ogden, D.A. and Holmes, J.H. Renal function in twenty-nine healthy adults before and after nephrectomy. J.A.M.A. 196:332-336, 1966.
35. Donadio, J.V., Farmer, C.D., Hunt, J.C., Tauxe, W.N., Hallenbeck, G.A. and Shorter, R.G. Renal function in donors and recipients of renal allotransplantation. Ann. Intern. Med. 66:105-

115, 1967.
36. Flanigan, W.J., Burns, R.O., Takacs, F.J. and Merrill, J.P. Serial studies of glomerular filtration rate and renal plasma flow in kidney transplant donors, identical twins and allograft recipients. Am. J. Surg. 116:788-794, 1968.
37. Boner, G., Shelp, W.D., Newton, M. and Rieselbach, R.E. Factors influencing the increase in glomerular filtration rate in the remaining kidney of transplant donors. Am. J. Med. 55:169-174, 1973.
38. Shimamura, T. and Morrison, A.B. A progressive glomerulosclerosis occurring in partial five-sixths nephrectomized rats. Am. J. Pathol. 79:95-106, 1975.
39. Hostetter, T.H., Meyer, T.W., Rennke, H.G. and Brenner, B.M. Chronic effects of dietary protein on renal structure and function in the rat with intact and reduced renal mass. Kidney Int. 30:509-517, 1986.
40. Fine, L.G. Preventing the progression of human renal disease: Have rational therapeutic principles emerged? Kidney Int. 33:116-128, 1988.
41. Ogden, D.A. Donor and recipient function 2 to 4 years after renal homotransplatation. Ann. Intern. Med. 67:998-1006, 1967.
42. Dean, S., Rudge, C.J., Joyce, M. Packham, D. and Bewick, M. Live related renal transplantation : an analysis of 141 donors. Transpl. Proc. 14:65-67, 1982.
43. Bricker, N.S., Guild, W.R., Reardon, J.B. and Merrill, J.P. Studies on the functional capacity of the denervated homotransplanted kidney in an identical twin with parallel observations in the donor. J. Clin. Invest. 35:1364-1380, 1956.
44. Pabico, R.C., McKenna B.A. and Freeman, R.B. Renal function before and after unilateral nephrectomy in renal donors. Kidney Int. 8:166-175, 1975.
45. Vincenti, F., Amend, W.J.C., Kaysen, G., Feduska, N., Birnbaum, J., Duca, R. and Salvatierra, O. Long term renal function in kidney donors. Sustained compensatory hyperfiltration with no adverse effects. Transplantation 36:626-629, 1983.
46. Hakim, R.M., Goldszer, R.C. and Brenner, B.M. Hypertension and proteinuria: Long term sequelae of uninephrectomy in humans. Kidney Int. 25:930-936, 1984.
47. Slack, T.K. and Wilson, D.M. Normal renal function, C_{IV} and C_{PAH} in healthy donors before and after nephrectomy. Mayo Clin. Proc. 51:296-300, 1976.
48. Aurell, M. and Ewald, J. Glomerular filtration rate during the first year after donor nephrectomy. Scand. J. Urol. Nephrol. 64(suppl):137-142,

1981.
49. Ringden, O., Friman, L., Lundgren, G. and Magnusson, G. Living related kidney donors: complications and long term renal function. Transplantation 25:221-223, 1978.
50. Miller, I.J., Suthanthiran, M., Riggio, R.R., Williams, J.J., Riehle, R.A., Vaughan, E.D., Stubenbord, W.T., Mouradian, J., Cheigh, J.S. and Stenzel, K.H. Impact of renal donation. Long-term clinical and biochemical follow up of living donors in a single center. Am. J. Med. 79:201-208, 1985.
51. Delano, B.G., Lazar, I.L. and Friedman, E.A. Hypertension, a late consequence of kidney donation. Kidney Int. 23:168, 1983 (abstr).
52. Sakellariou, G., Memmos, D., Alexopoulos, E., Tsobanelis, T., Karatzas, N., Bazakos, K., Liamos, O., Kalpakoglou, S. and Papadimitrou, M. Late renal function of the remaining kidney in related living donors. Transpl. Proc. 17:191-194, 1985.
53. Weiland, D., Sutherland, D.E.R., Chavers, B., Simmons, R.L., Ascher, N.L. and Najarian, J.S. Information on 628 living-related kidney donors at a single institution, with long-term follow-up in 472 cases. Transpl. Proc. 16:5-7, 1984.
54. Paul, L.C., Hoitsma, A.J., van Es, L.A. and Koene, R.A.P. Long term nephrologic follow up of living kidney donors. Transpl. Proc. 17:1592-1593, 1985.
55. Anderson, C.F., Velosa, J.A., Frohnert, P.P, Torres, V.E., Offord, K.P., Vogel, J.P., Donadio, J.V. and Wilson, D.M. The risks of unilateral nephrectomy: status of kidney donors 10 to 20 years postoperatively. Mayo Clin. Proc. 60:367-374, 1985
56. Williams, S.L., Oler, J. and Jorkasky, O.K. Long term renal function in kidney donors: a comparison of donors and their siblings. Ann. Intern. Med. 105:1-8, 1986.
57. Bertolatus, J.A., Friedlander, M.A., Scheidt, C. and Hunsicker, L.G. Urinary albumin excretion after donor nephrectomy. Am. J. Kid. Dis. 5:165-169, 1985.
58. Torres, V.E., Offord, K.P., Anderson, C.F., Velosa, J.A., Frohnert, P.P., Donadio, J.V. and Wilson, D.M. Blood pressure determinants in livining-related renal allograft donors and their receipients. Kidney Int. 31:1383-1390, 1987.
59. Bay, W.H. and Hebert, L.H. The living donor in kidney transplantation. Ann. Intern. Med. 106:719-727, 1987.
60. Bosch, J.P., Laver, A. and Glabman, S. Short-term protein loading in assessment of patients with renal disease. Am. J. Med. 77:873-879, 1984.
61. Chan, M.K. Aust. N.Z. Protein loading test before and after kidney donation. J. Med. 16:691-694,

1986.
62. Tapson, J.S., Mansy, H., Marshall, S.M., Tisdall, S.R. and Wilkenson, R. Renal functional reserve in kidney donors. Quart. J. Med. 60:725-732, 1986.
63. Eklof, O. and Ringertz, H. Kidney size and growth in unilateral renal agenesis and in the remaining kidney following nephrectomy for Wilm's tumor. Acta Radiol. Diag. 17:601-608, 1976.
64, Bhathena, D.B., Julian, B.A., McMorrow, R.G. and Baehler, R.W. Focal sclerosis of hypertrophied glomeruli in solitary functioning kidneys of humans. Am. J. Kid. Dis. 5:226-232, 1985.
65. Thorner, P.S., Arbus, G.S., Celermajer, D.S. and Baumal, R. Focal segmental glomerulosclerosis and progressive renal failure associated with unilateral kidney. Pediatrics 73:806-810, 1984.
66. Kiprov, D.D., Colvin, R.B. and McCluskey, R.T. Focal and segmental glomerulosclerosis and proteinuria associated with unilateral renal agenersis Lab. Invest. 46:275-281, 1982.
67. Gutierrez-Millet, V., Nieto, J., Praza, M. Usera, G., Martinez, M.A. and Morales, J.M. Focal glomerulosclerosis and proteinuria in patients with solitary kidneys. Arch. Intern. Med. 146:705-709, 1986.
68. Ashley, D.J.B. and Mustofi, F.K. Renal agenesis and dysgenesis. J. Urology 83:211-230, 1960.
69. Brenner, B.M., Meyer, T.W. and Hostetter, T.H. Dietary protein intake and progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. N. Eng. J. Med. 307:652-659, 1982.
70. Emanuel, B., Nachman, R., Aronson, N. and Weiss, H. Congenital solitary kidney: a review of 74 cases. J. Urology 111:394-397, 1974.
71. Kincaid-Smith, P. Glomerular and vascular lesions in chronic atrophic pyelonephritis and reflux nephropathy. Adv. Nephrol. 5:3-17, 1975.
72. Lutenegger, T.J., Gooding, C.A. and Fickenscher, L.G. Compensatory renal hypertrophy after treatment for wilin's tumor. Am. J. Roentgenol. 125:348-351, 1975.
73. Aperia, A., Broberger, O., Wikstad, I. and Wilton, P. Renal growth and function in patients nephrectomized in childhood. Acta Paediatr. Scand. 66:185-192, 1977.
74. Robitaille, P., Mongeau, J-G, Lortie, L. and Sinnassamy, P. Long term follow up of patients who underwent unilateral nephrectomy in childhood. Lancet 2:1297-1299, 1985.
75. Fries, J.U., Sandstrom, D., Meyer, T.W. and Rennke, H.G. Glomerular hypertrophy and epithe-

lial cell injury are determinants of progressive glomerulosclerosis in the rat. Kidney Int. 33:374, 1988 (abstr).

76. Mogensen, C.E. Glomerular filtration rate and renal plasma flow in short term and long-term juventule diabetes mellitus. Scan. J. Clin. Lab. Invest. 28:91-95, 1971.

77. Kleinman, K.S. and Fine, L.G. Prognostic implications of renal hypertrophy in diabetes mellitus. Diabetes/Metabolism Reviews (in press).

78. Cochran, S.T., Pagani, J.J. and Barbaric, T.L. Nephromegaly in hyperalimentation. Radiology 130:603-606, 1979.

GLOMERULONEPHRITIS

2

IgA NEPHROPATHY: CURRENT VIEWS ON PATHOGENESIS AND TREATMENT

H. SAKAI

Division of Nephrology and Metabolism, Department of Internal Medicine, School of Medicine, Tokai University, Isehara City, Kanagawa-ken 259-11, Japan

INTRODUCTION

IgA nephropathy was first described by Berger and Hinglais (1) in 1968, and has been referred to as Berger's disease. The term IgA nephropathy in this chapter is limited to primary IgA nephropathy because mesangial deposits of IgA are observed in various other diseases (2). IgA nephropathy is known to be one of the most common types of primary glomerulonephritis in many parts of the world, and its prognosis is not so benign as was initially thought (3). The most urgent requirement in the study of IgA nephropathy is to determine its pathogenesis and treatment. The aim of this chapter is to summarize recent advances in the knowledge of these aspects of this disease.

PATHOGENESIS

An increasing body of evidence suggests that IgA nephropathy is mediated by circulating IgA-dominant immune complexes which are deposited in the glomeruli. The reasons for this assumption are as follows: (a) IgA and C3 are observed in the glomerular mesangial areas by immunofluorescence (4), (b) electron-dense deposits are observed in the same areas (4), (c) IgA and/or C3 are also observed in the vascular walls of subcutaneous or intramuscular vessels by immunofluorescence (5), (d) IgA-dominant immune complexes in the circulation are

detected by several different techniques (6), (e) recurrences of IgA nephropathy occur frequently in allografted kidneys (7), and (f) rapid disappearance of glomerular IgA from kidneys with IgA nephropathy is observed when kidneys are transplanted in patients without IgA nephropathy (8). Immunological abnormalities which may lead to the formation of IgA-dominant immune complex in patients with IgA nephropathy have been investigated by many laboratories around the world, and the current progress in this area has been summarized in three reviews in 1987 (9, 10, 11). The following sections will discuss more recent progress in the studies on immunological and nonimmunological aspects of the pathogenesis of IgA nephropathy.

A. Immunological Aspects of Pathogenesis

1. Analysis of glomerular IgA

The most prominent finding in the glomeruli of renal biopsy specimens from patients with IgA nephropathy is mesangial, and on some occasions, capillary deposition of IgA. Analysis of glomerular IgA is thus expected to shed some light on the study of the pathogenesis of IgA nephropathy, although the amount of glomerular IgA is not correlated with the severity of tissue damage in the kidneys. The analysis of glomerular IgA relies mainly on the examination of patients and their renal specimens since appropriate animal models have not been developed in IgA nephropathy.

The subclass of IgA deposited in the glomeruli has been a matter of controversy but the majority of the reports has indicated that IgA1 is the dominant subclass throughout the world (12, 13, 14), although some French patients were reported to show IgA2 (15). These conflicting results could be caused by technical and/or geographical heterogeneity. The distribution of IgA1-, IgA2-, and J chain-containing cells in human tissues is

heterogeneous (16). However, the predominance of IgA1 or IgA2 in the mesangial areas does not implicate the source of these IgA subclasses in the body, because yet unknown antigen(s) in this disease may provoke either subclass of IgA. Although there are some exceptions (17), the presence of IgA with kappa and lambda light chains suggests that the glomerular IgA molecules in this disease are polyclonal antibodies.

As far as the size and charge distribution of IgA in the glomeruli are concerned, an increasing group of reports indicates the presence of a large number of IgA polymers in the mesangial areas of patients with IgA nephropathy (14, 18, 19). The J-chain was observed by the pretreatment of biopsy specimens with 6 M urea in glycine HCl (20). The identical distribution pattern of the binding sites of the secretory component with that of IgA1 implicates the dimeric nature of IgA deposits in patients with IgA nephropathy (14, 21). Kutteh and his associates (22) suggested that lymphoid tissues associated with secretory surfaces may provide a greater proportion of polymeric IgA than other lymphoid tissues or bone marrow. The isoelectric point of IgA molecules which were eluted by acid buffer from renal biopsy specimens of patients with IgA nephropathy ranged from 4.5 to 5.6, contrasting with the broader and more neutral nature of normal serum IgA (23). The same investigators could also detect a small but a significant amount of anionic IgA in the serum samples from the majority of their patients (24). The restricted range of the isoelectric point suggests a high content of acidic amino acids with or without particular carbohydrate compositions in the IgA molecules.

The antigenic specificity of glomerular IgA has been examined intensively with limited success. The acid-eluted IgA antibodies from renal biopsy specimens combined with the mesangial areas of allogeneic

glomeruli with IgA nephropathy, while these antibodies did not combine with renal tissues without IgA nephropathy (25). Examination of the cross reactivity of the acid-eluted IgA revealed that the recombination was observed not only between the specimens from the same patients but also between allogeneic patients with IgA nephropathy or with Henoch Schoenlein purpura nephritis suggesting the presence of common antigens between IgA nephropathy and Henoch Schoenlein purpura nephritis (26). The binding of the acid-eluted IgA with extrarenal materials was examined, and the nuclei of the epithelial cells from patients' upper respiratory tracts were found to combine with iodine-125 labeled acid-eluted IgA (27). The nuclei of human fibroblasts which were previously cocultured with the extract of the epithelial cells combined with radioactive acid-eluted IgA, indicating that some virus-like materials could be transmitted to the fibroblasts (28). Binding of serum IgA with the cultured fibroblasts was also observed in patients with IgA nephropathy (29). The antigenic substances in the glomeruli, however, could not be whole viruses because virus-like particles were not observed in the mesangial areas by electron microscopy. Except for the series of above-mentioned studies, there has been no report showing direct evidence of the antigenic specificity of glomerular IgA. The rest of the studies examined the presence of various antigenic substances in the glomeruli of patients with IgA nephropathy but none of them showed if those substances combine specifically with the glomerular IgA. Nevertheless, the observations of numerous substances in the glomeruli indicate that the antigenic materials in IgA nephropathy may be heterogeneous. These substances include herpes simplex virus, cytomegalovirus and Epstein-Barr virus nuclear antigen (30), and milk antigen (31). Some patients showed simultaneous presence of herpes simplex virus and

adeno virus in a glomerulus (32). No single antigen, however, has yet been identified definitely in a diffuse and generalized fashion in the glomeruli of patients with IgA nephropathy.

Activation of complement by glomerular IgA has not been fully confirmed. The presence of C3 and properdin in the glomeruli of the majority of patients with IgA nephropathy suggests the activation of C3 via the alternate pathway (33, 34). The detection of antigens of the membrane attack complex of complement further supports the pathogenetic role of complement activation in IgA nephropathy (35). Renal biopsy specimens from patients with IgA nephropathy were capable of activating human serum complement (36), but there is no direct evidence that the activation was mediated by IgA deposits in the glomeruli. Frequent activation of C3 was observed in the majority of adult and pediatric patients with IgA nephropathy, but the mediator as well as the pathophysiologic significance of this complement activation remains to be determined (37). The pathophysiologic significance of the observations of the altered phenotypes of C4 (38) and C3 (39) in patients with IgA nephropathy also remains to be elucidated.

Decreased immune clearance of IgA has been suspected as a mechanism of IgA deposition in the glomeruli. Phagocytosis of IgA1-dominant immune complexes by peripheral blood neutrophils was observed in patients with IgA nephropathy (40), and decreased phagocytic activity of polymorphonuclear leukocytes has also been reported (41). The emergence of Fc-receptor blocking factors in patients with IgA nephropathy (42) may be related to the decreased phagocytic activity of macrophages and other cells involved in the clearance of IgA from the circulation. A series of reports (43-47) indicated impairment of the reticuloendothelial system in IgA nephropathy, but the pathophysiological and

clinical significance remains to be examined.

2. Measurement of systemic IgA production

Persistent deposition of IgA in the glomeruli and persistent increase of serum levels of IgA in the majority of patients during a long term follow-up period (48) indicate increased production of IgA in patients with IgA nephropathy. Studies during the last two decades showed that IgA production is increased not only in the majority of patients but also in some of their family members (49).

In addition to the increased levels of serum IgA, various types of autoantibodies of the IgA class have been recognized recently. These autoantibodies include IgA-class rheumatoid factor (50, 51), antinuclear protein IgA antibodies (52, 53), and anticollagen IgA antibodies (54). It is not known, however, if these autoantibodies are deposited in the glomeruli of patients with IgA nephropathy. The increase of IgA antibodies is not restricted to autoantibodies but also includes those induced by exogenous antigenic stimulation. These IgA antibodies against exogenous antigens include anti-influenza virus antibodies (55), and more indirect cases such as increased levels of circulating IgA-class immune complexes following the administration of gluten (56) or cow's milk (57). It is interesting to note that the injection of influenza vaccines into patients with IgA nephropathy induced not only an increase of serum levels of IgA-class anti-influenza antibodies but also a simultaneous increase of IgA-class rheumatoid factor (55). This phenomenon was also observed in some healthy relatives of patients with IgA nephropathy (58). These observations indicate that the majority of patients with IgA nephropathy and some of their relatives are high responders for IgA. Detection of IgA-class circulating immune complexes was a controversial matter in the past, but recent studies

using more sensitive techniques have succeeded in detecting such immune complexes in patients with IgA nephropathy (6, 59, 60). The increase of IgA-class circulating immune complexes in IgA nephropathy is further supported by observations of high serum levels of the secretory component-binding IgA1 (14), polymeric IgA in 9-21S fractions (18), and bovine serum albumin-specific IgA immune complexes (61).

The increase of IgA production in patients with IgA nephropathy is not limited to humoral IgA but also includes cellular IgA. It has been a matter of controversy as to whether IgA-bearing lymphocytes are increased in the peripheral blood of patients with IgA nephropathy. The author's group observed an increase of these cells not only in patients but also in some of their family members (62, 63). On the other hand, subsequent reports showed that there was no such increase of these cells (64, 65). More recent reports, however, supported the increase of IgA-bearing peripheral blood lymphocytes in patients (66) and in their healthy relatives (67). Although the origin of the increased IgA-bearing lymphocytes is yet to be identified, two reports showed a marked increase of IgA-bearing lymphocytes in the tonsils of patients with IgA nephropathy (68, 69). It is interesting to note that the distribution patterns of immunoglobulin-bearing lymphocytes in the peripheral blood (62) and those in the tonsils (69) were strikingly similar, suggesting the migration of these cell populations from the tonsils. In addition to IgA-bearing lymphocytes, in vitro production of IgA from cultured B cells is also increased in patients with IgA nephropathy and some of their family members (70-72). Although there have been some discrepancies, it is now recognized that the activation of IgA-producing B cells occurs in the majority of patients with IgA nephropathy and in some of their family members.

3. Immunoregulatory mechanism of IgA production

It is well known that the production of IgA is highly T cell-dependent (73), and thus the increased activity of IgA-producing B cells in patients with IgA nephropathy has been suspected to be related to some abnormalities in the regulatory T cells.

The activity of IgA-specific suppressor T cells was found to be decreased in patients with IgA nephropathy (74) and some of their healthy relatives (75). Although a study on identical twins ruled out genetic control of IgA-specific suppressor T cells (74), the decreased activity of such T cells in family members indicates that some familial factors may be involved in the altered IgA immunity in this disease. Nevertheless, the decrease of IgA-specific suppressor T cell activity may work as a enhancing factor in the regulation of IgA production.

As far as the helper activity of T cells in patients with IgA nephropathy is concerned, an increase of the $OKT4^+/OKT8^+$ ratio in patients' peripheral blood has been reported by several laboratories (76-79). Although there were some discrepancies among these reports regarding the nature of the increase of the $OKT4^+/OKT8^+$ ratio, i.e. either an increase of $OKT4^+$ cells or a decrease of $OKT8^+$ cells, the helper/suppressor ratio in T cells of patients with IgA nephropathy seemed to be helper-dominant. As far as IgA-specific helper T cells are concerned, peripheral blood T cells with the Fc receptors for IgA (Tα cells) were shown to be a candidate (80), and these cells were significantly increased in patients with IgA nephropathy (81). Subsequently, it was demonstrated that more than 80% of Tα cells had OKT4 antigens on their surface (Tα4 cells)(82). These Tα4 cells were shown to convert IgM-bearing B cells to IgA-bearing B cells in vitro, and therefore regarded as IgA-specific switch T cells (83). IgA-specific switch T cells were first described by

Kawanishi and his associates (84) in T cells from murine Peyer's patches. Although Tα cells in mice were reported to suppress IgA production in vitro (85), the dichotomy between the murine and human systems might be due to the difference of the assay procedures. The mediators released from Tα4 cells to induce IgA-specific switch activity are presently unknown. However, recent developments in the studies on interleukin 5 in mice and humans suggest that this lymphokine specifically enhances the production of IgA (86).

B. Genetic Aspects of Pathogenesis

It is well known that the geographical distribution of IgA nephropathy is irregular (3). Although the incidence of this disease in the United Kingdom (87) and other countries in Northern Europe is reported to be increasing, it is very common in Southern Europe, Asia and Australia. Low incidence was reported in Blacks in the southeastern United States (88). The discovery of several large pedigrees in central and eastern Kentucky which gave rise to many patients (89) and the subsequent genetic analysis (90) further support the concept that IgA nephropathy has some genetic background.

The distribution of HLA antigens in patient populations has been examined in many countries, and their observations were reviewed recently by Egido, Julian and Wyatt (10). In brief, there has been no definite association of specific HLA antigens and IgA nephropathy. In addition to HLA antigens, some abnormalities have been reported in the complement system as described previously (38, 39). The clinicopathological significance of the deviation of the phenotypes of C4 and C3 is yet to be elucidated. There are a few reports showing the alteration of the amino acid sequence of the Fc portion of circulating IgA in patients with IgA nephropathy. These reports included the polymorphism of the chromosome 14-derived messenger RNA which regulates the

amino acids on the Fc portion of IgA (91), abnormal amino acid sequences in the switch region of the Fc portion of IgA (92), and altered composition of carbohydrates of the Fc portion of IgA (93). It is presently unknown if these abnormalities in the amino acid sequence of IgA are specific to IgA nephropathy or simply reflect increased production of IgA antibodies. Nevertheless, the aberrations in the amino acid sequences and the subsequent alteration of the carbohydrate compositions may increase the adhesion of IgA molecules to the mesangial areas of the glomeruli in patients with IgA nephropathy.

There have been sporadic reports of the emergence of patients with IgA nephropathy in the same family (94-96) but most patients around the world have shown sporadic emergence. The discovery of the large pedigrees in Kentucky (89, 90) provided an opportunity for evaluation of the immunogenetic aberrations in this disease. To date, however, no significant difference has been found between common "sporadic" patients and the "familial" patients (67).

C. Miscellaneous Aspects of Pathogenesis

Besides immunological and genetic analyses, various other approaches have been attempted to clarify the pathogenesis of IgA nephropathy. These efforts include the analyses of biochemical and histochemical changes of the mesangial cells, detection of hemodynamic alteration in the kidneys, endocrinological analyses and evaluation of nonspecific adhesion of IgA in the mesangial areas. None of these approaches, however, has yet succeeded in finding specific phenomena in IgA nephropathy. To date, clinical, histopathological, immunological and genetic approaches are regarded to have come close to understanding the pathogenesis of this disease. However, efforts should be continued to reinforce the accumulated knowledge.

TREATMENT

A. Treatment Protocols

No specific treatment is known to improve the clinical course of IgA nephropathy. The aim of treatment at this time is to preserve renal functions and to stabilize associated symptoms such as hypertension. In some cases, a prolonged remission or even a resolution of histologic abnormalities has been observed. In the majority of cases, however, the preservation of clinical states is the most important target for maintaining the quality of life in each patient. The selection of treatment protocols depends on the prediction of the prognosis of individual patients. The most reliable method for prediction of the prognosis is histopathological findings of renal biopsy specimens. Some pediatric patients were reported to be resolved during several years of follow-up (97, 98), while the majority of adult cases remained unchanged or were exacerbated (3, 99). In addition to the findings of renal biopsy specimens, several other parameters were reported to be correlated with the prognosis to a lesser degree. These parameters include severe proteinuria, hypertension, late onset, male sex and lack of macrohematuria (99, 100). To date, there are no international standards for the prediction of prognosis. Most institutes classify their patients into several categories, e.g. minimal, slight, moderate and advanced. No drug therapy is required for the treatment of patients with minimal to slight degrees because almost all patients in these categories remain unchanged in periodic checks. In patients with advanced IgA nephropathy, there is no effective method to prevent renal failure. In the author's opinion, these patients should avoid vigorous immunosuppressive treatment to preserve their general condition at the time of hemodialysis or

transplantation. Questions remain in the selection of treatment protocols in patients with the moderate degree of IgA nephropathy. Obviously the prognosis of these patients is heterogeneous, but because of the lack of a definitely reliable method for the prediction of prognosis, almost all patients in this category are administered some drugs in an attempt to prevent gradual development of renal failure.

B. Drugs Evaluated By Double Blind Studies

To the best knowledge of the author, only two drugs have been so far evaluated by multi-center, double blind studies (101, 102). These studies, however, were performed in Japan and the results were published only in Japanese. It is uncommon to refer to articles not in English, but results of these studies are described here because of the lack of information in this important aspect of clinical nephrology. These two studies were performed in patients with biopsy-proved chronic glomerulonephritis, and there was no significant difference between results of all patients and results of patients with IgA nephropathy because of the large number of cases of this disease in Japan. Sixty mg/day of trimetazidine dihydrochloride (t.i.d., p.o.) (101) and 300 mg/day of AS-05 (Dilazep) (t.i.d., p.o.) (102) were found to be effective in the improvement of renal functions and the reduction of proteinuria. Based on these results, these drugs and other anti-platelet agents such as dipyridamole are currently used in Japan for treatment of patients with moderate IgA nephropathy. These drugs can not be expected to provide dramatic effects, but can be utilized for long period because of the lack of severe side effects.

C. Drugs In Experimental Stages

Corticosteroids were used previously in patients with IgA nephropathy associated with the nephrotic syndrome. More routine use of steroids has been tried

in Japan recently (103). A cautious decision might be required when selecting patients for steroid therapy because of the pros and cons of corticosteroids.

Nonsteroidal anti-inflammatory drugs have been used in patients with various types of chronic glomerulonephritis in many countries. Although there are sporadic reports (104), there have been no double blind studies on this type of drugs in patients with IgA nephropathy. Gastric irritation and possible increase of serum creatinine levels are still debated when evaluating the efficacy of these drugs.

Other drugs which interfere with the blood coagulation system have also been reported. Eicosapentanotic acid was reported to be effective in a relatively small number of patients (105), but there have been no follow-up reports. Defibrination of intraglomerular fibrin deposits by urokinase has been attempted by the author's group (106). Staining of biopsy samples for α2-PI prior to the use of urokinase is recommended to predict the effectiveness (107). Although there are no serious side effects, the use of urokinase is limited because of the high cost of this drug.

Immune solubilization of IgA-dominant deposits in the glomeruli by complement in patients with IgA nephropathy was observed by the author's group (108, 109), and the results were applied to the treatment of this disease. Danazol (2,3 isoxazol derivative of 17α-ethyl testosterone) was selected to increase serum C3 levels, and this drug was effective in the reduction of proteinuria in patients with IgA nephropathy (110, 111). The limitations of this drug are its androgenic effects in female patients, occasional increase of serum transaminases, and relatively high cost.

Low doses of dopamine were reported to increase renal blood flow without influencing heart rate or systemic blood pressure in patients with IgA nephropathy

(112). Evaluation of long-term effects of this treatment is warranted.

Phenytoin sodium has been known to decrease serum levels of IgA in epileptic patients. Despite a fall in serum IgA concentrations, however, the administration of phenytoin showed no clinical or pathologic differences in patients with IgA nephropathy (113-115). Further studies are warranted to analyze the types of IgA which are susceptible and resistant to phenytoin.

Cyclosporine A is highly inhibitory to T cells, and thus expected to be effective in the T cell-dependent enhancement of IgA production in patients with IgA nephropathy. To date, however, no reports are available giving information on this drug.

Plasma exchange has been advocated by Coppo and her associates (116) in the treatment of patients with rapidly progressive IgA nephropathy. Experiences in Australia suggested that this treatment may alter the course of the disease only while it is continued (117).

Transplantation of allogeneic kidneys in patients with IgA nephropathy has been known to develop a relatively high rates of recurrence (7, 118). However, the majority of these recurrent cases remained unchanged and cases progressing to renal failure were rare except for rejection episodes. Transplantation is therefore not prohibited in the treatment of patients with IgA nephropathy.

CONCLUSION

The pathogenesis of IgA nephropathy is still unclear. Rapidly accumulating evidence in recent years, however, strongly suggests the abnormalities of immunoregulatory function in this disease. Efforts to elucidate the nature of these abnormalities are expected to clarify the pathogenesis and to provide specific treatment for this important disease in nephrology.

REFERENCES

1. Berger, J. and Hinglais, N.: Les Depots intercapillaires d'IgA-IgG. J. Urol. (Paris) 74:694-695, 1968.
2. Clarkson, A.R.: IgA nephropathy: history, classification and geographic distribution. In: IgA Nephropathy (Ed. A.R. Clarkson), Martinus Nijhoff Publishing, Boston, Dordrecht and Lancaster, 1987, pp. 1-8.
3. D'Amico, G.: Idiopathic IgA mesangial nephropathy. Nephron 41:1-13, 1985.
4. Berger, J.: IgA glomerular deposits in renal disease. Transplant. Proc. 1:939-944, 1969.
5. Lamperi, S. and Carozzi, S.: Skin-muscle biopsy in patients with various nephropathies. Nephron 24:46-50, 1979.
6. Hall, R.P., Stachura, I., Cason, J., Whiteside, T.L. and Lawley, T.J.: IgA-containing circulating immune complexes in patients with IgA nephropathy. Am. J. Med. 74:56-63, 1983.
7. Berger, J., Yaneva, H., Nabarra, B. and Barbanel, C.: Recurrence of mesangial deposition after renal transplantation. Kidney Int. 7:232-241, 1975.
8. Sanfilippo, F., Croker, B.P. and Bollinger, R.B.: Fate of four cadaveric donor renal allografts with mesangial IgA deposits. Transplantation 33:370-376, 1982.
9. Sakai, H.: Lymphocyte function in IgA nephropathy. In: IgA Nephropathy (Ed. A.R. Clarkson), Martinus Nijhoff Publishing, Boston, Dordrecht and Lancaster, 1987, pp. 176-187.
10. Egido, J., Julian, B.A. and Wyatt, R.J.: Genetic factors in primary IgA nephropathy. Nephrol. Dial. Transplant. 2:134-142, 1987.
11. Bene, M-C. and Faure, G.: Berger's disease: Recent advances in immunology and genetics. Adv. Nephrol. 16:281-290, 1987.
12. Conley, M.E., Cooper, M.D. and Michael, A.F.: Selective deposition of IgA1 in IgA nephropathy, anaphylactoid purpura nephritis, and systemic lupus erythematosus. J. Clin. Invest. 66:1432-1436, 1980.
13. Tomino, Y., Endoh, M., Nomoto, Y. and Sakai, H.: Immunoglobulin A1 in IgA nepdhropathy. N. Eng. J. Med. 305:1159-1160, 1981.
14. Valentijn, R.M., Radl, J., Haaijman, J.J., Vermeer, B.J., Weening, J.J., Kauffmann, R.H., Daha, M.R. and van Es, L.A.: Circulating and mesangial secretory component-binding IgA-1 in primary IgA nephropathy. Kidney Int. 26:760-766, 1984.
15. Andre, C., Berthoux, F.C., Andre, F., Gillon, J., Genin, C. and Sabatier, J-C.: Prevalence of IgA2 deposits in IgA nephropathies. N. Eng. J. Med.

303:1343-1346, 1980.
16. Crago, S.S., Kutteh, W.H., Moro, I., Allansmith, M.R., Radl, J., Haaijman, J.J. and Mestecky, J.: Distribution of IgA1-, IgA2-, and J chain-containing cells in human tissues. J. Immunol. 132:16-18, 1984.
17. Lai, K-N., Chan, K.W., Lai, F.M-C., Ho, C.P., Yan, K.W., Lam, C.W.K. and Vallance-Owen, J.: The immunochemical characterization of the light chains in the mesangial IgA deposits in IgA nephropathy. Am. J. Clin. Pathol. 85:548-551, 1986.
18. Trascasa, M.L., Egido, J., Sancho, J. and Hernando, L.: IgA glomerulonephritis (Berger's disease): Evidence of high serum levels of polymeric IgA. Clin. Exp. Immunol. 42:247-254, 1980.
19. Tomino, Y., Sakai, H., Miura, M., Endoh, M. and Nomoto, Y.: Detection of polymeric IgA in gloermuli from patients with IgA nephropathy. Clin. Exp. Immunol. 49:419-425, 1982.
20. Komatsu, N., Nagura, H., Watanabe, K., Nomoto, Y. and Kobayashi, K.: Mesangial deposits of J-chain linked polymeric IgA nephropathy. Nephron 33:61-64, 1983.
21. Bene, M-C., Faure, G. and Duheille, J.: IgA nephropathy: Characterization of the polymeric nature of mesangial deposits by in vitro binding of free secretory component. Clin. Exp. Immunol. 47:527-534, 1982.
22. Kutteh, W., Prince, S.J. and Mestecky, J.: Tissue origins of human polymeric and monomeric IgA. J. Immunol. 128:990-995, 1982.
23. Monteiro, R.C., Halbwachs-Mecarelli, L., Roque-Barreira, M.C., Noel, L-H., Berger, J. and Lesavre, P.: Charge and size of mesangial IgA in IgA nephropathy. Kidney Int. 28:666-671, 1985.
24. Monteiro, R.C., Chevailler, A., Noel, L.H. and Lesavre, P.: Negatively-charged serum IgA detected by in vitro binding to cationic proteins in patients with IgA nephropathy. In: Proceedings of the Xth International Congress of Nephrology (Ed. J.S. Cameron), 1987, p. 394.
25. Tomino, Y., Endoh, M., Nomoto, Y. and Sakai, H.: Specificity of IgA antibody in IgA nephropathy. Nephron 29:103-104, 1981.
26. Tomino, Y., Sakai, H., Endoh, M., Miura, M., Suga, T., Kaneshige, H. and Nomoto, Y.: Cross reactivity of eluted antibodies from renal tissues of patients with Henoch-Schoenlein purpura and IgA nephropathy. Am. J. Nephrol. 3:315-318, 1983.
27. Tomino, Y., Sakai, H., Endoh, M., Suga, T., Miura, M., Kaneshige, H. and Nomoto, Y.: Cross reactivity of IgA antibodies between renal mesangial areas and nuclei of tonsillar cells in patients with IgA nephropathy. Clin. Exp. Immunol. 51:605-611, 1983.

28. Tomino, Y., Sakai, H., Miura, M., Endoh, M. Suga, T. and Nomoto, Y.: Detection of antigenic substances in patients with IgA nephropathy. Contrib. Nephrol. 40:69-73, 1984.
29. Tomino, Y., Sakai, H., Miura, M., Suga, T., Endoh, M., Nomoto, Y., Umehara, K. and Hashimoto, K.: Specific binding of circulating IgA antibodies in patients with IgA nephropathy. Am. J. Kid. Dis. 3:149-153, 1985.
30. Nagy, J., Uj, M., Szucs, G., Trinn, Cs. and Burger, T.: Herpes virus antigens and antibodies in kidney biopsies and sera of IgA glomerulonephritis. Clin. Nephrol. 21:259-262, 1984.
31. Russell, M.W., Mestecky, J., Julian, B.A. and Galla, J.H.: IgA-associated renal diseases: Antibodies to environmental antigens in sera and deposition of immunoglobulins and antigens in glomeruli J. Clin. Immunol. 6:74-86, 1986.
32. Tomino, Y., Yagame, M., Omata, F., Nomoto, Y. and Sakai, H.: A case of IgA nephropathy associated with adeno and herpes simplex virus. Nephron, 47:258-261, 1987.
33. McCoy, R.C., Abramowsky, C.R. and Tisher, C.C.: IgA nephropathy. Am. J. Pathol. 76:123-144, 1974.
34. Evans, D.J., Williams, D.G., Peters, D.K., Sissons, J.G.P., Boulton-Jones, J.M., Ogg, C.S., Cameron, J.S. and Hoffbrand, B.I.: Glomerular deposition of properdin in Henoch-Schoenlein syndrome and idiopathic focal nephritis. Br. Med. J. iii:326-328, 1973.
35. Rauterberg, E.W., Lieberknecht, H-M., Wingen, A-M. and Ritz, E.: Complement membrane attack (MAC) in idiopathic IgA-gloemrulonephritis. Kidney Int. 31:820-829, 1987.
36. Tomino, Y., Endoh, M., Nomoto, Y. and Sakai, H.: Activation of complement by renal tissues from patients with IgA nephropathy. J. Clin. Pathol. 34:35-40, 1981.
37. Wyatt, R.J., Kanayama, Y., Julian, B.A., Negoro, N., Sugimoto, S., Hudson, E.C. and Curd, J.G.: Complement activation in IgA nephropathy. Kidney Int. 31:1019-1023, 1987.
38. McLean, R.H., Wyatt, R.J. and Julian, B.A.: Complement phenotypes in glomerulonephritis: Increased frequency of homozygous null C4 phenotypes in IgA nephropathy and Henoch-Schonlein purpura. Kidney Int. 26:855-860, 1984.
39. Wyatt, R.J., Julian, B.A., Galla, J.H. and McLean, R.: Increased frequency of C3 fast alleles in IgA nephropathy. Disease Marker 2:419-428, 1984.
40. Tomino, Y., Miura, M., Suga, T., Endoh, M., Nomoto, Y. and Sakai, H.: Detection of IgA1-dominant immune complexes in peripheral blood mononuclear leukocytes by double immunofluorescence in patients with

IgA nephropathy. Nephron 37:137-139, 1984.
41. Sato, M., Kinugasa, E., Ideura, T. and Koshikawa, S.: Phagocytic activity of polymorphonuclear leukocyte in patients with IgA nephropathy. Clin. Nephrol. 19:166-171, 1983.
42. Roccatello, D., Coppo, R., Piccoli, G., Cordonnier, D., Martina, G., Rollino, C., Picciotto, G., Sena, L.M. and Amoroso, A.: Fc receptors blocking factors in IgA nephropathies. Clin. Nephrol. 23:159-168, 1985.
43. Lawrence, S., Pussell, B.A. and Charlesworth, J.A.: Mesangial IgA nephropathy: detection of defective reticulophagocytic function in vivo. Clin. Nephrol. 19:280-283, 1983.
44. Ooi, Y.M. and Ooi, B.S.: Identification of a monocyte phogocytic defect in a subpopulation of patients with nephritis. Kidney Int. 23:851-854, 1983.
45. Roccatello, D., Coppo, R., Basolo, B., Cordonnier, D., Picciotto, G., Sena, M. and Piccoli, G.: Interaction between macrophage system and IgA immune complexes in IgA nephropathy. Kidney Int. 24:423-424, 1983.
46. Roccatello, D., Coppo, R. and Piccoli, G.: Monocyte macrophage system function in primary IgA nephropathy. Contrib. Nephrol. 40:130-136, 1984.
47. Bannister, K.M., Hay, J., Clarkson, A.R. and Woodroffe, A.J.: Fc specific reticulo-endothelial clearance in SLE and glomerulonephritis. Am. J. Kidney Dis. 3:287-292, 1984.
48. D'Amico, G., Imbasciati, E., di Belgioioso, G.B., Bertoli, S., Fogazzi, G., Ferrario, F., Fellin, G., Ragni, A., Colasanti, G., Minetti, L. and Pomticelli, C.: Idiopathic IgA mesangial nephropathy. Medicine 64:49-60, 1985.
49. Sakai, H.: Immune system abnormalities in IgA nephropathy especially T-cell functions. Plasma Ther. Transfus. Technol 6:677-686, 1985.
50. Endoh, M., Suga, T. and Sakai, H.: IgG, IgA and IgM rheumatoid factors in patients with glomerulonephritis. Nephron 39:330-335, 1985.
51. Sinico, R.A., Fornasieri, A., Oreni, N., Benuzzi, S. and D'Amico, D.: Polymeric IgA rheumatoid factor in idiopathic IgA mesangial nephropathy (Berger's disease). J. Immunol. 137:536-541, 1986.
52. Nomoto, Y., Miura, M., Suga, T., Endoh, M., Tomino, Y. and Sakai, H.: Cold reacting anti-nuclear factor (ANF) in families of patients with IgA nephropathy. Clin. Exp. Immunol. 58:63-67, 1984.
53. Nomoto, Y., Suga, T., Miura, M., Nomoto, H., Tomino, Y. and Sakai, H.: Characterization of an acidic nuclear protein recognized by autoantibodies in sera from patients with IgA nepdhropathy. Clin. Exp. Immunol. 65:513-519, 1986.
54. Cederholm, B., Wieslander, J., Bygren, P. and

Heinegard, D.: Patients with IgA nephropathy have circulating anti-basement membrane antibodies reacting with structures common to collagen I, II, and IV. Proc. Natl. Acad. Sci. USA 83:6151-6155, 1986.
55. Endoh, M., Suga, T., Miura, M., Tomino, Y., Nomoto, Y. and Sakai, H.: In vivo alteration of antibody production in patients with IgA nephropathy. Clin. Exp. Immunol. 57:564-570, 1984.
56. Coppo, R., Basolo, B., Rollino, C., Roccatello, D., Martina, G., Amore, A., Bongiorno, G. and Piccoli, G.: Mediterranean diet and primary IgA nephropathy. Clin. Nephrol. 26:72-82, 1986.
57. Sato, M., Takayama, K., Wakasa, M. and Koshikawa, S.: Estimation of circulating immune complexes following oral challenge with cow's milk in patients with IgA nephropathy. Nephron 47:43-48, 1987.
58. Sakai, H., Nomoto, Y., Tomino, Y., Endoh, M., Miura, M. and Suga, T.: Increases of in vitro and in vivo production of polyclonal IgA in patients and their family members with IgA nephropathy. In: Recent Advances in Mucosal Immunology, Part B (Eds. J.R. McGhee, J. Mestecky, P.L. Ogra and J. Bienenstock), Plenum Press, New York and London, 1987, pp. 1507-1514.
59. Lesavre, P.H., Digeon, M. and Bach, J.F.: Analysis of circulating IgA and detection of immune complexes in primary IgA nephropathy. Clin. Exp. Immunol. 48:61-69, 1982.
60. Yagame, M., Tomino, Y., Miura, M., Tanigaki, T., Suga, T., Nomoto, Y. and Sakai, H.: Detection of IgA-class circulating immune complexes (CIC) in sera from patients with IgA nephropathy using a solid-phase anti-C3 Facb enzyme immunoassay (EIA). Clin. Exp. Immunol. 67:270-276, 1987.
61. Yap, H.K., Sakai, R.S., Woo, K.T., Lim, C.H. and Jordan, S.C.: Detection of bovine serum albumin in the circulating IgA immune complexes of patients with IgA nephropathy. Clin. Immunol. Immunopathol. 43:395-402, 1987.
62. Nomoto, Y., Sakai, H. and Arimori, S.: Increase of IgA-bearing lymphocytes in peripheral blood from patients with IgA nephropathy. Am. J. Clin. Pathol. 71:158-160, 1979.
63. Sakai, H., Nomoto, Y., Arimori, S., Komori, K., Inouye, H. and Tsuji, K.: Increase of IgA-bearing peripheral blood lymphocytes in families of patients with IgA nephropathy. Am. J. Clin. Pathol. 72:452-456, 1979.
64. Cosio, F.G., Lam, S., Folami, A.O., Conley, M.E. and Michael, A.F.: Immune regulation of immunoglobulin production in IgA nephropathy. Clin. Immunol. Immunopathol. 23:430-436, 1982.
65. Fiorini, G., Fornasier, A., Sinico, R., Colasanti, G., Gibelli, A., Corneo, R. and D'Amico, G.:

Lymphocyte populations in the peripheral blood from patients with IgA nephropathy. Nephron 31:354-357, 1982.
66. Feehally, J., Beattie, T.J., Brenchley, P.E.C., Coupes, B.M., Mallick, N.P. and Postlethwaite, R.J.: Sequential study of the IgA system in relapsing IgA nephropathy. Kidney Int. 29:924-931, 1986.
67. Garcia-Hoyo, R., Lozano, L. and Egigo, J.: Immune abnormalities of IgA in six families with IgA nephropathy. In: Recent Advances in Mucosal Immunology, Part B (Eds. J.R. McGhee, J. Mestecky, P.L. Ogra and J. Beinenstock), Plenum Press, New York and London, 1987, pp. 1499-1505.
68. Bene, M-C., Faure, G., de Ligney, B.H., Kessler, M. and Duheille, J.: IgA nephropathy: Quantitative immunohistomorphometry of the tonsillar plasma cells evidences an inversion of the IgA versus IgG secreting cell membrane. J. Clin. Invest. 71:1342-1347, 1983.
69. Egido, J., Blasco, R., Lozano, L., Sancho, J. and Garcia-Hoyo, R.: Immunological abnormalities in tonsils of patients with IgA nephropathy: inversion in the percentage of IgA versus IgG-bearing lymphocytes and increased polymeric IgA synthesis. Clin. Exp. Immunol. 57:101-106, 1984.
70. Egido, J., Blasco, R., Sancho, J., Lozano, L., Sanchez-Crespo, M. and Hernando, L.: Increased rates of polymeric IgA synthesis by circulating lymphoid cells in IgA mesangial glomerulonephritis. Clin. Exp.Immunol. 47:309-316, 1982.
71. Hale, G.M., McIntosh, S.L., Hiki, Y., Clarkson, A.R. and Woodroffe, A.J.: Evidence for IgA-specific B cell hyperactivity in patients with IgA nephropathy. Kidney Int. 29:718-724, 1986.
72. Waldo, F.B., Beischel, L. and West, C.D.: IgA synthesis by lymphocytes from patients with IgA nephropathy and their relatives. Kidney Int. 29:1229-1233, 1986.
73. Elson, C.O.: T cell specific IgA switching and for IgA B-cell differentiation. Immunology Today 4:189-190, 1983.
74. Sakai, H., Nomoto, Y. and Arimori, S.: Decrease of IgA-specific suppressor T cell activity in patients with IgA nephropathy. Clin. Exp. Immunol. 38:243-248, 1979.
75. Egido, J., Blasco, R.A., Sancho, J. and Hernando,: Immunological abnormalities in healthy relatives of patients with IgA nephropathy. Am. J. Nephrol. 5:14-20, 1985.
76. Chatenoud, L. and Bach, M-A.: Abnormalities of T-cell subsets in glomerulonephritis and systemic lupus erythematosus. Kidney Int. 20:267-274, 1981.
77. Egido, J., Blasco, R., Sancho, J. and Lozano, L.: T-cell dysfunction in IgA nephropathy: Specific

abnormalities in the regulation of IgA synthesis. Clin. Immunol. Immnopathol. 26:201-212, 1983.
78. Rothschild, E. and Chatenoud, L.: T cell subset modulation of immunoglobulin production in IgA nephropathy and membranous glomerulonephritis. Kidney Int. 25:557-564, 1984.
79. Cagnoli, L., Beltrandi, E., Pasquali, S., Biagi, R., Casadei-Maldini, M., Rossi, L. and Zucchelli, P.: B and T cell abnormalities in patients with primary IgA nephropathy. Kidney Int. 28:646-651, 1985.
80. Endoh, M., Sakai, H., Nomoto, Y., Tomino, Y. and Kaneshige, H.: IgA-specific helper activity of Tα cells in human peripheral blood. J. Immunol. 127:2612-2613, 1981.
81. Sakai, H., Endoh, M., Tomino, Y. and Nomoto, Y.: Increase of IgA specific helper Tα cells in patients with IgA nephropathy. Clin. Exp. Immunol. 50:77-82, 1982.
82. Suga, T., Endoh, M., Sakai, H., Miura, M., Tomino, Y. and Nomoto, Y.: Tα cell subsets in human peripheral blood. J. Immunol. 134:1327-1329, 1985.
83. Sakai, H., Yasumoto, Y., Suga, T., Endoh, M., Tomino, Y. and Nomoto, Y.: Increase of IgA-specific switch T cells in patients with IgA nephropathy. In: Proceedings of the Xth International Congress of Nephrology (Ed. J.S. Cameron), London, 1987, p. 402.
84. Kawanishi, H., Saltzman, L.E. and Strober, W.: Mechanisms regulating IgA class-specific immunoglobulin production in murine gut-associated lymphoid tissues. 1. T cells derived from Peyer's patches that switch sIgM B cells to sIgA B cells in vitro. J. Exp. Med. 157:433-450, 1983.
85. Yodoi, J., Adachi, M. and Noro, N.: IgA binding factors and Fc receptors for IgA: Comparative studies between IgA and IgE Fc receptor system. Int. Rev. Immunol. 2:117-141, 1987.
86. Harriman, G.R. and Strober, W.: Interleukin 5, a mucosal lymphokine? J. Immunol. 139:3553-3555, 1987.
87. Power, D.A., Muirhead, N., Simpson, J.G., Nicholls, A.J., Horne, C.H.W., Gotto, G.R.D. and Edward, N.: IgA nephropathy is not a rare disease in the United Kingdom. Nephron 40:180-184, 1985.
88. Jennette, J.C., Wall, S.D. and Wilkman, A.S. Kideny Int.: Low incidence of IgA nephropathy in blacks. 28:944-950, 1985.
89. Julian, B.A., Quiggins, P.A., Thompson, J.S., Woodford, S.Y., Gleason, K. and Wyatt, R.J.: Familial IgA nephropathy. Evidence for an inherited mechanism of disease. N. Eng. J. Med. 312:202-208, 1985.
90. Wyatt, R.J., Rivas, M.L., Julian, B.A., Quiggins,

P.A., Woodford, S.Y., McMorrow, R.G. and Beahler, R.W.: Regionalization in hereditary IgA nephropathy. Am. J. Hum. Genet. 41:36-50, 1987.

91. Julian, B.A., Phillips, J.A.III., Orlando, P.J., Wyatt, R.J. and Butler, M.G.: Analysis of immunoglobulin heavy chain restriction fragment length polymorphisms in IgA nephropathy. Seminar in Nephrol. 7:306-310, 1987.
92. Rambausek, M., Knight, J.F., Williams, D.G., Welsh, K.I., Ritz, E. and Demaine, A.G.: Relation of mesangial IgA-GN to polymorphism of immunoglobulin heavy chain switch region. In: Proceedings of the Xth International Congress of Nephrology (Ed. J.S. Cameron), London, 1987, p. 400.
93. Davin, J.D., Malaise, M., Foidart, J.B. and Mahieu, P.: Evidence that carbohydrates of the Fc domain of IgA are involved in the formation of large IgA-immune complexes in IgA-associated nephropathies. In: Proceedings of the Xth International Congress of Nephrology (Ed. J.S. Cameron), London, 1987, p. 322.
94. DeWerra, P., Morel-Marogeer, L., Leroux-Robert, C. and Richet, P.: Glomerulites a depots d'IgA diffus dans le mesangium. Schweiz. Med. Wochenschr. 761-768, 797-803, 1973.
95. Sissons, J.G., Woodrow, D.F., Curtis, J.G., Evans, D.J., Goover, P.E. and Slopper, J.G.: Isolated glomerulonephritis with mesangial IgA deposits. Br. Med. J. iii:611-614, 1975.
96. Tolkoff-Rubin, N.E., Cosimi, A.B., Fuller, T., Rubin, R.H. and Colvin, R.B.: IgA nephropathy in HLA-identical siblings. Transplantation 26:430-433, 1978.
97. Yoshikawa, T., Ito, H., Nakahara, C., Yoshihara, S., Yoshiya, K., Matsuo, T., Hasegawa, O., Hazikano, H. and Okada, S.: Glomerular electron-dense deposits in childhood IgA nephropathy. Virchows Arch. A. 406:33-43, 1985.
98. Hogg, R.J. and Silva, F.G.: IgA nephropathy in children. In: IgA Nephropathy (Ed. A.R. Clarkson), Martinus Nijhoff Publishing, Boston, Dordrecht and Lancaster, 1987, pp. 16-38.
99. Droz, D.: IgA nephropathy: clinicopathological correlations. ibid. pp. 97-107.
100. D'Amico, G., Minetti, L., Ponticelli, C., Fellin, G., Ferrario, F., Barbiano di Belgioioso, G., Imbasciati, E., Ragni, A., Bertoli, S., Fogazzi, G. and Duca, G.: Prognostic indicators in idiopathic IgA mesangial nephropathy. Quart. J. Med. New Series 59:363-378, 1986.
101. Tojo, S., Narita, M., Miyahara, T., Sakai, O., Ohno, J., Soeda, N., Honda, N., Nagase, M., Sibata, M., Orita, Y., Ishikawa, H., Hara, K. and Sakuma, A.: Manseisikyuutaijinen ni taisuru trimetazidine

dihydrochloride no rinshokouka. Jin to Toseki 19:1367-1380, 1985.
102. Tojo, S., Honda, N., Sibata, M., Narita, M., Miyahara, T., Sakai, O., Katoh, E., Kida, H., Orita, Y., Ishikawa, H., Hara, K., Tanaka, T. and Takasaki, H.: Manseisikyuutaijinen ni tausuru AS-05 (Dilazep) no rinshouhyouka. Jin to Toseki 20:289-313, 1986.
103. Kobayashi, Y., Fujii, K., Hiki, Y. and Tateno, S.: Steroid therapy in IgA nephropathy: A prospective pilot study in moderate proteinuric cases. Quart. J. Med. New Series 61:935-943, 1986.
104. Laurent, J., Belghiti, D., Bruneau, C. and Lagrue, G.: Diclofenac, a nonsteroidal anti-inflammatory drug, decreases proteinuria in some glomerular diseases: A controlled study. Am. J. Nephrol. 7:198-202, 1987.
105. Hamazaki, T., Tateno, S. and Shishido, H.: Eicosapentaenoic acid and IgA nephropathy. Lancet i: 1017-1018, 1984.
106. Tomino, Y., Miura, M., Suga, T., Endoh, M., Nomoto, Y. and Sakai, H.: Defibrination of intraglomurular fibrin deposits by urokinase in patients with IgA nephropathy. Jpn. J. Nephrol. 26:275-280, 1984.
107. Miura, M., Tomino, Y., Yagame, M., Inoue, W., Suga, T., Nomoto, Y. and Sakai, H.: Significant correlation between the immunofluorescence of alpha 2-plasmin inhibitor in glomeruli and the effects of urokinase therapy in patients with IgA nephropathy. Annals Acad. Med. 15:255-257, 1986.
108. Tomino, Y., Sakai, H., Suga, T., Miura, M., Kaneshige, H., Endoh, M. and Nomoto, Y.: Impaired solubilization of glomerular immune deposits by sera from patients with IgA nephropathy. Am. J. Kidney Dis. 3:48-53, 1983.
109. Tomino, Y., Sakai, H., Woodroffe, A.J. and Clarkson, A.R.: Studies on glomerular immune solubilization by complement in patients with IgA nephropathy. Acta Pathol. Jpn. 37:1763-1767, 1987.
110. Tomino, Y., Sakai, H., Miura, M., Suga, T., Endoh, M. and Nomoto, Y.: Effect of danazol on solubilization of immune deposits in patients with IgA nephropathy. Am. J. Kidney Dis. 4:135-140, 1984.
111. Tomino, Y., Sakai, H., Hanzawa, S., Ohno, J., Kitajima, T. and Sakai, O.: Clinical effect of Danazol in patients with IgA nephropathy. Jpn. J. Med. 26:162-166, 1987.
112. Beukhof, H.R., ter Wee, P.M., Sluiter, W.J. and Donker, A.J.M.: Effect of low-dose dopamine on effective renal plasma flow and glomerular filtration rate in 32 patients with IgA nephropathy. Am. J. Nephrol. 5:267-270, 1985.
113. Lopez-Trascasca, M., Egido, J., Sancho, J. and Hernando, L.: Evidence of high polymeric IgA levels

in serum of patients with Berger's disease and its modification with phenytoin treatment. Proc. Eur. Dial. Transplant. Assoc. 16:513, 1979.
114. Clarkson, A.R., Seymour, A.E., Woodroffe, A.J., McKenzie, P.E., Chan, Y-L. and Wootton, A.M.: Controlled trial of phenytoin therapy in IgA nephropathy. Clin. Nephrol. 13:215-218, 1980.
115. Coppo, R., Blasco, B., Bulzomi, M.R. and Piccoli, G.: Ineffectiveness of phenytoin treatment on IgA-containing circulating immune complexes in IgA nephropathy. Nephron 36:275-276, 1984.
116. Coppo, R., Basolo, B., Giachino, O., Rocatelli, D., Lajola, D., Mazzucco, G., Amore, A. and Picoli, G.: Plasmapheresis in a patient with rapidly progressive idiopathic IgA nephropathy: removal of IgA-containing immune complexes and clinical recovery. Nephron 40:488-490, 1985.
117. Clarkson, A.R.: The treatment of IgA nephropathy. In: IgA Nephropathy (Ed. A.R. Clarkson), Martinus Nijhoff Publishing, Boston, Dordrecht and Lancaster, 1987, p. 219.
118. Cameron, J.S. and Turner, D.R.: Recurrent glomerulonephritis in allografted kidneys. Clin. Nephrol. 7:47-51, 1977.

INFECTIONS

3

SINGLE-DOSE ANTIBIOTIC THERAPY IN URINARY TRACT INFECTION.

W. BRUMFITT and J.M.T. HAMILTON-MILLER

Department of Medical Microbiology, The Royal Free Hospital and School of Medicine, London NW3 2QG, England.

INTRODUCTION

As recently as the early 1960's urinary infections were often treated with antibiotics for six months or more - perhaps changing the antibiotic every month. This was due to the belief that such infections often progressed to chronic pyelonephritis, a view discredited by the studies of Kimmelstiel (1).

Subsequently the length of treatment and the dosage used became shorter but still arbitrary, despite clinical trials showing that the duration of treatment was often still excessive. For example Kincaid-Smith and Fairley (2) found that for chronic urinary infection a 2-week course of ampicillin was as effective as a 6-week course. In uncomplicated infections a 5-day course of ampicillin produced a 85% cure rate (3). Charlton et al. (4) showed that in uncomplicated infections in general practice a 3-day and 10-day course gave similar results.

Nevertheless at present patients with many varieties of urinary infection receive a therapeutic course of 5 to 10 days in the United Kingdom whereas 10 to 14 days seems to be preferred in the United States (5).

Recent work has now shown that these periods may be unnecessarily long, and are undesirable in terms of expense, side-effects and the selection of antibiotic-resistant bacteria. Therefore, shortened courses of antibiotic treatment have been suggested with single-dose treatment (SDT) as the logical end-point.

Urinary infection is associated with a number of clearly defined clinical syndromes and so is not a simple entity. When discussing

the management of urinary infection patient groups must be defined accurately.

The most widely studied group in respect of SDT has been women with "simple" infections, who suffer acute dysuria and/or frequency with an infection acquired outside hospital. There are over one million per year such patients in the United Kingdom alone, and this group is suitable for trials of new treatment regimens. Spontaneous cure occurs in over 50% of these patients, within 3 days. The expected cure rate following antibiotic treatment is at least 85%, and the consequences of failure of treatment (should the regimen prove inadequate) are usually not serious, although the occasional patient progresses to acute pyelonephritis.

Many studies have now shown that the length of treatment in "simple" infections may be reduced to a single dose of an appropriate compound without discernible loss of therapeutic efficacy (6). However, practitioners have been slow to accept this policy as they are reasonably wary of altering therapeutic regimens which they know are effective. The family practitioner's choice of length of treatment may be influenced by the need to avoid criticism (or worse) from patients should SDT fail. For obvious reasons pharmaceutical companies may view with apprehension the introduction of SDT instead of the current practice of giving the antibiotic for 5 days. At present in the UK no single-dose regimens are recommended (7).

THE DEVELOPMENT OF SINGLE-DOSE TREATMENT

This approach dates back to 1967 when Grüneberg & Brumfitt (8) showed that a single dose (2 g) sulfadoxine (sulphormethoxine) was as effective as a conventional 7-day course of ampicillin in simple urinary infections but produced less side-effects. The use of a long-acting sulphonamide ($t_{\frac{1}{2}}$=150 hr) meant that inhibitory concentrations of antibiotic in the urine were maintained for 7 days.

The effect of reducing the time for which an effective concentration of antibiotic was present in the urine was next investigated. Brumfitt et al. (9) used one dose of 2 g cephaloridine IM, which made the urine antibacterial for at least 12 hours. However,

results in "simple" infections were unsatisfactory, a cure rate of only 35% being achieved (it is interesting to note that in none of the studies done subsequently has a cephalosporin proved adequate for SDT - see below). Brumfitt et al. (9) also showed that patients with renal involvement (judged by raised titres of anti-O antibodies) were rarely cured by SDT. Ronald et al. (10) reached the same conclusion using a bladder wash-out technique to localise infection and a single IM injection of 500 mg kanamycin for treatment: 92% of female patients with infections confined to the bladder were cured but only 28% of those with upper tract involvement.

Bailey & Abbott (11) were the first to test a conventional oral agent with a short half-life for SDT: one large dose of amoxycillin (3 g) was as effective as a 5- to 7-day course (250 mg tds). Although a small study (only 20 adult women being assessed) this was nevertheless an important landmark.

ANALYSIS OF PUBLISHED STUDIES OF SDT IN "SIMPLE" INFECTIONS.

Few of the many studies carried out using SDT have been planned, executed and analysed satisfactorily (12,13). The efficacy of treatment is becoming clear only for amoxycillin and co-trimoxazole, and even for these the minimal effective dose has not been agreed upon. It is doubted whether the results obtained in "simple" infections can be extrapolated to other patient groups.

It is essential to have adequate microbiological follow-up: the first follow-up must take place within a week of the end of treatment, allowing sufficient time for the antibiotic to be eliminated from the urine. For example, for a potent antibiotic with a long half-life such as trimethoprim (MIC < 1 µg/ml, $t_{\frac{1}{2}}$ c. 10 h) it will take as long as 5 days for the urine to cease being antibacterial following SDT. Thus SDT with trimethoprim would be analogous to giving an antibiotic with a short half-life (eg., amoxycillin) for 5 days. Follow-up earlier than before 7 days post treatment may give misleading results. A second follow-up should be carried out one month later when a small but significant number of patients with simple infections will have relapsed. Relapse (the reappearance of the original infecting organisms) must be differentiated from

reinfection (the appearance of a different pathogen) - otherwise proper analysis of treatment is impossible. While a relapse is a failure of antibiotic therapy, reinfection is not, usually indicating a defect in the host defence system. Detection of relapse is especially important in view of reports that this may occur more frequently after SDT (14,15).

We have analysed 7 fully randomized "like versus like" comparative studies carried out in women with "simple" infections, where follow-up has been carried out at least 4 weeks after the end of treatment, and in which numbers of patients in each group exceeded 20.

** SDT with co-trimoxazole is as effective as a 3- to 10-day course (16,17). Schultz et al. (15) found a significantly higher incidence of relapse following SDT.

** Cefaclor and cefadroxil are inferior in single dose to a conventional course (17,18).

** Leigh et al. (19) found a single dose of amoxycillin (3 g) inadequate.

** Nitrofurantoin is as effective in a single dose as in a 10-day course (20).

Philbrick and Bracikowski (12) have pooled data from several similar trials (which may or may not be valid), and conclude that SDT with amoxycillin 3 g gives less satisfactory results than are obtained with conventional treatment, while for co-trimoxazole there was no significant difference between the two regimens.

Studies using a less rigorous protocol, but still having at least 20 patients in each group, show that several more regimens are also satisfactory for SDT. However, few, if any, trials of SDT have involved large enough numbers of patients to avoid a large beta-error, which means that there is a danger of a significant difference between groups being missed because the study groups were too small. Several studies report good results using single dose amoxycillin (eg., 14, 21-24) or trimethoprim, a sulphonamide or the combination (21,25,26). In addition, SDT with cephalexin (3 g), kanamycin (0.5 g), sulfadoxine (2 g), fosfomycin trometamol (3 g) and tetracycline (2 g) were found satisfactory (8,10,27-29) while single doses of cyclacillin (3 g) or cephaloridine (2 g) were unsatisfactory (9,30).

SINGLE-DOSE THERAPY FOR OTHER THAN "SIMPLE" INFECTIONS.

There are several classes of urinary infection for which SDT will clearly be unsuitable - eg., in prostatitis, where at least 4-weeks therapy is required (31), and in acute uncomplicated pyelonephritis for which a minimum of 5 days therapy is needed (32). However, the success of SDT in "simple" infections has led to its use in bacteriuria in pregnancy and paediatric infections.

Bacteriuria in pregnancy.

The cure rate in this condition with conventional treatment is considerably lower (70 - 75%) than that found in "simple" infections (at least 85%). One of the earliest studies in pregnant patients was carried out by Williams et al. (33) using a long-acting sulphonamide. They obtained different results in two cities - a cure rate of 79% in London, but only 59% in Birmingham. This difference was thought to be due to non-compliance owing to language difficulties in the Birmingham study. Williams & Smith (34) found that the combination of a long acting sulphonamide and a single dose of streptomycin (1 g IM) gave a cure rate which was superior (77%) to that achieved by either antibiotic alone. Brumfitt et al. (9) reported a cure rate of only 52% following a single dose of 2 g cephaloridine; almost all the failures occurred in patients with elevated titres of O antibodies, suggesting renal involvement.

More recent studies with short-acting oral compounds have given mixed results. Harris et al. (35) reported an unacceptably high failure rate (45%) using 2 g cephalexin + probenicid, but their results with three other regimens were satisfactory (2 g ampicillin + probenicid, 200 mg Macrodantin, 2 g sulphafurazole), the cure rates being between 71 and 75%. Campbell-Brown & McFadyen (36) in a non-comparative study of 37 patients obtained an overall cure rate of 70% after 3 g of cephalexin. Masterson et al. (37) found a cure rate of 88% using 3 g amoxycillin.

Differences observed with the various antibiotics and doses used, as well as the potential risk to mother and foetus, indicate the need for further studies before SDT can be recommended in pregnancy.

Children

Kallenius & Winberg (38) treated 29 girls aged 6 - 14 y with

200 mg/kg sulphafurazole (an average 10 yr old child of 30 kg would thus receive 6 g of antibiotic). The cure rate was at least 93%; no mention was made of side-effects. Avner et al. (39) randomized 49 children aged 2½ - 14 yr, predominantly female, to treatment with either single dose amoxycillin (1 - 3 g depending on weight) or a 10-day course of conventional dosage: the SDT cured significantly fewer patients (63% vs 92%, $P < 0.01$). In contrast Shapiro & Wald (40) studying a similar group of 35 children found no significant difference in cure rates following either a single dose or a conventional course of amoxycillin. Wallen et al. (41) compared sulphafurazole in conventional dosage for 10 days with one IM injection of amikacin (7.5 mg/kg) in a group of girls aged 1 - 12 yr. Cure rates were not significantly different.

Since the first urinary infection in a female child may indicate vesico-ureteric reflux or other abnormality it can be argued that such infections are unsuitable for SDT: a 5-day course of treatment followed by appropriate investigations are advised.

It is unclear from available evidence whether SDT is suitable for female children, and the need for more carefully controlled studies is apparent.

POSSIBLE ADVANTAGES OF SINGLE-DOSE TREATMENT.

It is easy to visualise several advantages of reducing the total antibiotic dose. Unfortunately, the most important of those to be discussed below have often been assumed to be self-evident, and actual field testing has only rarely been carried out.

Ecological effects.

There are strong theoretical grounds and indirect evidence (42) to assume that restricting antibiotic therapy will limit the selection of resistant bacteria. However, there are little, if any, convincing data relating to SDT to give specific support to this proposal. Anderson et al. (43) reported that a 7-day course of amoxycillin (250 mg tds) caused patients' faecal coliforms to become resistant, but that a single 1 g dose did not. Fair et al. (5) suggested that a 1-day course of co-trimoxazole selected resistant periurethral flora, but Pfau et al. (44) found little or no differ-

ence between the ecological effects of 1- and 10-day courses of treatment.

Our own observations (45) that trimethoprim-resistant faecal E. coli strains are acquired at a constant and predictable rate in patients taking 100 mg trimethoprim each night supports the ecological desirability of limiting the length of treatment. There seems no advantage in terms of avoiding the selection of resistant flora by combining trimethoprim with a sulphonamide (46).

Further, ampicillin (and presumably amoxycillin) acts as an excellent selective agent not only for resistance to itself but also to tetracycline (47). Selection of multiple resistance is clearly undesirable and every effort should be made to avoid this dangerous outcome.

Side effects.

It has been widely assumed, without much evidence, that with shorter courses of treatment the incidence of side-effects will be lower. In practice, variable results have been obtained. This is because firstly, most studies have been too small to have much statistical power (due to beta-error), secondly, some side-effects, such as immunological phenomena, are not dose-related, and thirdly a specific side-effect may be due not to the total antibiotic load summated over a period of several days, but to the size of each individual challenge dose.

In 5 comparative studies (involving amoxycillin, tetracycline, nitrofurantoin, cefaclor and co-trimoxazole) a significant reduction in adverse effects has been shown between a conventional and either a shortened course or SDT (14-16, 18,20,29). In a further 5 instances (11,17,22,48) however, no statistically significant differences were observed with cefadroxil, co-trimoxazole (3 studies) and amoxycillin. Leigh et al. (19) found that a single dose of 3 g amoxycillin caused a significantly greater incidence of diarrhoea than a conventional course (250 mg tds for 10 days). Rosenstock et al. (29) reported nausea in patients taking 2 g tetracycline in one dose but not in those taking 2 g in four divided doses (of 500 mg). Paradoxically, they also found severe nausea after 5 days in patients taking tetracycline in a conventional dosage.

It is difficult to make proper comparisons between the incidence of side-effects in different studies, unless standard methodology is used, because the assessment of an "adverse effect" varies widely.

Costs.

The simplistic proposition that "less costs less" is not always true. The cost of a course of antibiotic treatment is not a reflection only of the price of the raw material. Special packs may be used (eg., a 3 g sachet of amoxycillin) and there may be a flat-rate dispensing fee. In the UK under the National Health Service, a single course of treatment costs the patient £2.80 whether the prescription is for one dose, one hundred doses or more. However, in most cases where the patient pays for the drug it may be assumed that shorter courses are less expensive that conventional ones. Formal cost analyses have been carried out by Fair et al. (5), Wong et al. (49) and Schultz et al. (15) among others. However, the absence of a generally available SDT regimen makes it impossible to make a factual comparison at present.

Compliance.

There is circumstantial evidence for the idea that patients comply better with a shorter course of treatment (50). Compliance can only be assured with SDT if the patient is handed the medication and is seen to swallow it (28) or it is administered parenterally at the time (9,10). There is no guarantee that patients who collect their medication at a Pharmacy, even if it is only a single dose, will take it as directed.

Unfortunately in most studies the authors fail to state whether the single dose was taken under supervision or not. This information may be very important in judging compliance which could effect the philosophy of SDT.

PHARMACODYNAMIC FACTORS IN SDT

For infections confined to the bladder urine, the major determinant to the outcome of treatment is the concentration and antibacterial activity of the antibiotic in the urine (51). There is no evidence that a bactericidal action is necessary in order to cure a lower tract infection. A bacteriostatic activity combined

with the hydrokinetic effect of a normal urine excretion by the kidneys (about 1 ml/min) and regular bladder emptying should be sufficient to clear the bladder of bacteria, in the absence of complicating factors. Since most antibiotics are concentrated by the kidneys, attaining levels in the urine sufficient to prevent bacterial multiplication is not difficult, even using very small doses of reasonably well absorbed antibiotics by mouth. Moreover, a single dose of an antibiotic having a comparatively short half-life enables antibacterial levels in the urine to be maintained for a relatively long time. Thus, Ronald et al. (10) state that kanamycin ($t_{\frac{1}{2}}$=2.5 hr) provides bactericidal urine for 24 hr after a 500 mg IM dose, and Kallenius & Winberg (38) report a figure of 36 hr following sulphafurozole ($t_{\frac{1}{2}}$=6 hr).

Several studies have shown (52,53,54) that viable bacteria are very rapidly removed from the bladder when treatment starts, even using a very small dose of a wide variety of antibiotics. However, factors such as incomplete bladder emptying may prevent such success. For a compound with a longer half-life such as trimethoprim (10 hr) a single dose can give an antibacterial level in the urine for up to 5 days. Increasing the dose has surprisingly little effect: while 250 mg of amoxycillin provides antibacterial urine for up to 10 hr, a 2.5 g dose only increased the antibacterial effect by 4 hours (55). The clear implication of this is that a 3 g amoxycillin dose is not economical, or necessary for successful treatment.

A large dose of antibiotic may even be less effective than a smaller dose. Both beta-lactams and quinolones are less bactericidal at higher concentrations (eg., MIC x 1000) than at lower concentrations (eg., MIC x 10). Gould et al. (52) found that very small doses of streptomycin (0.2 - 22.5 mg) or tetracycline (0.8 - 2.4 mg) given 6-hourly for 5 days or less were sufficient to cure urinary infections.

Thus the available experimental and clinical evidence suggests that large doses are not necessarily required for effective SDT. In particular, 3 g amoxycillin may be excessive.

FACTORS AFFECTING OUTCOME OF SHORTENED COURSE TREATMENT.

Bacterial resistance.

In many reports patients with bacteria resistant to the antibiotics used have either been excluded from analysis or have been too few in number for meaningful conclusions to be drawn. Of the 5 studies specifically addressing this problem, in only 1 (24) were significantly reduced cure rates associated with resistant strains (amoxycillin). Other studies - using amoxycillin or ampicillin (17,22,26), cephalosporins (17,27), co-trimoxazole (26) or tetracycline (29) - did not find that "bacterial resistance" (as judged by conventional disc testing) increased the failure rate when using SDT. On the other hand, when a long-acting sulphonamide was used, patients infected with resistant strains often failed (3,34).

The very high levels of beta-lactam antibiotics found in the urine make results of standard laboratory sensitivity tests (using a 30 μg disc) invalid. However, a somewhat different situation applies to trimethoprim. Strains resistant to trimethoprim can grow in the presence of at least 1 mg/ml, which greatly exceeds attainable urine levels. Plasmid mediated resistance to trimethoprim is high in some countries - eg., c. 30% has been found in London (56) - and consequently SDT with trimethoprim may fail. Combination with a sulphonamide will not help this situation, as most trimethoprim-resistant strains are also highly sulphonamide-resistant (56).

Antibody-coating of bacteria (ACB).

In some studies (14,25) results of the ACB test were helpful in predicting patients less likely to respond to SDT. However, in other trials (15,22,29,30) this test was not found useful. This disagreement is due to the lack of standardized methodology (57). Greenberg et al. (17,18) used various criteria for scoring a positive test, and concluded that even this complicated procedure was not helpful. Thus a potentially useful test is only of value to those in the particular service when the test is done.

Patient characteristics.

Measurement of resistance and carrying out the ACB test give results which are not available to the clinician until after the

patient has left the consulting room. They are thus of no help in immediate decision-making for those patients who require treatment. The physician has to rely on the patients' history, the clinical examination, their previous medical records and the results of any rapid test on the urine, if done. Symptoms may be deceptive, as it is well known that bacteriuria may be asymptomatic. By contrast, less than 50% of symptomatic patients have a significant bacteriuria (58).

SUMMARY

In "simple" infections in non-pregnant women SDT can be as effective as a conventional course of antibiotics. Co-trimoxazole appears to be the drug of choice at present but the minimum effective dosage is still unclear. The efficacy of amoxycillin (most commonly given in a 3 g dose) was not proven, and cephalosporins seem to be unsuitable for single-dose use. Other agents, such as fosfomycin trometamol and the quinolones (given orally) need to be tested further (59). It is particularly important to ensure that patients given SDT are properly followed up after treatment since the early detection of failure and alternative therapy measures, possibly followed by investigation, is essential.

SDT is unsuitable for febrile patients who have loin pain or tenderness suggesting renal involvement. The same applies to males or women with recurrent infections or with known abnormalities of the urinary tract. Bacterial prostatitis is an absolute contra-indication. In pregnancy and in childhood until more data is available SDT should be used with caution and only where continuous supervision is assured.

REFERENCES

1. Kimmelstiel, P. Significance of chronic pyelonephritis. In: Biology of Pyelonephritis (Eds. E.L. Quinn and E.H. Kass) Churchill, London, pp. 215-224, 1960.
2. Kincaid-Smith, P. and Fairley, K.F. Controlled trial comparing effect of two and six weeks' treatment of recurrent urinary tract infection. Brit. Med. J. ii: 145-146, 1969.
3. Brumfitt, W., Percival, A. and Carter, M.J. Treatment of urinary-tract infections with ampicillin: a clinical trial. Lancet i: 130-133, 1962.
4. Charlton, C.A.C., Crowther, A., Davies, J.G., Dynes, J., Haward, M.W.A., Mann, P.G. and Rye, S. Three-day and ten-day chemotherapy for urinary tract infections in general practice. Brit. Med. J. i: 124-126, 1976.
5. Fair, W.R., Crane, D.B., Peterson, L.J., Dahmer, C., Tague, B. and Amos, W. Three-day treatment of urinary tract infections. J. Urol. 123: 719-721, 1980.
6. Bailey, R.R. Single dose therapy of urinary tract infection. Adis Health Science Press, Sydney, 1983.
7. ABPI Data Sheet Compendium 1988-89. Datapharm, London, 1988.
8. Grüneberg, R.N. and Brumfitt, W. Single-dose treatment of acute urinary tract infection: a controlled trial. Brit. Med. J. 3: 649-651, 1967.
9. Brumfitt, W., Faiers, M.C. and Franklin, I.N.S. The treatment of urinary infection by means of a single dose of cephaloridine. Postgrad. Med. J. 46: (Suppl) 65-68, 1970.
10. Ronald, A.R., Boutros, P. and Mourtada, H. Bacteriuria localization and response to single-dose therapy in women. J. Amer. Med. Ass. 235: 1845-1846, 1976.
11. Bailey, R.R. and Abbott, G.D. Treatment of urinary tract infection with a single dose of amoxycillin. Nephron 18: 316-320, 1977.
12. Philbrick, J.T. and Bracikowski, J.P. Single-dose antibiotic treatment for uncomplicated urinary tract infections. Arch. Int. Med. 145: 1672-1678, 1985.
13. Souney, P and Polk, B.F. Single-dose antimicrobial therapy for urinary tract infections in women. Rev. Infect. Dis. 4: 29-34, 1982.
14. Fang, L.S.T., Tolkoff-Rubin, N.E. and Rubin, R.H. Efficacy of single-dose and conventional amoxicillin therapy in urinary-tract infection localized by the antibody-coated bacteria technic. N. Eng. J. Med. 298: 413-416, 1978.
15. Schultz, H.J., McCaffrey, L.E., Keys, T.F. and Nobrega, F.T. Acute cystitis: a prospective study of laboratory tests and duration of therapy. Mayo Clin. Proc. 59: 391-397, 1984.
16. Gossius, G. and Vorland, L. A randomized comparison of single-dose vs. three-day and ten-day therapy with trimethoprim-sulfamethoxazole for acute cystitis in women. Scand. J. Infect. Dis. 16: 373-379, 1984.
17. Greenberg, R.N., Reilly, P.M., Luppen, K.L., Weinandt, W.J., Ellington, L.L. and Bollinger, M.R. Randomized study of single-dose, three-day, and seven-day treatment of cystitis in women. J. Infect. Dis. 153: 277-282, 1986.

18. Greenberg, R.N., Sanders, C.V., Lewis, A.C. and Marier, R.L. Single-dose cefaclor therapy of urinary tract infection: evaluation of antibody-coated bacteria test and C-reactive protein assay as predictors of cure. Amer. J. Med. 71: 841-845, 1981.
19. Leigh, D.A., Marriner, J. and Fabb, J. Treatment of domiciliary urinary tract infections with a single dose of amoxycillin J. Antimicrob. Chemother. 5: 403-405, 1980.
20. Gossius, G. Single-dose nitrofurantoin therapy for urinary tract infections in women. Curr. Ther. Res. 35: 925-931, 1984.
21. Harbord, R.B. and Grüneberg, R.N. Treatment of urinary tract infection with a single dose of amoxycillin, co-trimoxazole, or trimethoprim. Brit. Med. J. 283: 1301-1302, 1981.
22. Savard-Fenton, M., Fenton, B.W., Reller, L.B., Lauer, B.A. and Byyny, R.L. Single-dose amoxicillin therapy with follow-up urine culture. Amer. J. Med. 73: 808-813, 1982.
23. Rubin, R.H., Fang, L.S.T., Jones, S.R., Munford, R.S., Slepack, J.M., Varga, P.A., Onheiber, L., Hall, C.L. and Tolkoff-Rubin, N.E. Single-dose amoxicillin therapy for urinary tract infection. J. Amer. Med. Ass. 244: 561-564, 1980.
24. Tolkoff-Rubin, N.E., Wilson, M.E., Zuromskis, P., Jacoby, I., Martin, A.R. and Rubin, R.H. Single-dose amoxicillin therapy for acute uncomplicated urinary tract infections in women. Antimicrob. Ag. Chemother. 25: 626-629, 1984.
25. Buckwold, F.J., Ludwig, P., Harding, G.K.M., Thompson, L., Slutchuk, M., Shaw, J. and Ronald, A.R. Therapy for acute cystitis in adult women. J. Amer. Med. Ass. 247: 1839-1842, 1982.
26. Dubi, J., Chappuis, P.H. and Darioli, R. Traitment de l'infection urinaire par une dose unique de co-trimoxazole comparee a une dose unique d'amoxycilline et a un placebo. Schweiz. med. Wschr. 112: 90-92, 1982.
27. Cardenas, J., Quinn, E.L., Rooker, G., Bavinger, J. and Pohlod, D. Single-dose cephalexin therapy for acute bacterial urinary tract infections and acute urethral syndrome with bladder bacteriuria. Antimicrob. Ag. Chemother. 29: 383-385, 1986.
28. Cooper, J., Raeburn, A., Brumfitt, W. and Hamilton-Miller, J.M. T. Single-dose fosfomycin trometamol compared with a 5-day course of Augmentin in the treatment of urinary infection in general practice. Brit. Med. J. (in press) 1988.
29. Rosenstock, J., Smith, L.P., Gurney, M., Lee, K., Weinberg, W. G., Longfield, J.N., Tauber, W.B. and Karney, W.W. Comparison of single-dose tetracycline hydrochloride to conventional therapy of urinary tract infections. Antimicrob. Ag. Chemother 27: 652-654, 1985.
30. Hooton, T.M., Running, K. and Stamm, W.E. Single-dose therapy for cystitis in women. J. Amer. Med. Ass. 253: 387-390, 1985.
31. Krieger, J.N. Prostatitis syndromes: pathophysiology, differential diagnosis, and treatment. Sex. Trans. Dis. 11: 100-112, 1984.
32. Bailey, R.R. and Peddie, B.A. TReatment of acute urinary tract infection in women. Ann. Int. Med. 107: 430, 1987.

33. Williams, J.D., Reeves, D.S., Condie, A.P., Franklin, I.N.S., Leigh, D.A. and Brumfitt, W. The treatment of bacteriuria in pregnancy. In: Urinary Tract Infection (Eds. F. O'Grady and W. Brumfitt) Oxford University Press, 1968, pp. 160-168.
34. Williams, J.D. and Smith, E.K. Single dose therapy with streptomycin and sulfamethopyrazine for bacteriuria during pregnancy. Brit. Med. J. 4: 651-653, 1970.
35. Harris, R.E., Gilstrap, L.C. and Pretty, A. Single-dose antimicrobial therapy for asymptomatic bacteriuria during pregnancy. Obs. Gynecol. 59: 546-548, 1981.
36. Campbell-Brown, M. and McFadyen, I.R. Bacteriuria in pregnancy treated with a single dose of cephalexin. Brit. J. Obs. Gynaecol. 90: 1054-1059, 1983.
37. Masterton, R.G., Evans, D.C. and Strike, P.W. Single-dose amoxycillin in the treatment of bacteriuria in pregnancy and the puerperium - a controlled clinical trial. Brit. J. Obs. Gynaecol. 92: 498-505, 1985.
38. Kallenius, G. and Winberg, J. Urinary tract infections treated with single dose of short-acting sulphonamide. Brit. Med. J. i: 1175-1176, 1979.
39. Avner, E.D., Ingelfinger, J.R., Herrin, J.T., Link, D.A., Marcus, E., Tolkoff-Rubin, N.E., Russell-Getz, L. and Rubin, R.H. Single-dose amoxicillin therapy of uncomplicated pediatric urinary tract infections. J. Pediat. 102: 623-627, 1983.
40. Shapiro, E.D. and Wald, E.R. Single-dose amoxicillin treatment of urinary tract infections. J. Pediat. 99: 989-992, 1981.
41. Wallen, L., Zeller, W.P., Goessler, M., Connor, E. and Yogev, R. Single-dose amikacin treatment of first childhood E. coli lower urinary tract infections. J. Pediat. 103: 316-319, 1983.
42. Stuart-Harris, C.H. and Harris, D.M. The Control of Antibiotic -Resistant Bacteria. Academic Press, London, 1982.
43. Anderson, J.D., Aird, M.Y., Johnson, A.M., Ree, R., Goresky, D., Brumwell, C.A. and Percival-Smith, R.K.L. The use of a single 1 g dose of amoxycillin for the treatment of acute urinary tract infection. J. Antimicrob. Chemother. 5: 481-483, 1979.
44. Pfau, A., Sacks, T.G., Shapiro, A. and Shapiro, M. A randomized comparison of 1-day versus 10-day antibacterial treatment of documented lower urinary tract infection. J. Urol. 132: 931-933, 1984.
45. Brumfitt, W., Smith, G.W., Hamilton-Miller, J.M.T. and Gargan, R.A. A clinical comparison between Macrodantin and trimethoprim for prophylaxis in women with recurrent urinary infections. J. Antimicrob. Chemother. 16: 111-120, 1985.
46. Lacey, R.W., Lord, V.L., Gunasekera, H.K.W., Lieberman, P.J. and Luxton, D.E.A. Comparison of trimethoprim alone with trimethoprim-sulphamethoxazole in the treatment of respiratory and urinary infections with particular reference to selection of trimethoprim resistance. Lancet i: 1270-1273, 1980.
47. Datta, N., Faiers, M.C., Reeves, D.S., Brumfitt, W., Orskov, F. and Orskov, I. R factors in Escherichia coli in faeces after oral chemotherapy in general practice. Lancet i: 312-315, 1971.

48. Bailey, R.R. and Blake, E. Treatment of uncomplicated urinary tract infections with a single dose of co-trimoxazole. N.Z. Med. J. 92: 285-286, 1980.
49. Wong, E.S., McKevitt, M., Running, K., Counts, G.W., Turck, M. and Stamm, W.E. Management of recurrent urinary tract infections with patient-administered single-dose therapy. Ann. Int. Med. 102: 302-307, 1985.
50. Gately, M.S. To be taken as directed. J. Roy. Coll. Gen. Practit. 16: 39-44, 1968.
51. Jackson, G.G. Methods for the clinical evaluation of antibiotics in urinary tract infections. Scand. J. Infect. Dis. 14: 289-294, 1978.
52. Gould, J.G., Bowie, J.H. and Cameron, J.D.S. Dosage of antibiotics: relation between the in vitro and in vivo concentrations effective in urinary-tract infections. Lancet i: 361-364, 1953.
53. Cattell, W.R., Sardeson, J.M., Sutcliffe, M.B. and O'Grady, F. Kinetics of urinary bacterial response to antibacterial agents. In: Urinary Tract Infections (Eds. F. O'Grady and W. Brumfitt) Oxford University Press, pp. 212-225, 1968.
54. Suzuki, K., Naide, Y., Fujita, T., Okishio, N., Asano, H., Yamakoshi, T. and Okada, K. Comparative clinical studies of single-dose cefatrizine and cephalexin in treatment of acute uncomplicated cystitis. In: Current Chemotherapy and Infectious Diseases (Eds. J.D. Nelson and C. Grassi) American Society of Microbiology, Washington DC, pp. 1295-1297, 1980.
55. Brumfitt, W. and Hamilton-Miller, J.M.T. The optimal duration of antibiotic treatment of urinary infections. In: Urinary Tract Infections. Karger, Basel, in press. 1988.
56. Hamilton-Miller, J.M.T. and Purves, D. Trimethoprim resistance and trimethoprim usage in and around The Royal Free Hospital in 1985. J. Antimicrob. Chemother. 18: 643-644, 1986.
57. Gargan, R.A., Brumfitt, W. and Hamilton-Miller, J.M.T. Antibody-coated bacteria in urine: criterion for a positive test and its value in defining higher risk of treatment failure. Lancet ii: 704-706, 1983.
58. Mond, N.C., Percival, A., Williams, J.D. and Brumfitt, W. Presentation, diagnosis and treatment of urinary tract infections in general practice. Lancet i: 514-516, 1965.
59. Ode, B., Walder, M. and Forsgren, A. Failure of a single dose of 100 mg ofloxacin in lower urinary tract infections in females. Scand. J. Infect. Dis. 19: 677-679, 1987.

RENAL STONE DISEASE

4

PREVENTION OF CALCIUM OXALATE RENAL STONES

CHARLES Y.C. PAK, M.D.

Center on Mineral Metabolism and Clinical Research, Department of Internal Medicine, Southwestern Medical School at Dallas, Dallas, Texas, USA

Once a stone has formed in the urinary tract, it may cause considerable morbidity such as pain, bleeding and infection. Such stone episodes generally recur in most patients suffering from nephrolithiasis(1).

The management of nephrolithiasis therefore entails (a) the removal of already formed stones and (b) the prevention of recurrent stone formation. Much progress has been made recently with the introduction of nephrostolithotomy(2) and extracorporeal lithotripsy(3). Most stones can now be removed with greater ease and less morbidity.

An equally notable progress has been made in the medical area. It is now possible to prevent or retard new stone formation in the majority of patients using a variety of drugs and dietary programs. This advancement in part has been the result of improved understanding of causes of stone formation and availability of reliable diagnostic techniques.

This chapter will, therefore, review first the pathophysiology and the diagnostic criteria of calcium oxalate nephrolithiasis. Various prophylactic modalities will then be discussed.

PATHOPHYSIOLOGY OF PHYSIOLOGICAL DERANGEMENTS

Several metabolic-physiological derangements have been identified in patients with calcium nephrolithiasis. Principal disturbances include: hypercalciuria, hyperuricosuria, hyperoxaluria, hypocitraturia and "gouty diathesis" (Table 1).

Table 1. Classification of Calcium Oxalate Nephrolithiasis

- Hypercalciuria
  - Absorptive
  - Renal
  - Resorptive
  - Renal Phosphate Leak
  - Primary 1,25-$(OH)_2D$ Production
  - Combined Renal Tubular Disturbances
  - Renal Prostaglandin Excess
- Hyperuricosuria
- Hyperoxaluria
  - Primary
  - Intestinal
  - Substrate Excess
  - Mild Metabolic Hyperoxaluria
- Hypocitraturia
  - Distal Renal Tubular Acidosis
  - Chronic Diarrheal State
  - Thiazide-induced Hypokalemia
  - Strenuous Physical Exercise
  - High Sodium Intake
  - Urinary Tract Infection
  - Idiopathic
- Gouty Diathesis

Pathophysiology of Hypercalciuria

There is substantive evidence supporting the view that hypercalciuria of nephrolithiasis is comprised of several entities of heterogeneous origin(4). This approach permits incorporation of prevailing major theories of hypercalciuria.

Absorptive Hypercalciuria(4). This condition is due to the primary enhancement of intestinal calcium absorption occurring independently of 1,25-$(OH)_2$ vitamin D (1,25-$(OH)_2$D). The ensuing increased renal filtered load of calcium and parathyroid suppression produce hypercalciuria.

The exact cause for the enhancement of intestinal calcium absorption is not known. It is not due to stimulated 1,25-$(OH)_2$D synthesis, since the hyperabsorption of calcium cannot be corrected by treatment with adrenocorticosteroids(5), thiazide(6) and orthophosphate(7). A strong genetic predisposition is indicated by the finding of an autosomal dominant mode of inheritance in select family studies(8). This picture of absorptive hypercalciuria has been recently described in genetically inbred hypercalciuric rats(9).

Metabolically, the existence of absorptive hypercalciuria is supported by intact calcium conservation(10). Serum osteocalcin, alkaline phosphatase, urinary hydroxyproline and bone density (radial and vertebral) are normal. Calcium balance is not negative even when calcium absorption is reduced by sodium cellulose phosphate.

Absorptive hypercalciuria Type II represents a less severe form of the Type I presentation(11).

Renal Hypercalciuria(4,12). The primary abnormality is the renal leak of calcium. The ensuing parathyroid stimulation augments the renal synthesis of 1,25-$(OH)_2$D and in some patients causes a compensatory intestinal hyperabsorption of calcium. The existence of 1,25-$(OH)_2$D-dependent intestinal hyperabsorption of calcium is shown by a positive correlation between fractional (intestinal) calcium absorption and serum 1,25-$(OH)_2$D(4), and by the restoration of normal serum 1,25-$(OH)_2$D and intestinal calcium absorption upon correction of renal calcium leak with thiazide(6).

The presence of primary renal calcium leak is supported by (a) fasting hypercalciuria associated with high serum PTH in the setting of normocalcemia(4,12), (b) exaggerated natriuretic response to thiazide(13) and abnormally high calciuric response to carbohydrate load(14). Metabolically, renal hypercalciuria is

characterized by fasting hypercalciuria which is poorly or cannot be corrected by sodium restriction or limitation of intestinal calcium absorption with sodium cellulose phosphate(15), parathyroid stimulation which can sometimes be unmasked by sodium cellulose phosphate, and in some cases poor calcium conservation and reduced bone density(16). No clear-cut genetic predisposition has been described. However, there is less marked male predominance as in absorptive hypercalciuria. Moreover, a substantial fraction of patients have a history of prior urinary tract infection, a finding suggestive of an infectious etiology as originally suggested by Henneman et al in their initial description of idiopathic hypercalciuria(17).

Resorptive Hypercalciuria. Typified by primary hyperparathyroidism, the primary event is the excessive resorption of bone resulting from the overproduction of PTH by abnormal parathyroid tissue. This is a bihormal disease since 1,25-$(OH)_2D$ synthesis is also enhanced. The intestinal calcium absorption is often secondarily increased from the 1,25-$(OH)_2D$ excess(18). Fasting hypercalciuria may be present due to high skeletal mobilization of calcium and secondary renal calcium leak from hypercalcemia. Calcium balance may be negative and bone disease (osteitis) may be present. Resorptive hypercalciuria may also develop from other conditions, such as thyrotoxicosis or oncogenic hypercalcemia. However, nephrolithiasis is uncommonly encountered in these conditions.

Renal Phosphate Leak. In this condition, hypophosphatemia resulting from the primary impairment in renal tubular reabsorption of phosphate, is believed to stimulate 1,25-$(OH)_2D$ synthesis and cause the picture of absorptive hypercalciuria secondarily(19,20). The occurrence of this entity is supported by the finding of low threshold concentration of phosphate and hypophosphatemia in some patients with hypercalciuric nephrolithiasis, ability of induced hypophosphatemia from intestinal phosphate binding to stimulate 1,25-$(OH)_2D$ synthesis, significant inverse correlation between serum 1,25-$(OH)_2D$ concentration and serum P concentration, and abnormal histomorphometric picture of bone(21).

However, no clear-cut documentation of this scheme has been reported in patients with hypercalciuric nephrolithiasis(7). Moreover, the treatment with orthophosphate does not restore normal intestinal calcium absorption even though it may reduce serum concentration of 1,25-$(OH)_2$D(7).

Primary 1,25-$(OH)_2$D Production(22). Primary renal overproduction of 1,25-$(OH)_2$D could account for the picture of absorptive hypercalciuria. It could also cause fasting hypercalciuria, a feature sometimes encountered in patients with hypercalciuric nephrolithiasis, by stimulating bone resorption. This scheme is supported by the finding in some patients with hypercalciuric nephrolithiasis of high serum 1,25-$(OH)_2$D(18) and of accelerated 1,25-$(OH)_2$D synthesis(22).

Combined Renal Tubular Disturbances. This unifying scheme implicates co-occurrence of several defects in renal proximal tubular function in the same subject, characterized by varying degrees of calcium leak, renal phosphate leak and accelerated 1,25-$(OH)_2$D synthesis(23). This combined presentation, e.g. of renal calcium leak with primary 1,25-$(OH)_2$D overproduction, could explain fasting hypercalciuria with normal parathyroid function, a picture which strictly depicts neither absorptive nor renal hypercalciuria.

Renal Prostaglandin Excess(24). It has been reported that treatment with inhibitors of prostaglandin synthesis reduces renal calcium excretion in patients with hypercalciuric nephrolithiasis. It has, therefore, been suggested that an excessive production of prostaglandins particularly of the E series could cause hypercalciuria by increasing renal blood flow and of glomerular filtration rate, and by stimulating bone resorption. This scheme has not yet been documented.

Pathogenesis of Other Derangements

Hyperuricosuria usually results from dietary overindulgence with purine-rich foods in patients with calcium nephrolithiasis(25). Less commonly, it is caused by uric acid overproduction.

Marked hyperoxaluria is encountered in primary hyperoxaluria from enzymatic disturbances in the oxalate biosynthetic pathway (rare) or in ileal disease with fat malabsorption from intestinal hyperabsorption of oxalate(26). Mild hyperoxaluria may develop from the high substrate availability, for example following ingestion of oxalate-rich foods or of excessive amount of ascorbic acid. It may also be found in patients with mild metabolic hyperoxaluria. This entity is characterized by association with an enhanced renal excretion of glycolic acid, amelioration by treatment by pyridoxine, and onset in adulthood.

Hypocitraturia results from acidosis of varying etiologies, such as distal renal tubular acidosis (usually in an incomplete form in patients with stones)(27,28), metabolic acidosis of excessive intestinal alkali loss (chronic diarrheal states)(29), intracellular acidosis of thiazide-induced hypokalemia(30), consumption of a diet rich in acid ash content (animal proteins)(31), and lactic acidosis (from strenuous physical exercise)(32). Urinary citrate may also be reduced following a high sodium intake and in urinary tract infection (probably from bacterial enzymatic degradation of oxalate).

Gouty diathesis may be associated with calcium oxalate nephrolithiasis as well as uric acid stones(33). Probably a forme frust of primary gout, gouty diathesis is characterized by a persistent passage of unusually acid urine (pH < 5.5) unexplained by excessive intestinal alkali loss or consumption of high acid-ash diet, uric acid and/or calcium nephrolithiasis, and in some patients, hyperuricemia, hypertriglyceridemia, and family or personal history of gouty arthritis.

MEDICAL DIAGNOSIS OF NEPHROLITHIASIS

Diagnostic separation based on stone composition alone has limitations since certain stones (e.g. calcium oxalate) could be associated with many pathophysiologic backgrounds. Thus, most diagnostic protocols are based on underlying metabolic or environmental derangements. In such classification, it is

generally assumed that these derangements or risk factors contribute to the formation of renal stones.

Most protocols include analysis of urine for risk factors (e.g. calcium, uric acid, oxalate, citrate, pH and total volume), as well as routine blood screen for calcium, phosphorus, electrolytes and uric acid. Urinary risk factors are typically performed on samples collected on a random diet and fluid intake. They are sometimes repeated in a sample collected after imposition of a diet restricted in calcium, sodium and oxalate, in order to assess the contribution of particular dietary factors. Some laboratories differentiate different forms of hypercalciuria by obtaining fasting urinary calcium (as a measure of renal calcium leak) and calciuric response to oral calcium load (as an indirect measure of intestinal calcium absorption)(34,35), as well as serum PTH. A qualitative cystine determination, stone analysis, urine culture and appropriate radiological examination of the urinary tract are done for a full examination.

A detailed evaluation, similar to the one just described, may be employed in patients with metabolically-active recurrent renal calculi(36). A simplified version is generally employed in patients with a single stone episode or with an inactive disease. Using available protocols, it should be possible to discern the cause(s) of stone formation in most patients with stones. Some patients may present with more than one disturbance. The derangements identified may be both metabolic or environmental in origin.

MEDICAL PROPHYLAXIS OF RECURRENT CALCIUM NEPHROLITHIASIS

The objective of medical therapy of nephrolithiasis is to prevent the recurrence of stone formation in patients who are at risk for further stone formation. There is no medical treatment that is known to provide a complete cure in most forms of stone disease. Primary hyperparathyroidism is one uncommon cause of nephrolithiasis, where further stone formation could be completely halted by parathyroidectomy alone. However, in most forms of

stone disease, medical treatments as conservative measures or medications must be continually provided in order to maintain normal urinary biochemical and physicochemical environment and prevent recurrence of stone formation (Table 2).

Conservative Management(37,38)

Conservative measures of high fluid intake and avoidance of dietary excesses should be useful in all patients with nephrolithiasis. They may be used alone in patients with a single stone episode and in those with inactive stone disease. They are generally instituted together with a specific medical program in patients with recurrent active stone disease. Some conservative programs are applicable to all forms of stone disease whereas others are used for particular causes.

High fluid intake is the only nutritional modification that is universally agreed to be useful in all forms of nephrolithiasis(38). By increasing urine output, urinary concentration of constituent ions and saturation of stone-forming salts are lowered. Although dietary restriction of oxalate may be beneficial in any cause of calcium nephrolithiasis, it is particularly indicated where there is increased intestinal absorption of oxalate, such as in ileal disease and in the presence of enhanced intestinal calcium absorption. Rigid calcium restriction of less than 400 mg/day is ill-advised even in patients with absorptive hypercalciuria, since it is difficult to follow, may adversely affect general nutrition, may cause negative calcium balance, and augment oxalate excretion. However, a moderate calcium restriction (400 to 600 mg/day) may be useful in absorptive hypercalciuria, since it alone may control the hypercalciuria in the less severe (Type II) presentation(39) or permit reduction of the dosage of medication necessary to restore normal urinary calcium in the more severe (Type I) presentation. With this degree of calcium restriction, calcium conservation is intact and there is no evidence for adverse effect on the skeleton. Severe calcium restriction is neither indicated nor necessary in patients with normal intestinal absorption of calcium

or in those with renal hypercalciuria.

A moderate sodium restriction (100 meq/day) may be helpful in all forms of calcium nephrolithiasis. It may prevent or attenuate sodium-induced hypercalciuria and hypocitraturia and urate-induced calcium oxalate crystallization(40).

Prophylactic Treatment with Medications

Use of medications for the prevention of stone formation is indicated in metabolically active stone disease, in situations where conservative measures are ineffective or when the stone disease is accompanied by extraskeletal manifestations. Most groups practice varying degrees of "selective" therapy, where specific treatments are chosen toward correction of underlying derangements(39). Surely, the preferred treatment in uric acid lithiasis or renal tubular acidosis is alkali therapy and that for infection stones would be appropriate antibiotic therapy or acetohydroxamic acid. However, less rigorous selective treatments are often employed in hypercalciuric nephrolithiasis, probably due to continuing controversy in pathogenetic mechanisms.

Treatment of Hypercalciuria

Thiazides (and related compounds such as chlorthalidone) are unique among diuretics in their ability to augment the renal tubular reabsorption of calcium and therefore to reduce urinary calcium(41). At a dosage of hydrochlorothiazide of 50 mg once or twice a day, or an equivalent amount of related drugs, thiazides represent the treatment of choice for renal hypercalciuria(6). Thiazides correct the renal leak of calcium and thereby reverse the sequence of parathyroid hyperactivity, increased synthesis of $1,25\text{-}(OH)_2D$, and enhanced absorption of intestinal calcium(6). Thiazides may be equally effective in the control of absorptive hypercalciuria, at least during the first two years of therapy. However, some patients may show an attenuation of the hypocalciuric response with chronic treatment(42). Moreover, it may cause hypokalemia and hypocitraturia(43). To overcome these problems, urinary calcium should be monitored, and potassium supplement (preferably as potassium citrate) provided(30,43).

Table 2. Mechanism of Action of Various Treatment Programs

Indication	Treatment	Physiological Action	Physicochemical Action
Renal hypercalciuria (also combined renal tubular disturbances)	Thiazide	↓ Urinary Ca (sustained) ↓ Intestinal Ca absorption	↓ Urinary saturation of Ca salts
Absorptive hypercalciuria Type II	Low Ca diet	↓ Intestinal Ca absorption ↓ Urinary Ca	↓ Urinary saturation of Ca oxalate and Ca phosphate
Renal phosphate leak	Orthophosphate	↓ $1,25\text{-}(OH)_2D$ ↓ Intestinal Ca absorption ↓ Urinary Ca ↑ Urinary citrate and pyrophosphate	↓ Urinary saturation of Ca oxalate ↑ Inhibitor activity
Absorptive hypercalciuria Type I (also $1,25\text{-}(OH)_2D$ excess)	Sodium cellulose phosphate	↓ Intestinal Ca absorption ↓ Urinary Ca	↓ Urinary saturation of Ca oxalate ↓ Ca phosphate saturation
	Thiazide	= Intestinal Ca absorption ↓ Urinary Ca (may not be sustained)	↓ Urinary saturation of Ca salts

Hyperuricosuric Ca nephrolithiasis	Allopurinol	↓ Urinary uric acid	↓ Urate-induced crystallization of Ca salts
	Potassium citrate	↑ Urinary citrate	↓ Urinary saturation of Ca oxalate ↓ Urate-induced crystallization of Ca salts
Enteric hyperoxaluria	↓ Oxalate intake	↓ Urinary oxalate	↓ Urinary saturation of Ca oxalate
	Potassium citrate	↑ Urinary citrate ↑ Urinary pH	↓ Urinary saturation of Ca oxalate ↑ Inhibitor activity
	Magnesium gluconate	↑ Urinary Mg	↓ Urinary saturation of Ca oxalate
Hypocitraturic Ca nephrolithiasis	Potassium citrate	↑ Urinary citrate ↑ Urinary pH	↓ Urinary saturation of Ca oxalate ↑ Inhibitor activity
Gouty diathesis	Potassium citrate	↑ Urinary pH ↓ Undissociated uric acid	↓ Urinary saturation of uric acid

↑, increase; ↓, decrease; =, no change

Sodium cellulose phosphate should ideally be used only in patients with a severe form of absorptive hypercalciuria (Type I presentation) without bone disease in whom hypercalciuria cannot be controlled by dietary calcium restriction(10,44). When given orally, it forms a nonabsorbable complex with calcium that is then excreted in the feces. About 2.5 to 5 grams of this resin with each meal is sufficient to limit the amount of luminal calcium available for absorption and to restore normal urinary calcium. Urinary oxalate may increase, because less calcium may be available intraluminally to complex oxalate, so that a moderate dietary restriction of oxalate is recommended. Oral magnesium supplementation should be provided, since this drug also binds magnesium. Sodium cellulose phosphate is contraindicated in primary hyperparathyroidism, in other states of excessive skeletal calcium mobilization, in renal hypercalciuria, and in states of normal intestinal calcium absorption, because it could stimulate parathyroid function and produce or aggravate bone disease.

Orthophosphates, as neutral or alkaline soluble salts of sodium and/or potassium, are potentially absorbable from the intestinal tract, unlike sodium cellulose phosphate. When given orally (at a dosage of 1.5 to 2.0 grams of phosphorus per day in divided doses), they decrease urinary calcium and increase urinary phosphate(45,46). Moreover, they increase renal excretion of inhibitors, such as pyrophosphate and citrate. Orthophosphates are optimally indicated in the management of renal phosphate leak because of the possibility that they may restore normal serum $1,25\text{-}(OH)_2D$(7,47) and calcium absorption. Orthophosphates are contraindicated in moderate or severe hypercalcemia and in renal failure because of the danger of metastatic calcification and in urinary tract infection because of the danger of struvite or calcium phosphate stone formation.

A practical approach gaining acceptance is the use of thiazide with potassium citrate (to prevent hypokalemia and hypocitraturia)(30) in all patients with normocalcemic hypercalciuric nephrolithiasis. If this treatment is clinically

ineffective, or if attenuation of hypocalciuric action develops(42), alternative treatments may be used (e.g. sodium cellulose phosphate in absorptive hypercalciuria, or orthophosphate).

Treatment of Hyperuricosuric Calcium Nephrolithiasis

While this condition should usually be amenable to dietary purine restriction, many patients cannot or do not choose to maintain this dietary restraint. Allopurinol (300 mg/day) may be used, especially in the setting of marked hyperuricosuria (> 800 mg/day) and hyperuricemia(25,48). If hypocitraturia co-exists, potassium citrate alone may be effective especially in mild-moderate hyperuricosuria (< 800 mg/day)(49).

Treatment of Enteric Hyperoxaluria

Dietary oxalate restriction is mandatory. Calcium supplementation and bile acid sequestrants have a limited long-term value. Concurrent abnormalities should be treated, e.g. hypocitraturia by potassium citrate(50), hypomagnesiuria by magnesium gluconate or citrate, and low urine output by enforcing high fluid intake.

Treatment of Hypocitraturic Calcium Nephrolithiasis

In renal tubular acidosis (distal), sodium citrate or potassium citrate(28) (60-120 meq per day in divided doses) may augment citrate excretion. In the absence of renal insufficiency or substantial renal sodium wasting, potassium citrate is preferable because it could reduce urinary calcium, improve calcium balance and correct potassium deficiency. In chronic diarrheal states, potassium citrate could be useful, but may be ineffective in correcting hypocitraturia even at a high dosage (120 meq/day) in severe cases(29,50). If sodium deficiency is present, mixed citrate salts of sodium and potassium would be desirable. In thiazide-induced hypocitraturia, potassium citrate (30-60 meq/day in divided doses) is generally sufficient to correct both hypokalemia and hypocitraturia(30,43), unless there is rare chloride deficiency. In other causes of hypocitraturia, a dose sufficient to restore normal urinary citrate should be

provided (usually 30-60 meq/day in divided doses)(51). The tablet preparation is generally better tolerated and is preferred except in chronic diarrheal states(50).

Treatment of Gouty Diathesis

Either sodium alkali or potassium citrate is effective in preventing uric acid lithiasis by raising urinary pH and creating an environment in which uric acid is more soluble. Only moderate amounts of alkali (40-60 meq/day in divided doses) are usually required to raise urinary pH to an effective range of 6-6.5. There is preliminary evidence that the complication of calcium stones, albeit rare, may occur with sodium alkali therapy, but not with potassium citrate(33). Since both uric acid and calcareous stones occur in gouty diathesis, potassium citrate may be preferrable. If hyperuricemia or marked hyperuricosuria is present, allopurinol is recommended.

Selective vs Non-Selective Therapy

A theoretical advantage of the selective approach resides in the possibility that it might be more effective than the non-selective approach in preventing new stone formation since it is purposely chosen to correct underlying physiological and physicochemical derangements. However, there is no conclusive evidence that such is the case. It has been reported that a generalized use of thiazide, orthophosphate or allopurinol is effective in preventing new stone formation in "idiopathic" calcium oxalate nephrolithiasis, comprising hypercalciuria as well as normocalciuria, and both hyperuricosuria and normouricosuria. The adoption of a less selective approach has an obvious advantage, since it would obviate the need for a careful diagnostic differentiation.

With the recent interest in citrates in nephrolithiasis, a wider use of potassium citrate has been suggested. An approach gaining popularity is the provision of potassium citrate alone in normocalciuric calcium nephrolithiasis, and of potassium citrate with thiazide in hypercalciuric calcium nephrolithiasis.

Despite the simplicity and attractiveness of non-selective simplified approach, it is suggested that a consideration be given to the continued application and refinement of the selective approach. First, our experience with the non-selective use of potassium citrate in normocitraturic patients with calcium nephrolithiasis has disclosed a less favorable response than in those with hypocitraturic calcium nephrolithiasis. Second, selective approach avoids potential misuse of drugs, e.g. sodium cellulose phosphate in renal hypercalciuria which could exaggerate parathyroid stimulation and cause bone disease. Third, certain selective therapy has the potential for the correction of non-renal manifestations of the particular stone disease. Thus, potassium citrate treatment of distal renal tubular acidosis has been shown to avert negative calcium balance (and bone disease) by reducing urinary calcium and augmenting intestinal calcium absorption(52). Thiazide therapy of renal hypercalciuria typically corrects secondary hyperparathyroidism(4,12), whereas it may further exaggerate the hypercalcemia of primary hyperparathyroidism.

REFERENCES

1. Coe FL, Keck J, Norton ER. The natural history of calcium urolithiasis. J Am Med Assoc. 238:1519-1523, 1977.
2. Segura JW, Patterson DE, LeRoy AJ, May GR, Smith LH. Percutaneous lithotripsy. J Urol. 130:1051-1054, 1983.
3. Chaussy C, Brendel W, Schmiedt E. Extracorporeally induced destruction of kidney stones by shock waves. Lancet. 2:1265-1267, 1980.
4. Pak CYC. Physiological basis for absorptive and renal hypercalciurias. Am J Phys. 237:F415-F423, 1979.
5. Zerwekh JE, Pak CYC, Kaplan RA, McGuire JL, Upchurch K, Breslau NA, Johnson R. Pathogenetic role of 1α,25-dihydroxyvitamin D in sarcoidosis and absorptive hypercalciuria: Different response to prednisolone therapy. J Clin Endo Metab. 51:381-386, 1980.
6. Zerwekh JE, Pak CYC. Selective effects of thiazide therapy on serum 1α,25-dihydroxyvitamin D and intestinal calcium absorption in renal and absorptive hypercalciurias. Metabolism. 29:13-17, 1980.

7. Barilla DE, Zerwekh JE, Pak CYC. A critical evaluation of the role of phosphate in the pathogenesis of absorptive hypercalciuria. Min Elect Metab. 2:302-309, 1979.
8. Pak CYC, McGuire J, Peterson R, Britton F, Harrod MJ. Familial absorptive hypercalciuria in a large kindred. J Urol. 126:717-719, 1981.
9. Bushinsky DA, Johnston RB, Nalbantian CE, Favus MJ. Increased calcium absorption and retention, without elevated serum $1,25(OH)_2D$, in genetically hypercalciuric rats. The American Society of Nephrology 20th Annual Meeting, December 13-16, 1987, p 189A.
10. Pak CYC. Pathogenesis of hypercalciuria. IN: Peck WA, ed. Bone and Mineral Research/4. New York: Elsevier, pp. 303-334, 1986.
11. Pak CYC. Pathogenesis, consequences and treatment of the hypercalciuric states. Seminars in Nephrology. 1:356-365, 1981.
12. Coe FL, Canterbury JM, Firpo JJ, Reiss E. Evidence for secondary hyperparathyroidism in idiopathic hypercalciuria. J Clin Invest. 52:134-141, 1973.
13. Sakhaee K, Nicar MJ, Brater DC, Pak CYC. Exaggerated natriuretic and calciuric response to hydrochlorothiazide in renal hypercalciuria but not in absorptive hypercalciuria. J Clin Endo and Metab. 61:825-829, 1985.
14. Barilla DE, Townsend J, Pak CYC. An exaggerated augmentation of renal calcium excretion following oral glucose ingestion in patients with renal hypercalciuria. Invest Urol. 15:486-488, 1978.
15. Pak CYC, Galosy RA. Fasting urinary calcium and adenosine 3'-5'-monophosphonate: A discriminant analysis for the identification of renal and absorptive hypercalciuria. J Clin Endo Metab. 48:260-265, 1979.
16. Lawoyin S, Sismilich S, Browne R, Pak CYC. Bone mineral content in patients with primary hyperparathyroidism, osteoporosis, and calcium urolithiasis. Metab. 28:1250-1254, 1979.
17. Henneman PH, Benedict PH, Forbes AP. Idiopathic hypercalciuria. NE J Med. 259:801-807, 1958.
18. Kaplan RA, Haussler MR, Deftos LF, Bone H, Pak CYC. The role of 1α, 25-dihydroxyvitamin D in the mediation of intestinal hyperabsorption of calcium in primary hyperparathyroidism and absorptive hypercalciuria. J Clin Invest. 59:756-760, 1977.
19. Shen FH, Baylink DJ, Nielson RL, Sherrard DJ, Ivey JL, Haussler MR. Increased serum 1,25-dihydroxyvitamin D in idiopathic hypercalciuria. J Lab Clin Med. 90:955-962, 1977.
20. Gray RW, Wilz DR, Caldas AE, Lemann J. The importance of phosphate in regulating plasma $1,25-(OH)_2$vitamin D levels in humans: Studies in healthy subjects, in calcium-stone formers and in patients with primary hyperparathyroidism. J Clin Endo Metab. 45:299-306, 1977.

21. Bordier R, Ryckewart A, Gueris J, Rasmussen HR. On the pathogenesis of so-called idiopathic hypercalciuria. Am J Med. 63:398-409, 1977.
22. Insogna KL, Broadus AE, Dreyer BE, Ellison AF, Gertner JM. Elevated production rate of 1,25-dihydroxyvitamin D in patients with absorptive hypercalciuria. J Clin Endo Metab. 61:490-495, 1985.
23. Coe FL, Favus MJ, Crockett T, Strauss AL, Parks MB, Porat A, Gantt CL, Sherwood LM. Effects of low-calcium diet on urine calcium excretion, parathyroid function and serum 1,25-$(OH)_2D_3$ levels in patients with idiopathic hypercalciuria and in normal subjects. Am J Med. 72:25-32, 1982.
24. Buck AC, Lote CJ, Sampson WF. The influence of renal prostaglandins on urinary calcium exretion in idiopathic urolithiasis. J Urol. 129:421-426, 1983.
25. Coe FL, Kavalach AG. Hypercalciuria and hyperuricosuria in patients with calcium nephrolithiasis. NE J Med. 291:1344-1350, 1974.
26. Smith LH, Fromm H, Hofmann AF. Acquired hyperoxaluria, nephrolithiasis and intestinal disease. NE J Med. 286:1371-1375, 1972.
27. Simpson DP. Regulation of renal citrate metabolism by bicarbonate ion and pH: Observations in tissue slices and mitochondria. J Clin Invest. 16:225-238, 1967.
28. Preminger GM, Sakhaee K, Skurla C, Pak CYC. Prevention of recurrent calcium stone formation with potassium citrate therapy in patients with distal renal tubular acidosis. J Urol. 134:20-23, 1985.
29. Rudman D, Dedonis JL, Fountain MT, Chandler JB, Gerron GG, Fleming GA, Kutner MH. Hypocitraturia in patients with gastrointestinal malabsorption. NE J Med. 303:657-661, 1980.
30. Pak CYC, Peterson R, Sakhaee K, Fuller C, Preminger G, Reisch J. Correction of hypocitraturia and prevention of stone formation by combined thiazide and potassium citrate therapy in thiazide-unresponsive hypercalciuric nephrolithiasis. Am J Med. 78:284-288, 1985.
31. Breslau NA, Brinkley L, Hill KD, Pak CYC. Relationship role of animal protein-rich diet to kidney stone formation and calcium metabolism. J Clin Endo Metab. 66:140-146, 1988.
32. Sakhaee K, Nigam S, Snell P, Hsu MC, Pak CYC. Assessment of the pathogenetic role of physical exercise in renal stone formation. J Clin Endo Metab. 65:974-979, 1987.
33. Pak CYC, Sakhaee K, Fuller C. Successful management of uric acid nephrolithiasis with potassium citrate. Kid Int. 30:422-428, 1986.
34. Broadus AE, Dominguez M, Bartter FC. Pathophysiological studies in idiopathic hypercalciuria: Use of an oral calcium tolerance test to characterize distinctive hypercalciuric subgroups. J Clin Endo Metab. 47:751-760, 1978.

35. Pak CYC, Kaplan RA, Bone H, Townsend J, Waters O. A simple test for the diagnosis of absorptive, resorptive and renal hypercalciurias. NE J Med. 292:497-500, 1975.
36. Pak CYC, Britton F, Peterson R, Ward D, Northcutt C, Breslau NA, McGuire J, Sakhaee K, Bush S, Nicar M, Norman D, Peters P. Ambulatory evaluation of nephrolithiasis: Classification, clinical presentation and diagnostic criteria. Am J Med. 69:19-30, 1980.
37. Pak CYC, Smith LH, Resnick MI, Weinerth JL. Dietary management of idiopathic calcium urolithiasis. J Urol. 131:850-852, 1984.
38. Pak CYC, Sakhaee K, Crowther C, Brinkley L. Evidence justifying a high fluid intake in treatment of nephrolithiasis. Ann Int Med. 93:36-39, 1980.
39. Pak CYC, Peters P, Hurt G, Kadesky M, Fine M, Reisman D, Splann F, Caramela C, Freeman A, Britton F, Sakhaee K, Breslau NA. Is selective therapy of recurrent nephrolithiasis possible? Am J Med. 71:615-622, 1981.
40. Pak CYC, Holt K, Zerwekh JE. Attenuation by monosodium urate of the inhibitory effect of glycosaminoglycans on calcium oxalate nucleation. Invest Urol. 17:138-140, 1979.
41. Brickman AS, Massry SG, Coburn JW. Changes in serum and urinary calcium during treatment with hydrochlorothiazide studies on mechanisms. J Clin Invest. 51:945-954, 1972.
42. Preminger GM, Pak CYC. Eventual attenuation of hypocalciuric response to hydrochlorothiazide in absorptive hypercalciuria. J Urol. 137:1104-1109, 1987.
43. Nicar MJ, Peterson R, Pak CYC. Use of potassium citrate as potassium supplement during thiazide therapy of calcium nephrolithiasis. J Urol. 131:430-433, 1984.
44. Pak CYC. A cautious use of sodium cellulose phosphate in the management of calcium nephrolithiasis. Invest Urol. 19:187-190, 1981.
45. Smith LH, Thomas WC Jr, Arnaud CD. Orthophosphate therapy in calcium renal lithiasis. IN: Delatte LC, Rapado A, Hodgkinson A, eds. Urinary calculi. Basel, S. Karger. pp 188-197, 1973.
46. Pak CYC, Holt K, Zerwekh J, Barilla DE. Effects of orthophosphate therapy on the crystallization of calcium salts in urine. Min Elect Metab. 1:147-154, 1978.
47. Van Den Berg J, Kumar R, Wilson DM, Heath H III, Smith LH. Orthophosphate therapy decreases urinary calcium excretion and serum 1,25-dihydroxyvitamin D concentrations in idiopathic hypercalciuria. J Clin Endo Metab. 51:998-1001, 1980.
48. Ettinger B, Tang A, Citron JT, Livermore B, Williams T. Randomized trial of allopurinol in the prevention of calcium oxalate calculi. NE J Med. 315:1386-1389, 1986.
49. Pak CYC, Peterson R. Successful treatment of hyperuricosuric calcium oxalate nephrolithiasis with potassium citrate. Arch Int Med. 146:863-867, 1986.

50. Pak CYC, Fuller C, Sakhaee K, Preminger GM, Britton F. Long term treatment of calcium nephrolithiasis with potassium citrate. J Urol. 134:11-19, 1985.
51. Pak CYC, Fuller C. Idiopathic hypocitraturic calcium oxalate nephrolithiasis successfully treated with potassium citrate. Ann Int Med. 104:33-37, 1986.
52. Preminger GM, Sakhaee K, Pak CYC. Hypercalciuria and altered intestinal calcium absorption occurring independently of vitamin D in distal renal tubular acidosis. Metab. 36:176-179, 1987.

HYPERTENSION

5

CALCIUM CHANNEL BLOCKING DRUGS AS ANTIHYPERTENSIVE AGENTS

AUSTIN E. DOYLE
Emeritus Professor of Medicine, Department of Physiology, University of Melbourne, Parkville 3052, Australia.

Drugs which block the calcium channels are not a homogeneous group either chemically or in their physiological actions. These differences are reflected in their actions on the circulation, and lead to differences in their clinical actions as antihypertensive drugs.

Although there are several different chemical classes of calcium antagonist drugs, in practical terms they can be divided into two main groups depending on their relative actions on cardiac and vascular smooth muscle respectively. Those with major actions on slow calcium channels in the heart are represented by verapamil, methoxy-verapamil (D600, gallapomil) and diltiazem. Those without major cardiac effects are represented by the di-hydropyridine drugs, the prototype of which is nifedipine. There are now numerous di-hydropyridine derivatives in clinical use.

In the heart muscle, the rapid depolarization phase is due to to the rapid inward movement of sodium ions. This action potential is followed by a plateau due to the inward movement of calcium[1], related to the external calcium concentration. The slow calcium dependent current is activated by the opening of calcium

channels, triggered by the fast change in voltage induced by the inward movement of sodium. The calcium influx is involved in the contractile process, and plays a major role in the spontaneous activity of the SA node, AV nodal conduction and automaticity. The calcium channel blocking drugs inhibit the inward calcium current with inhibitory effects on excitation-contraction coupling in the myocardium[2], and for these reasons are used therapeutically to affect various cardiac arrhythmias, particularly of supraventricular origin. Nifedipine also inhibits the slow inward current[3], but the di-hydropyridine drugs have much weaker actions on cardiac muscle than on vascular smooth muscle, and some of the newer di-hydropyridine drugs such as felodipine[4], nicardipine[5] and nisoldipine[6] have much more selectivity for peripheral vascular muscle than for cardiac muscle. Vascular smooth muscle, like cardiac and skeletal muscle, depends on a rise in intracellular calcium concentration for the initiation of contraction. The increased levels of intracellular calcium concentration in vascular smooth muscle are in part dependent on calcium influx through calcium channels, and drugs like verapamil which have major effects on cardiac slow calcium channels, also induce vasodilatation. However, vascular smooth muscle can be relaxed with di-hydropyridine drugs at concentrations which have little or no effect on cardiac contractility. While this might be due to the presence in vascular tissue of channels particularly sensitive to di-hydropyridines, it is more likely that other mechanisms not involving influx of extracellular calcium are involved in the increase in intracellular calcium in vascular smooth muscle. The di-hydropyridines may have an action in the calcium binding protein calmodulin[7] or on a surface membrane Ca^{++} pump[8]. No final

explanation for the differential sensitivity to various classes of drug is yet available.

In this chapter, the clinical uses of verapamil, of diltiazem and of the di-hydropyridine derivatives will be discussed separately.

VERAPAMIL

Verapamil is a chemical derivative of papaverine. Although widely used as an antiarrhythmic drug and for angina since about 1978, its clinical effectiveness in hypertension has only been convincingly documented since about 1980. Its place in the available spectrum of antihypertensive drugs is now established.

Hemodynamic Effects

a) Parenteral Administration The intravenous administration of verapamil in healthy volunteers induced a fall in arterial pressure with an increase in heart rate of about 15%. Cardiac output increased, with a fall in peripheral resistance[9].

Intra-arterial infusion into the brachial artery induced a marked fall in vascular resistance[10].

These data indicate that after intravenous administration in persons with normal cardiac function the predominant effect is a fall in peripheral resistance, with some reflex rise in heart rate.

b) Oral Administration After oral administration of verapamil in doses up to 480 mg daily, the dominant effect is a fall in blood pressure associated with a fall in peripheral resistance[11]. Heart rate is usually little altered and cardiac index may increase slightly or be unchanged.

Verapamil in Hypertension

a) Clinical Reports One paper from Japan in 1968[12] described the use of verapamil for treating hypertension, but further papers describing its use as an antihypertensive drug were not published until 1978. Verapamil was used in doses of 120 mg t.i.d. in a double-blind comparison with propranolol in the treatment of stable angina[13]. Both drugs were equally effective in reducing the frequency and severity of angina, in reducing nitroglycerine intake and in preventing ECG changes during exercise. The authors also noted that blood pressure fell in hypertensive patients treated with verapamil.

The first systematic study of verapamil as an antihypertensive agent was in 1978[14], in a placebo controlled study of the use of verapamil at doses of 80-120 mg t.i.d. in 21 patients with mild to moderate hypertension. Verapamil induced significantly larger falls of blood pressure than placebo. Side effects were few, with the major symptomatic side effect being constipation. Midtbo and Hals[15], using a double-blind, placebo controlled crossover design study in 23 patients with mild to moderate hypertension, reported very similar findings.

The effects of verapamil were studied in 20 patients with essential hypertension, using 24 hr. intra-arterial ambulatory monitoring of blood pressure[16]. Doses of 120 mg t.i.d. caused a reduction in blood pressure for most of the 24 hours with preservation of the circadian pattern of blood pressure variation. The hourly mean heart rate and the pressor responses to hand grip and to exercise were reduced. More recently the effects of conventional verapamil tablets have been compared with an equivalent single daily dose of sustained release verapamil[17].

This study, using ambulatory blood pressure monitoring, demonstrated a significant fall in blood pressure in both regimens, which had no significantly different effects on blood pressure.

The efficacy of verapamil as an antihypertensive agent has been compared with a number of other drugs. The antihypertensive effects of 360-480 mg of verapamil daily were compared with the effects of 240 mg of propranolol t.i.d.[18]. Both drugs satisfactorily reduced blood pressure, the response to verapamil being slightly greater. The effects of verapamil in doses of 120-160 mg t.i.d. and of pindolol in a dose of 10 mg b.i.d. were compared in a group of patients with mild to moderate hypertension[19]. All patients took a diuretic throughout the study, which was of a double-blind crossover design. The falls in blood pressure were the same for each drug. The hemodynamic effects of both drug regimes were compared using an echocardiographic technique. Verapamil induced a small increase in cardiac index with a fall in peripheral resistance, whereas pindolol induced small but insignificant changes in both cardiac index and peripheral resistance. Verapamil was compared with labetalol in a group of elderly mild to moderate hypertensive patients who also had chronic obstructive airways disease non responsive to bronchodilator therapy. Both drugs reduced blood pressure equally effectively. The forced expiratory volume (FEV) was slightly increased during verapamil treatment, but was reduced by labetalol[20]. Ambulatory 24 hr. monitoring was used to evaluate the effects of long term treatment with either propranolol or verapamil[21]. The study was an open, randomized crossover study in which 19 patients took part. Ambulatory blood pressure measurements were made for 24 hours, before treatment, after stabilization of blood

pressure with one drug, and again after stabilization with the other drug. The mean dose of propranolol was 120 mg twice daily and of verapamil 185 mg twice daily. Mean daytime pressures fell from 174/101 to 139/80 during propranolol treatment and to 148/85 during verapamil. Neither drug changed the circadian curve of blood pressure over the 24 hour period. Both drugs reduced heart rate, the reduction being greater with propranolol. Five patients taking verapamil and three taking propranolol did not attain the goal blood pressure of 140/90 mmHg.

Two studies have reported the long term effects of treating hypertension with verapamil. Lewis[22] reported on 75 patients treated with verapamil for 1 year. Of these 14 discontinued because of adverse effects (11), poor control or failure of compliance[3]. Blood pressure control was moderate, with blood pressures falling from 190/110 to 162/91 at 1 year. Blood pressure did not alter significantly between 1 and 12 months after commencing treatment. There were no significant changes in serum cholesterol, triglycerides or HDL cholesterol. The major side effect necessitating withdrawal was constipation. Midtbø et al[23] studied 2 previously untreated patients who took verapamil for more than 1 year. Mean dose was 270 mg per day, the dose being titrated to achieve a diastolic pressure of 85 mmHg or less. No tolerance or metabolic effects were noted.

Bühler and his colleagues[24,25] have compared the effects of verapamil and propranolol in relation to age, initial blood pressure and the renin sodium index. In one study they compared the antihypertensive efficacy of verapamil monotherapy in 43 patients with the previous response to propranolol in 29 patients and with the previous response to diuretics in 18. Although they

found no overall difference in the fall in blood pressure between any of the three agents, both verapamil and diuretics were claimed to give larger responses in older patients and in those with higher initial blood pressures, whereas propranolol responses correlated indirectly with the patient's age and directly with pre-treatment plasma renin activity (PRA). These data have led Bühler to suggest that calcium channel blocking drugs in general are more effective in elderly patients with low renin hypertension. However, experimental data suggest that renin levels do not influence the response to calcium blockers[26] and the correlation between fall in blood pressure and initial blood pressure is a feature common to many antihypertensive drugs[27]. On the basis of numerous studies, Midtbø[23] found verapamil to be efficacious in the treatment of mild to moderate hypertension in all age groups.

An interesting study on the effects of intravenous verapamil in 4 patients with phaeochromocytoma has been recently reported[28]. The intravenous infusion of verapamil produced a significant fall in mean arterial pressure without affecting either heart rate or plasma epinephrine or norepiniphrine levels.

Adverse Effects

a) Constipation Constipation is a frequent and troublesome side effect of verapamil[14,15]. It is almost certainly due to an action in preventing the inward movement of calcium ions into the smooth muscle cells of the gastro-intestinal tract. It is of sufficient severity to cause non-compliance, or withdrawal in up to 10% of patients, particularly the elderly[23]. Constipation appears to be an effect which is specific for verapamil, since the other drugs such as diltiazem or the dihydropyridine drugs rarely cause it.

b) Cardiac Effects Serious cardiac effects are uncommon. There is often slight prolongation of the P-Q-T interval[20]. A few patients may develop sinus arrest but this is very unusual[29]. However, the combination of verapamil and Beta-blocking drugs may lead to extreme bradycardia[22]. The intravenous administration of verapamil to patients taking long term Beta blockers may induce ventricular standstill, or bradycardia and hypotension[30]. While adverse cardiac effects of the combination of oral verapamil and Beta blockers are probably uncommon, some adverse effects have been reported[31]. Many believe that the combination is better avoided.

c) Hepatotoxicity There have been a few cases of hepatotoxicity due to verapamil[32]. Right upper quadrant pain, jaundice and a raised alkaline phosphatase are characteristic features. Withdrawal of verapamil is followed usually by rapid recovery, but symptoms recur on challenge. The mechanism seems to be a hypersensitivity response similar to that reported for papaverine[33].

d) Drug Interactions An important clinical interaction occurs between verapamil and digoxin, with patients taking both drugs developing digoxin toxicity after verapamil is added. The mechanism appears to be a reduction in both renal[32] and extrarenal[34] digoxin clearance.

Overview of verapamil as antihypertensive therapy

Verapamil is now well established as an efficacious and generally well tolerated antihypertensive drug. It is of particular value in the treatment of patients in whom angina and hypertension co-exist[30]. It is useful in patients with hypertension co-existing with bronchial asthma or obstructive airways disease[20]. It is effective in patients of all ages[23]. The hemodynamic

profile of a rise in cardiac index with vasodilation make it a more logical choice than Beta blocking drugs, which have their primary effect in reducing cardiac output. However, verapamil may have negative inotropic effects on heart muscle, and should be avoided if there is evidence of significant left ventricular dysfunction.

DILTIAZEM

Diltiazem shares many properties with verapamil and in clinically relevant doses it may inhibit SA and AV nodal function. Like verapamil it is a dilator of peripheral vascular arterial smooth muscle.

Diltiazem in Hypertension

Clinical Studies The effects of diltiazem in hypertension are broadly similar to those of verapamil. In 12 patients, diltiazem in doses of 120 mg twice daily had identical effects to verapamil slow release 240 mg daily[30]. Using a Latin square design Yamakado et al[35] compared propranolol 60 mg twice daily with diltiazem 180 mg daily and with placebo. Both drugs produced similar falls of blood pressure, even at a rather low dose of propranolol. Heart rate fell more with propranolol than with diltiazem. In a double-blind crossover study, diltiazem 60 mg four times daily was as effective as metoprolol 100 mg twice daily. Frishman[36] reported that diltiazem in a mean dose of 342 mg/day produced similar falls of blood pressure to a mean dose of 96 mg/day of nifedipine. Diltiazem reduced heart rate, whereas nifedipine increased it. Both drugs reduced the frequency of angina pectoris in this group of patients.

Adverse Effects

a) Cardiac Effects Few adverse cardiac effects of diltiazem have so far been reported. The actions of diltiazem on the SA node and AV conduction resemble those of verapamil, and it is likely that as the drug is

more widely used, occasional disturbances of AV conduction may be observed.

b) Other Effects Diltiazem, unlike verapamil, does not appear to induce constipation. Dizziness, facial flushing and gastro-intestinal disturbances have been reported.

Overview of the Use of Diltiazem in Hypertension

From the rather meagre evidence as yet available it is likely that diltiazem will prove to be as effective as verapamil as an antihypertensive agent. It appears to lack the major disadvantage of verapamil, namely the constipating effect. It slows heart rate slightly more than verapamil for a given antihypertensive action.

DI-HYDROPYRIDINE DRUGS

There are now a large number of these agents available. In addition to nifedipine, the prototype of this group, the drugs available include nitrendipine, nicardipine, nimodipine, nisoldipine and felodipine. It has been claimed that some of these compounds are relatively more selective for various vascular beds than others; nimodipine, for example, has been claimed to have a selective action on cerebral vasculature[37]. It is not clear whether these differences are real, and there is no explanation available to account for such differences. The drugs differ from each other in terms of selectivity for vascular sites rather than cardiac effects; felodipine is more selective than nifedipine, which is more selective than diltiazem or verapamil[3].

The most selective drugs act on vascular smooth muscle at concentrations which have no myocardial actions. They also differ in their potency and duration of action, nifedipine being short acting, while nitrendipine, nimodipine, nicardipine and felodipine are relatively long acting. In spite of these differences,

the clinical spectrum of activity of all these dihydropyridines seems fairly uniform. For this reason, data on nifedipine will be mainly reviewed, and where differences are evident, reference will be made to the other drugs.

Hemodynamic Effects

a) Parenteral Administration Intravenous administration of nifedipine in healthy volunteers led to a reduction in systolic and diastolic blood pressures, with an increase of heart rate which averaged 25 beats/min and a rise of cardiac output from 8-12L/min[38].

Intra-arterial administration produced a marked fall in resistance, the effects of nifedipine being about three times as potent on a molar basis as those of verapamil[10]. Nifedipine failed to relax norepinephrine induced venoconstriction.

b) Oral Administration Acute oral or sublingual administration of both nifedipine and nisoldipine caused a fall in arterial blood pressure with a reflex tachycardia and increase in cardiac index[39]. In patients restudied after taking nifedipine or nisoldipine for 1 year blood pressure remained reduced, but the tachycardia and raised cardiac output were no longer present. In SH rats, acute felodipine administration caused a marked tachycardia which disappeared with continued administration[40], an effect which has been attributed to resetting of the baroreceptors[41].

CLINICAL STUDIES IN HYPERTENSION

(1) Acute Studies

The acute effects of oral or sublingual administration of nifedipine have been studied in a group of patients with diastolic blood pressures of 120 mmHg or more[42]. Thirty minutes after a 10 mg oral

dose, mean supine blood pressure had fallen by 21%, with a 17% increase in heart rate and 40% fall in systemic vascular resistance. These effects persisted for more than 2 hours. After sublingual doses of 10 mg, blood pressure began to fall within 10 min.

These rapid effects of nifedipine have been utilized in the emergency treatment of severe hypertension associated with either hypertensive encephalopathy or acute pulmonary edema. Seven cases with severe hypertension and pulmonary edema were treated with initial doses of 10 mg of nifedipine sublingually[43]. Blood pressure fell rapidly, with a rise in cardiac output, an increase in left ventricular ejection and a fall in pulmonary artery and wedge pressures. There was symptomatic relief of dyspnoea, of hilar congestion or alveolar edema and a reduction in heart size. These findings have been confirmed by other workers[41]. A rapid antihypertensive effect in a patient with phaeochromocytoma[44] similar to that reported with intravenous verapamil[28] has also been described[44].

Felodipine is also effective in hypertension and congestive heart failure[45]. Systemic pressure and pulmonary wedge pressure fell, with an increase in cardiac index and stroke volume. It has been suggested that the selectivity of felodipine for vascular smooth muscle and the absence of any demonstrable negative inotropic effects may allow the effective use of felodipine in non-hypertensive heart failure, by afterload reduction. Nitrendipine[46] has also been shown to reduce both pulmonary wedge pressures and systemic vascular resistance, while increasing cardiac index with no change in heart rate. Similar effects have been demonstrated with nicardipine[5] and nisoldipine[47].

(2) Chronic Administration in Hypertension

There have now been a large number of studies of the antihypertensive effects of nifedipine in ambulatory patients with mild to moderate hypertension. Nifedipine capsules, given sublingually or orally, produce a rapid antihypertensive effect with a duration of 4-6 hours or less. The first report of the antihypertensive use of nifedipine was made in 1972[48]. Subsequent early reports[49,50,51,52,53] confirmed that nifedipine reduced blood pressure more in hypertensive than in in normotensive patients. While all reported falls in blood pressure, doubts were expressed by some[50] as to the suitability of nifedipine as a sole agent for treating hypertension in the long term because of subjective side effects and fluid retention. Others, however, claimed satisfactory antihypertensive effects[53].

With the introduction of the slow release tablet form of nifedipine, and with the availability of the newer di-hydropyridine drugs such as nitrendipine, nisoldipine and felodipine, there is a general consensus that these drugs can be used effectively as first line antihypertensive therapy. Erne[53], using slow release nifedipine tablets, treated 60 patients with doses up to a maximum of 40 mg twice daily. In 12 patients treatment had to be discontinued within 4 weeks because of symptomatic side effects, but in the remaining 48 patients, blood pressure was normalized in 41. The magnitude of the fall in blood pressure was related to pre-treatment blood pressures. This group claimed that like verapamil, nifedipine was most effective in older patients with low PRA. Intra-arterial ambulatory recordings of blood pressure in patients taking slow release nifedipine[54] indicated that nifedipine, like verapamil, lowered blood pressure over the whole 24 hr.

period without altering the circadian variation. Nifedipine produced small increases in heart rate. Of the more recently introduced di-hydropyridine derivatives, the actions of felodipine in hypertension were reviewed recently by Elmfeldt et al[55]. Forty studies were reviewed involving 1,000 patients, 350 of whom had been treated for more than 6 months and 250 for a year or more. In comparison with placebo, the average blood pressure reduction was 10-20%, but in some of these studies felodipine was given in combination with a diuretic or a Beta blocking drug. It was concluded that the average dose of felodipine required was 5 mg twice daily, but some patients responded to 2.5 mg while others required twice daily doses of 10 mg. Both elderly and young patients responded satisfactorily. In comparison with other drugs, felodipine reduced blood pressure more and controlled blood pressure in more patients than prazosin[56,57], hydralazine[58], nifedipine[59] or hydrochlorothiazide[60]. Felodipine was found to be as effective as minoxidil[61].

Nitrendipine[62] and nisoldipine[39] have likewise been shown to control blood pressure in patients with mild to moderate hypertension with twice daily administration.

The administration of di-hydropyridine drugs to induce vasodilatation in hypertension evokes baroreceptor responses with tachycardia, facial flushing and occasionally headache[50]. Plasma renin levels may rise transiently[50]. These effects are similar to those which have been reported with other peripheral vasodilator drugs such as hydralazine, minoxidil or with the alpha$_1$ blocking drug prazosin. Although these symptoms are not always severe, and there is evidence that due to baroreceptor resetting[63], the symptoms do not persist, many patients find them unpleasant and may

stop treatment. The numbers who do this vary from one series to the next, but up to 15-20% have been reported to cease treatment[53]. These symptoms seem less severe with longer acting preparations than with nifedipine capsules. As with other vasodilators, many of these symptoms can be avoided by combining the di-hydropyridines with a Beta blocking drug. The combination of nifedipine with propranolol[64,65] is extremely effective in reducing blood pressure and avoiding adverse symptoms. Likewise felodipine in combination with a Beta blocker has been shown to be highly effective[66,67]. The combination of nifedipine with methyl dopa has also been reported to be an effective antihypertensive regimen[43], with potentiation of the hypotensive response, and blunting of the tachycardia. Some patients have been reported to have had sustained reduction of blood pressure for 3 years on this regime.

More recently, the combination of nifedipine with angiotensin converting enzyme inhibitors has been found to be effective, which is surprising since both induce vasodilatation.

Adverse Effects The major adverse effects of the di-hydropyridine drugs are the reflex tachycardia, with facial flushing and headache referred to above,

Ankle edema has been described in up to 20% taking nifedipine or other di-hydropyridines. This is independent of sodium or water retention, and appears to occur with all drugs of this group. The edema appears to be due to a selective dilatation of precapillary vessels with little effect on the postcapillary vessels. A comparison of five calcium channel blockers showed that at the same degree of local vasodilation, each drug caused the same increase in capillary hydrostatic pressure and transcapillary fluid transfer[68]. The

edema does not respond to diuretics, and may be of sufficient severity to necessitate withdrawal.

Gingival enlargement has been reported in a few cases following nifedipine[69] and felodipine[55].

Renal Effects Vasodilating drugs such as hydralazine and minoxidil generally lead to retention of water and sodium as part of the readjustment of the circulation consequent on the fall of blood pressure. This, together with the reflex activation of the sympathetic nervous system, usually blunts the hypotensive response to vasodilators.

All the calcium antagonists increase sodium and water excretion. This has been reported for verapamil[70,71], nifedipine[72,73,74], gallapomil[75], diltiazem[76], nitrendipine[77,78], felodipine[79] and nicardipine[80]. In man, the acute administration of these drugs is associated with an early increase in both sodium and water excretion, which begins at about the same time as the blood pressure falls. With continued administration, the natriuresis and diuresis decline, but there does not seem to be any phase of retention of sodium and water[74]. In a study of the use of felodipine in hypertensive patients with chronic renal failure[81], in whom previous treatment including the use of an angiotensin converting enzyme inhibitor had failed to control blood pressure with pre-felodipine levels of 206/119 mmHg, felodipine successfully controlled blood pressure over a period of a month or more, with average post-treatment blood pressure levels of 154/89 mmHg. This control of blood pressure was accompanied by a small improvement in renal function in all but one case.

The mechanism of action of calcium antagonists on the kidney has been studied by Di Bona[82]. In dogs, unilateral renal artery infusion of felodipine produced

an ipsilateral diuresis and natriuresis without changing blood pressure, renal blood flow or glomerular filtration rate. In rats, intravenous administration of felodipine produced diuresis and natriuresis without changing blood pressure, renal blood flow or whole kidney or single nephron glomerular filtration rate. In conscious spontaneously hypertensive rats, bolus i.v. doses of felodipine produced falls in blood pressure and renal vascular resistance, with an increase in renal blood flow, GFR, and water and sodium excretion.

Renal tubular reabsorption of water and sodium were inhibited in the distal tubule and collecting duct. On the other hand Haberle et al[83] found inhibition of proximal salt and water reabsorption in rats given nitrendipine during hydropenia. However, Giebisch et al[84] found that nitrendipine directly inhibited sodium transport along the superficial distal tubule of the rat kidney. It seems that the mechanism of the effects on sodium and water excretion are not finally settled.

From the clinical viewpoint, the combination of peripheral vasodilation and natriuresis is unusual, and can be regarded as a generally favourable property since this combination of actions might be expected to prevent the tolerance due to sodium retention which is a feature of most vasodilator drugs. There are other interesting findings related to the effects of calcium antagonist drugs on the kidney. Nitrendipine seems to confer partial protection against acute ischemic renal failure in rats[85] and protects against aminoglycoside nephrotoxicity in the rat[86]. Nitrendipine has also been reported partly to preserve renal function during experimental immune glomerulonephritis, although the histologic appearances were not altered by nitrendipine[87]. These renal effects may be unrelated to either the vascular or the natriuretic effects, and

clearly merit further study.

OVERVIEW OF CALCIUM ANTAGONISTS AS ANTIHYPERTENSIVE AGENTS

Calcium antagonist drugs represent a major addition to the spectrum of antihypertensive therapy. They lower blood pressure mainly by producing arteriolar vasodilatation, and undoubtedly act by interfering with the fundamental calcium mediated mechanisms of smooth muscle contraction. Since they produce much larger falls of blood pressure in hypertensive than in normotensive humans or animals, it has been speculated that they may be interfering with some specific calcium mediated pathogenetic factor in vascular smooth muscle. However, the increased sensitivity to both constrictor and dilator agents in hypertension is well recognized[88] and is undoubtedly in large part due to smooth muscle hypertrophy and a change in the geometry of small arterioles[89]. Although, therefore, the effects of calcium antagonists do not necessarily have implications for the pathogenesis of hypertension, it is clear that from an empirical point of view they are powerful and effective antihypertensive drugs, which are comparatively easy to use and are generally well tolerated.

The different physiological effects may indicate fundamental differences in the mechanisms which control calcium transport in various tissues. The concept of relative selectivity of different drugs for heart muscle and arterial smooth muscle has now emerged, and it may be that further differences in selectivity for different vascular beds or different functions of calcium transport may become apparent in the future.

REFERENCES

1. Reuter,H. The dependence of the slow inward current in Purkinje fibres on the external calcium concentration. J. Physiol. 192:475-492, 1967.
2. Fleckenstein,A., Trittart,H., Fleckenstein,B., Herbst,A., Grun,G. A new group of competitive Ca-antagonists (Iproveratril, D600 Prenylamine) with highly potent inhibitory effects on excitation-contraction coupling in mammalian myocardium. Pflügers Arch. Ges. Physiol. 307:R25, 1969.
3. Kohlhardt,M., Fleckenstein,A. Inhibition of the slow inward current by nifedipine in mammalian ventricular myocardium. Naunyn Schmiedebergs Arch. Pharmacol.298:267-272, 1977.
4. Ljung,B., Kjellstedt,A., Oreböck,B. Vascular versus myocardial selectivity of calcium antagonists studied by concentration-time-effect relations. J. Cardiovasc. Pharmacol.10 (Suppl.1):S34-S39, 1987.
5. Rousseau, M.F., Etienne,J., Van Mechelen,H., Veriter,C., Pouleur,H. Hemodynamic effects of nicardipine in patients with coronary artery disease. J. Cardiovasc.Pharmacol. 6:833-839, 1984.
6. Maxwell,G.M., Crompton,S., Rencis,V. Effect of nisoldipine upon the general and coronary hemodynamics of the anesthetized dog. J. Cardiovasc. Pharmacol. 4:393-397, 1984.
7. Boström,S-L, Ljung,B., Märdh,S., Forsén,S., Thulin,E. Interaction of the antihypertensive drug Felodipine with calmodulin. Nature 292:777-778, 1981.
8. Hiraoki,T. Vogel,J. Structure and function of calcium-binding proteins. J.Cardiovasc.Pharmacol. 10 (Suppl. 1):S14-S31, 1987.
9. Bass,O., Friedman,E. Ein beitrag zum anti-arrhythmishen wirkungs-mechanismus von Verapamil. Schweiz.Med.Wschr. 101: 792-798, 1971.
10. Robinson,B.F., Collier,J.G., Dobbs, R.J. Comparative dilator effect of verapamil and sodium nitroprusside in forearm arterial bed and dorsal hand veins in man. Cardiovasc.Res. 13:16-26, 1979.
11. Leon,M.B., Bonow,R.D., Rosung,D.R., Kent, K.M., Lipson,L.C., Bacharac,S.L., Green,M.V., Epstein, S.E. Effects of verapamil alone and combined with propranolol in left ventricular function in patients with coronary artery disease. Circulation 62 (Suppl.III):288-299, 1980.
12. Hagino,D. Application of Improveratril in the pharmacotherapy of hypertension. Japan. J. Clin. Exp.Med. 45:208-14, 1968.

13. Livesley,B., Catley,P.F., Campbell,R.C., Oram,S. Double-blind evaluation of verapamil, propranolol and isorbide dinitrate against placebo in the treatment of angina pectoris.Brit.Med.J. i:375-378, 1973.
14. Lewis,G.R.J., Morley,K.D., Lewis,B.M. The treatment of hypertension with verapamil. N.Z. Med. J. 87:351-354, 1978.
15. Midtbø,K., Hals,O. Verapamil in the treatment of hypertension. Curr.Ther.Res. 27:830-838, 1980.
16. Gould,B.A., Mann,S., Kiese,H., Subramanian,V.B.. Raftery,E.B. The 24 hour ambulatory blood pressure profile with verapamil. Circulation 65:22-27, 1982.
17. Zachariah,P.K., Sheps,S.G., Schirger,A., Spiekerman, R.E., O'Brien,P.C., Simpson,K.O. Verapamil and 24-hour ambulatory blood pressure monitoring in essential hypertension. Am.J.Cardiol.57: 74D-79D, 1986.
18. Leonetti,G., Pasotti,C., Ferrari,G.P., Zanchetti,A. Double-blind comparison of antihypertensive effects of verapamil and propranolol. In Calcium Antagonists in Cardiovascular Therapy. Eds. Zanchetti,A., Krikler,D.M. Excerpta Medica Amsterdam, p.260.
19. Anavekar,S.N., Christophidis,N., Louis,W.J., Doyle,A.E. Verapamil in the treatment of hypertension. J.Cardiovasc.Pharmacol. 3, 287-292, 1981.
20. Doyle,A.E. Comparison of Beta-adrenoceptor blockers and calcium antagonists in hypertension. Hypertension 5 (Suppl.II):II103-II108, 1983.
21. Hornung,R.S., Jones,R.I., Gould,B.A., Sonedra,R., Raftery, E.B. Twice daily verapamil for hypertension: a comparison with propranolol. Am.J.Cardiol. 57 Suppl:93D-98D, 1986.
22. Lewis,G.R.J. Long term results with Verapamil in essential hypertension and its influence on serum lipids.Am.J.Cardiol. 57 Suppl:35D-38D, 1986.
23. Midtbø,K., Hals.O., Van der Meer,J., Storstein,L., Lauve, O. Instant and sustained release verapamil in essential hypertension. Am.J.Cardiol. 57 Suppl:59D-63D, 1986.
24. Bühler,F.R., Hulthén,L., Kiowski,W., Müller,F.B., Bolli,P.J. The place of the calcium antagonist verapamil in antihypertensive therapy.J.Cardiovasc. Pharmacol.4:S350-S357, 1982.
25. Müller,F.B., Bolli,P., Erne,P., Kiowski,W., Bühler,F.R. Calcium antagonism - a new concept for treating hypertension. Am.J.Cardiol. 57 (Suppl.) 50D-53D,1986.
26. Waeber,B., Nussberger,J., Brunner,H.R. Does renin determine the blood pressure response to calcium entry blockers? Hypertension 7:223-27,1985.

27. Doyle,A.E., Smirk,F.H. The neurogenic component in hypertension. Circulation 12:543-558, 1955.
28. Maunelli,M., DeFeo,M.L., Maggi,M., Gepetti,P., Baldi,E., Pupilli,C., Seno,M. Effect of Verapamil on catecholamine secretion by human pheochromocytoma. Hypertension 8:813-814, 1986.
29. Benaim,M.E. Asystole after verapamil. Brit.Med.J. 2:169-170, 1972.
30. Wayne,V.S., Harper,R.W., Laufer,E., Federman,J., Anderson,S.T., Pitt,A. Adverse reaction between Beta-adrenergic blocking drugs and verapamil. Report of three cases. Aust.N.Z.J. Med. 12:285-289, 1982.
31. Hare,D.L., Horowitz,J.D. Verapamil hepatotoxicity: a hypersensitivity reaction. Am.Heart J. III:610-611, 1986.
32. Ronnov-Jensen,V., Tjernlund,A. Hepatotoxicity due to treatment with papaverine. Report of four cases. N.Eng.J.Med. 281:1333-1335, 1969.
33. Klein,H.O., Lang,W.R., Weiss,E., Segui,E.D., Libhaber,C., Guerrero,J., Kaplinsky,E. The influence of verapamil on serum digoxin concentrations. Circulation 65:998-1003, 1982.
34. Pedersen,K.E., Dorph-Pedersen,A., Hvidt,S., Klitgaard,N.A., Nielsen-Kudsk,F. Digoxin-verapamil interaction. Clin.Pharmacol.Ther. 30:311-316, 1981.
35. Yamakado,T., Oonishi,N., Kondo,S., Nozin,A., Nakano,T., Takezawa,H. Effects of diltiazem on cardiovascular responses during exercise in systemic hypertension and comparison with propranolol. Am.J.Cardiol.52:1023- 1027, 1983.
36. Frishman,W.H., Charlap,S., Goldberger,J., Kimmel,B., Stroh,J., Corsa,F., Allen,L., Strom,J. Comparison of diltiazem and nifedipine for both angina pectoris and systemic hypertension. Am.J. Cardiol. 56:41H-46H, 1985.
37. Hoffmeister,F., Kazda,S., Kauze,H.P. Influence of nimodipine (Baye 9736) on the post-ischemic changes of brain function. Acta Neurol. Scand. 60(Suppl. 72):358-9, 1979.
38. Lydtin,H., Lohmoller,G., Lohmoller,R., Schmitz,H., Walter,I. Hemodynamic studies on adalat in healthy volunteers and in patients.Proc. 2nd. Int. Adalat Symposium. Eds. W. Lochner, W. Braasch, G. Kronenberg. Springer-Verlag, Berlin, Heidelberg, New York, p.112. 1975.
39. Lund-Johansen,P., Omvik,P. Central hemodynamic changes of calcium antagonists at rest and during exercise in essential hypertension. J.Cardiovasc. Pharmacol. 10(Suppl. 1)S139-S148, 1987.
40. Nordlander,M. Hemodynamic effects of short and long term administration of felodipine in spontaneously hypertensive rats. Drugs 29(Suppl.2):90-101, 1985.

41. Hallback-Nordlander,M., Thalen,P. Differentiated resetting of vagal and sympathetic component of baroreflex control in SHR - Effects of antihypertensive therapy with felodipine. J.Hypertension 1(Suppl.2):217-219, 1983.
42. Guazzi,M., Olivari,M.T., Polese,A., Fiorentini,C., Magrini,F., Maruzzi,P. Nifedipine, a new antihypertensive with rapid action. Clin.Pharmacol.Ther. 22: 528-531, 1977.
43. Guazzi,M., Fiorentini,C., Bartorelli,A., Necchi, G., Polese,A. Short and long term efficacy of a calcium antagonistic agent (nifedipine) combined with methyl dopa in the treatment of severe hypertension. Circulation 61 913-916, 1980.
44. Guazzi,M. Use of calcium channel blocking agents in the treatment of systemic arterial hypertension. In Calcium Channel Blocking Agents in the Treatment of Cardiovascular Diseases. Eds. P.H. Stone and E.M. Antman. Futura Publishing Co. N.Y. P.387,1983.
45. Timmis,A.D., Jewitt,D.E. Studies with felodipine in congestive heart failure. Drugs 29(Suppl. 2): 66-75, 1985.
46. Olivari,M.T., Levine,T.B., Cohn,J.N. Acute hemodynamic effects of nitrendipine in chronic congestive heart failure. J.Cardiovasc.Pharmacol. 6 (Suppl.7): S1002-S1005, 1984.
47. Tumas,J., Deth,R., Kloner,R.A. Effects of nisoldipine, a new calcium antagonist on myocardial infarct size and cardiac dynamics following acute myocardial infarction. J.Cardiovasc.Pharmacol.7: 361-367, 1985.
48. Murakami,M., Murakami,E., Takekoshi,N., Tsochiya, M., Kin,T., Onoe,T., Takeuchi,N., Funatsu,T., Hara,S., Isise,S., Mifune,J., Maeda,M. Antihypertensive effect of 4-2 nitrophenyl-2, 6 dimethyl-1, 4-dihydropyridine-3, 5 dicarbonic acid dimethyl ester (Nifedipine, Bay a 1040) a new coronary vasodilator. Japan Heart J.13:128-136, 1972.
49. Aoki,K., Kondo,S., Mochijuchi,A., Yoshida,T., Kato,S., Kato,K., Takikawa,K. Antihypertensive effect of cardiovascular Ca^{2+} antagonism in hypertensive patients in the absence and presence of Beta adrenergic blockade. Am.Heart J. 96: 218-222, 1978.
50. Lederballe-Pedersen,O., Mikklesen,E. Acute and chronic effects of nifedipine in arterial hypertension.Eur.J.Clin. Pharmacol. 14 :375- , 1978.

51. Olivari,M.T., Bartorelli,C., Polese,A., Fiorentini, C., Moruzzi,O., Guazzi,M.D. Treatment of hypertension with nifedipine, a calcium antagonistic agent. Circulation 59:1056-1059, 1979.
52. Bayley,S., Dobbs,R.J., Robinson,B.F. Nifedipine in hypertension: report of a double blind controlled trial. Br.J.Clin. Pharmacol. 14:529-532, 1982.
53. Erne,P., Bolli,P., Bertel,O., Hulthén,L.,Kiowski,W. Müller,F.B., Bühler,F. Factors influencing the hypotensive effects of calcium antagonists. Hypertension 5 (Suppl.II): II97-II102, 1983.
54. Gould,B.A., Hornung, R.S., Mann,S., Subramanian, V.B., Raftery, E.B. Nifedipine or verapamil as sole treatment of hypertension. An intraarterial study. Hypertension 5(Suppl.II):II91-II96, 1983.
55. Elmfeldt,D., Hedner,T., Westerling,S. Felodipine in hypertension - a review. J. Cardiovasc. Pharmacol. 10(Suppl. 1):S154-S160, 1987.
56. Westermann,B., Houtzagers,J.J.R., Meulesteen,P. Felodipine in comparison with prazosin in hypertensive patients inadequately controlled on blockade. Drugs 29(Suppl. 2):159-160, 1985.
57. Jackson,B., Morgan,T.O., Gibson,J., Anderson,A. Felodipine versus prazosin as an addition to a β-blocker in the treatment of essential hypertension. Drugs 34 (Suppl.3):109-119, 1987.
58. The Cooperative Study Group. Felodipine versus hydrallazine: a controlled trial as third line therapy in hypertension. Brit.J.Clin.Pharmacol. 21:571-575, 1986.
59. Åberg,H., Lindsjö,M., Mörlin,B. Comparative trial of felodipine and nifedipine in refractory hypertension. Drugs 29 (Suppl.2):117-123, 1985.
60. Borgmästers,H., Forsén,B., Tuomilehto,J., Hellebø, R., Walle,P.O., Nielsen,H.M., Nielsen,E., Winkel,O., Steiners,E., Ibsen,H. Felodipine versus hydrochlorothiazide as an addition to a β-blocker in the treatment of hypertension. Drugs 34 (Suppl.3):136-138, 1987.
61. Muir,A.L., Wathen,C.G. The use of felodipine in the treatment of severe hypertension. Drugs 34 (Suppl. 3):120-124, 1987.
62. Müller,F.B., Bolli,P., Erne,P., Block,L.H., Kiowski, W., Bühler,F.R. Therapy with long acting calcium antagonist nitrendipine.J.Cardiovasc. Pharmacol. (Suppl.): S1073-S1076, 1984.
63. Smith,S.A., Maco,P.J.E., Littler,W.A. Felodipine, blood pressure and certain cardiovascular reflexes in man. Hypertension 8:1172-1178, 1986.

64. Yagil,Y., Kobrin,I., Stessman,J., Ghanem,J.N., Leibel,B., Ben-Ishay,D. Effectiveness of combined nifedipine and propranolol treatment in hypertension.Hypertension 5(Suppl.II):II113-II117, 1983.
65. Murphy,M.B., Scriven,A.J.J., Dollery,C.T. Efficacy of nifedipine as a step 3 antihypertensive. Hypertension 5 (Suppl.II): II118-II123, 1983.
66. Carruthers,S.G., Bailey,D.G. Tolerance and cardiovascular effects of single dose Felodipine/β blocker combinations in healthy subjects. J.Cardiovasc. Pharmacol. 10(Suppl. 1):S169-S176, 1987.
67. Hedner,T., Sjögren,E., Elmfeldt,D. Antihypertensive effects and pharmacokinetics of Felodipine combined with a β-blocker and a diuretic.J.Cardiovasc. Pharmacol. 10(Suppl.1):S177-S184, 1987.
68. Gustaffson,D. Microvascular mechanisms involved in calcium antagonist edema formation. J.Cardiovasc. Pharmacol. 10(Suppl.1): S121-S131, 1987.
69. Ramon,Y., Behar,S., Kishon,Y., Engleberg,I.S. Gingival hyperplasia caused by nifedipine - a preliminary report. Int.J.Cardiol. 5:195-204, 1984.
70. Leonetti,G., Sala,C., Bianchini,C., Tergoli,L., Zanchetti,A. Antihypertensive and renal effects of orally administered verapamil. Eur.J.Clin.Pharmacol. 18:375-382, 1980.
71. McLaughlin,M., de Mello Aires,M., Malnic,G. Verapamil effect on renal function of normotensive and hypertensive rats. Renal Physiol. 8:112-119, 1985.
72. Austin,M.B., Robson,R.A., Bailey,R.R. Effect of nifedipine on renal function of normal subjects and hypertensive patients with renal function impairment. N. Z. Med. J. 96:824-31, 1983.
73. Bell,A.J., Lindner,A. Effects of verapamil and nifedipine on renal function and hemodynamics in the dog. Renal Physiol. 7:329-43, 1984.
74. Leonetti,G., Cuspidi,C., Sampieri,L., Terzoli,L., Zanchetti,A. Comparison of cardiovascular, renal and humoral effects of two calcium channel blockers in normotensive and hypertensive subjects. J.Cardiovasc.Pharmacol. 4 (Suppl.3):S319-24, 1982.
75. Brown,B., Churchill,P. Renal effects of methoxyverapamil in anesthetized rats. J.Pharmacol. Exp.Ther. 225:372-77, 1983.
76. Johns,E.J. The influence of diltiazem and nifedipine on renal function in the rat. Brit. J. Pharmacol. 84:703-13, 1983.

77. Ene,M.D., Williamson,P.J., Roberts,C.J., Weddell, G. Natriuretic effects of nifedipine and nitrendipine. Brit. J. Clin.Pharmacol. 19:423-427, 1985.
78. Garthoff,B., Knorr,A., Thomas,G., Kazda,S. Nitrendipine increases sodium excretion in acutely saline loaded rats.Biochem.Pharmacol. 31:3015-6, 1982.
79. Leonetti,G., Fuscio.M., Terzoli,L., Rupoli,L., Graduik,R., Sampieri,L., Cuspidi,C., Boselli,L., Bolla,G., Zanchetti,A. Antihypertensive and water and sodium balance effects of felodipine, a new vasodilating calcium antagonist in hypertensive patients. Drugs 29(Suppl 2):185-191, 1985.
80. Abe,Y., Kamori,T., Miura,K., Takada,T.,Imauishi,M., Okahara,Y., Yamamoto,K. Effect of the calcium antagonist nicardipine on renal function and and renin release in dogs. J.Cardiovasc.Pharmacol.5: 254-259, 1983.
81. Herlitz,H., Aurell,M., Björk,S., Granérus,G. Renal effects of felodipine in hypertensive patients with reduced renal function. Drugs 29(Suppl.2): 192-197. 1985.
82. Di Bona,G.F., Sawin,L.L. Renal tubular site of action in felodipine. J.Pharmacol.Exp.Ther. 228: 420-424, 1984.
83. Häberle,D.A., Kawata,T., Davis,J.M. The site of action of nitrendipine in rat kidney. J.Cardiovasc. Pharmacol. 9(Suppl.i) S17-S23, 1987.
84. Giebisch,G., Guckian,V.A., Klein-Robbenhar,G., Klein-Robbenhar,M.T. Renal clearance and micropuncture studies of nisoldipine effects in spontaneously hypertensive rats. J.Cardiovasc.Pharmacol. 9 (Suppl.1):S24-S31, 1987.
85. Rose,H., Philipson,J., Puschett,J.B. Effect of nitrendipine in a rat model of ischemic acute renal failure. J.Cardiovasc. Pharmacol. 9 (Suppl. i) S57-S59, 1987.
86. Lee,S.M., Pattison,M.E., Michael,U.F. Nitrendipine protects against aminoglycoside toxicity in the rat. J.Cardiovasc.Pharmacol. 9(Suppl.i):S65-S69, 1987.
87. Sterzel,R.B., McKenzie,D.E. Effects of nitrendipine on the course of experimental immunologic glomerulonephritis.J.Cardiovasc.Pharmacol. 9 (Suppl.i):S60-S64, 1987.
88. Folklow,B. Physiological aspects of primary hypertension. Physiol.Rev. 62:347-5-4, 1982.
89. Doyle,A.E., Fraser,J.R.E., Marshall,R.J. Reactivity of forearm vessels to vasoconstrictor substances in hypertensive and normotensive persons.Clin.Sci. 18:431-454.

6

ANGIOTENSIN CONVERTING ENZYME INHIBITORS AS ANTIHYPERTENSIVE THERAPY

A. STEINER, D. EDMONDS, P. GREMINGER, W. VETTER

Department of Internal Medicine, University Hospital , 8091 Zürich, Switzerland

Over the past ten years, angiotensin converting enzyme (ACE) inhibitors have become increasingly established in the therapy of hypertension and congestive heart failure. Worldwide experience to date with ACE inhibitors indicates that these agents are becoming one of the drugs of choice for large unselected hypertensive populations.

INHIBITION OF THE RENIN-ANGIOTENSIN SYSTEM - PHARMACOLOGICAL CONCEPT

Angiotensin II, known as the most potent naturally occuring vasoconstrictor, is generated by release of the enzyme renin from the kidney that acts upon its substrate, circulating angiotensinogen, to free the vasoinactive decapeptide angiotensin I from its protein substrate (Fig.1). Angiotensin I promptly loses its terminal two peptides with

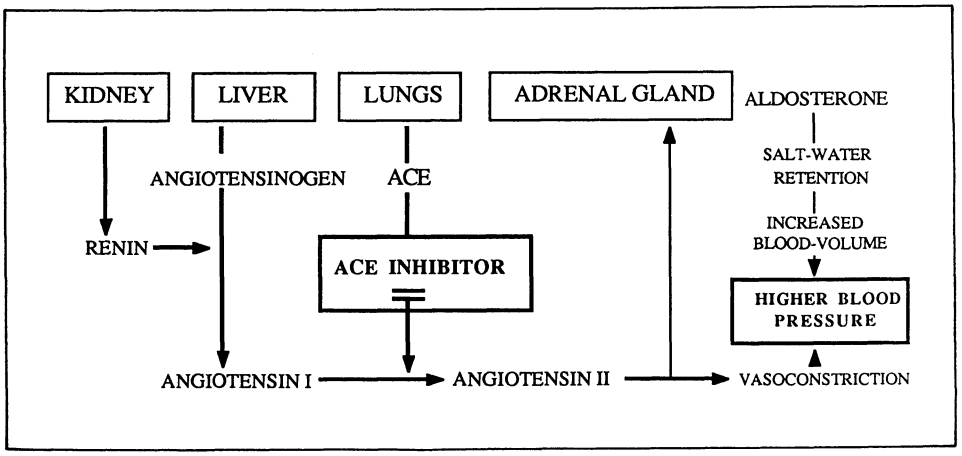


Figure 1. General scheme of the renin - angiotensin system

passage primarily through the lung by the action of the angiotensin-converting enzyme,

and forms the vasoactive octapeptide angiotensin II. Converting enzyme not only activates the vasoconstrictor angiotensin II but also inactivates bradykinin, the most potent vasodilator in the body. These series of biochemical events suggest several potential levels of the renin-angiotensin system that may be inhibited pharmacologically. All agents which inhibit neural input to the kidney inhibit renin release from the kidney and therefore less angiotensin II is generated (1).

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

An increasing number of ACE inhibitors are now in the stage of clinical testing. Captopril and lisinopril are ingested in the active form; enalapril and ramipril are administred as an inactive prodrug, which is de-esterified in the liver to the active form.

At present two ACE inhibitors are available for prescription, captopril and enalapril.

Both captopril and enalapril inhibit conversion of angiotensin I to angiotensin II and reduce arterial pressure through arteriolar dilation, i.e. reduced vascular resistance (2).

Captopril is a compound having sulfhydryl groups, a property that may provide affinity for the basement membrane.

The principal action of enalapril is the same as that of captopril. Clinical experience to date includes its use in approximately 11'000 patients, primarily those with mild to moderate hypertension. Data indicate that it is an effective antihypertensive agent with a low incidence of adverse effects (3).

ACE INHIBITORS AS A DIAGNOSTIC TOOL IN RENOVASCULAR HYPERTENSION

Several studies have shown that the renin-angiotensin system plays a fundamental role in the genesis of human renovascular hypertension. Various reports showed that blood pressure response to the prolonged administration of captopril may predict the surgical outcome of patients with renovascular disease (4). Newer data suggest that that acute administration of captopril seems to have at least the same predictive value as its prolonged administration, having the obvious advantages of a rapid information without the possible risk of developing acute renal failure (in patients with bilateral renal artery stenosis or with a solitary kidney) or the rare occurence of thrombotic occlusion of the renal artery. In one study, a single oral dose of captopril was given to patients with renovascular disease and its hypotensive effect was compared with that of surgery or of percutaneous transluminal angioplasty. The results suggest that patients

who responded well to captopril therapy prior to surgery were more likely to have a favorable response to the operation (5).

HYPERTENSIVE EMERGENCIES

ACE inhibitors offer substantial advantages compared to other vasodilating agents, not only for long-term antihypertensive treatment but also for hypertensive emergencies. Favorable results of acute treatment have been published recently (6). However, the acute blood pressure reduction in the individual patients is difficult to predict, since the hypotensive action depends on the level of pretreatment activity of the renin-angiotensin system and in addition is substantially more pronounced in patients with reduced intravascular volume or pretreatment with diuretic drugs. Therefore, a careful titration of the dose, and in certain patients who are resistant to monotherapy , the addition of a loop diuretic is recommendable. Basic laboratory workup before acute treatment is necessary to avoid unwanted effects on renal function, serum potassium or to rule out contraindications as in patients with suspected connective tissue disease. These time-consuming procedures exclude the use of ACE inhibitors as primary drugs in hypertensive emergencies (7).

MILD AND MODERATE ESSENTIAL HYPERTENSION

The effectivness of the ACE inhibitors captopril and enalapril as monotherapy for uncomplicated mild to moderate essential hypertension has been demonstrated in a variety of clinical trials (8,9,10). The observed response-rates ranged between 50 % and 60 % and are therefore comparable to those for beta-blockers (11). In agreement with these results we found in a double-blind crossover study (12) with enalapril and atenolol after a two-week therapy almost identical response-rates (diastolic pressure lower than 95 mmHg) in 57% of the enalapril group and in 59% of the Atenolol group. After an additional two weeks of therapy and in spite of having doubled the dosages, no further decrease in the blood pressure of patients with diastolic pressures higher than 90 mmHg was observed in either group (Fig.2). The observation that doubling the enalapril dose caused no further blood-pressure lowering is inconsistant with other investigations (13) which report a marked increase of the response-rates from 27 % to 53 % after doubling of the dosage. Other studies found that predominantly patients suffering from moderate to serious hypertension profit from an increased enalapril dosage (9).

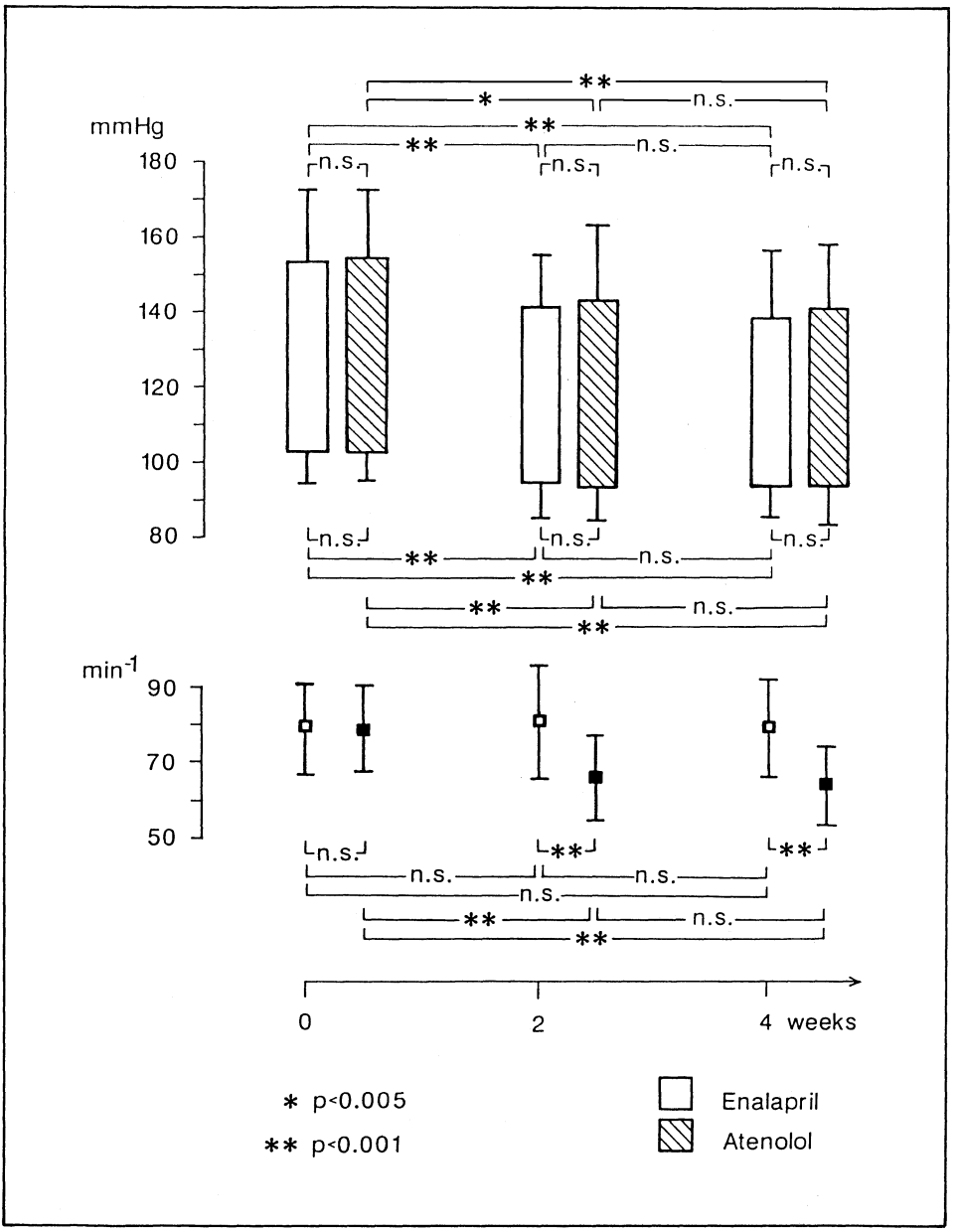


Figure. 2. Blood pressure (mmHg) and heart rate (min^{-1}) values under enalapril and atenolol (n = 58)

These conflicting data indicate that no general agreement exists about the optimal dosage of enalapril. However, it is a generally accepted fact that a once-a-day administration of enalapril causes a blood-pressure decrease lasting over a 24-hour period (14).

In long-term studies with captopril a comparable 24-hour blood-pressure lowering was achieved with a dosage between 2 x 25 mg and 2 x 50 mg a day as opposed to an administration three-times a day. In a direct comparison test captopril and enalapril showed over ten weeks an almost identical blood pressure decrease under a maximum of 3 x 100 mg captopril and 2 x 20 mg enalapril (15).
From these results it may be concluded that ACE inhibitors can to be seen as potent antihypertensive drugs for uncomplicated essential hypertension, comparable with beta-blockers and diuretics.

THERAPY RESISTANT ESSENTIAL HYPERTENSION

The treatment of therapy-resistant hypertension was the original indication for the use of ACE inhibitors. This may explain the large number of investigations about the employment of captopril in the treatment of essential hypertension resistant to standard antihypertensive drugs. The majority of these studies found a significant decrease in blood-pressure with an ACE-inhibitor, mainly in combination with a diuretic and/or a betablocker(16,17). Relatively high daily doses of up to 450 mg were administred to patients with serious hypertension during the first investigations (17,18). Newer studies proved a daily dose of 100 mg up a maximum of 200 mg to provide satisfactory blood-pressure control while burdening less with side-effects(19,20). In accordance with these investigations a study from our group showed in a comparison test between Minoxidil and captopril in patients with serious, to diuretics and beta-blockers resistant hypertension, no further decrease of blood-pressure with a dose greater than 2 x 100 mg daily (21). Both substances lead to a significant decrease of the average systolic and diastolic blood-pressure. Minoxidil showed a slightly higher response-rate than captopril. Nevertheless a higher side-effect rate under Minoxidil was determined.

SECONDARY HYPERTENSION

Renovascular hypertension

For many years nephrectomy was the only possible treatment of renovascular hypertension. Reconstructive surgical measures were increasingly applied since 1960 while at the same time potent antihypertensive agents started to be developed. The first studies of the effect of ACE inhibitors on renovascular hypertension (22) and of the introduction of the percutaneous transluminal angioplasty (PTA) of renal artery stenosis (23) appeared in 1978.

Various studies have shown that comparable curing and improving rates of surgical treatment and transluminal dilation may bee expected (24,25,26). The use of conventional antihypertensive agents allows a satisfactory blood-pressure control in approximately 50% of the patients (27). This figure may rise, according to our experience and the observations of other investigators, up to 80% (28). Recent data indicate that a reversible rise in the level of creatinine in patients with renovascular hypertension may be expected under therapy with captopril (29,30,31). The studied cases were predominantly patients with bilateral renal artery stenosis or patients with a single kidney and renal artery stenosis.

A possible explanation for the decrease in renal function in these patients is an inhibition of the contraction of the efferent arteriole, which is normally caused by angiotensin II (32). The inhibited constriction of the efferent arteriole leads to a decrease of the glomerular filtration fraction because renal perfusion pressure is normally lowered in renal artery stenosis .

Our observations indicate that the increase of the creatinine was most pronounced in patients with bilateral renal artery stenosis and in those with unilateral stenosis and markedly increased plasma renin activity before therapy. These findings indicate that it is prudent to monitor the renal function of patients with renovascular hypertension who are undergoing treatment with ACE inhibitors. Conversely, an increase in the creatinine in patients with the diagnosis of essential hypertension during treatment with ACE inhibitors should alert the clinician to the possibility of an undiagnosed renal artery stenosis.

Renal parenchymatous hypertension

The efficacy of captopril has also been demonstrated in patients with chronic renal failure (33). This is especially true in patients with terminal renal insufficiency and

uncontrollable hypertension (34,35). These cases show a low extracellular fluid volume and an increased peripheral vascular resistance (36).

We examined patients with various renal diseases who were not yet dependent on dialysis and were treated with captopril (Fig. 3). An excellent response to this therapy

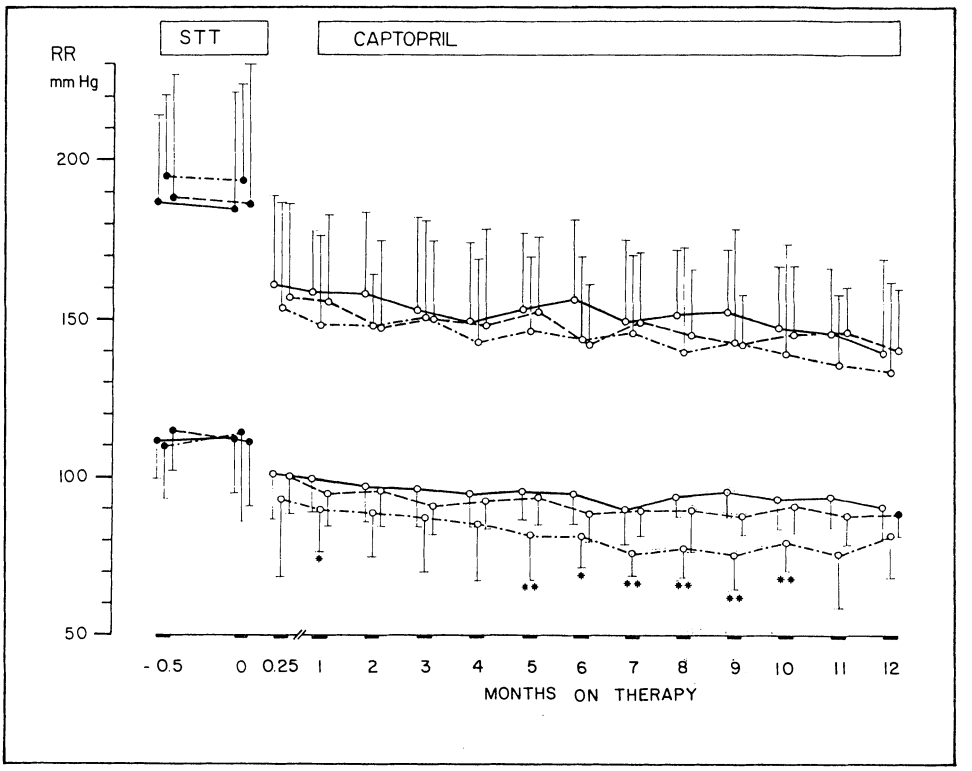


Figure. 3. Systolic and diastolic blood pressure mean values and standard deviation of 20 cases with essential (____), 15 cases with renovascular (_ . _ . _) and 16 cases with renalparenchymatous hypertension (_ _ _) during the initial phase of standard triple thearpy (STT) and the following 12 month of captopril. Statistically significant differences compared to STT are marked by open circles (o). Significant differences between the groups of patients are indicated by * for renovascular vs. essential and by ** for renovascular vs. essential and renalparenchymatous hypertension ($p<0.05$ - <0.001)

was found, the systolic mean pressure being consistently ≤160 mm Hg and the mean diastolic pressure being consistently ≤95 mm Hg. As expected, there was also an increase in average creatinine level. The serum potassium increased significantly from 4,0 to 4,5 mmol/l. In none of the patients, however, did the potassium reach dangerous levels. Other investigators found that dangerous hyperkalemia is found primarily in severe renal insufficiency with preexisting high plasma renin activity (37).

Primary aldosteronism

The plasma renin activity is suppressed in primary aldosteronism. Consequently no blood pressure lowering effect of ACE inhibitor administration is to be expected in patients with Conn's syndrome. This fact has been proven in various studies (38,39). In our observations (40), we found no decrease in blood-pressure after application of 25 mg captopril p.o. in 3 patients with single unilateral aldosterone-producing adenoma of the adrenal gland . However, a significant decrease in blood-pressure was observed after 4 weeks of therapy with 25 mg captopril and 400 mg spironolactone daily in all 3 patients. The administration of spironolactone changed the "renin-independent" form of hypertension into a "renin-dependent" form, which may explain the effectiveness of captopril. Therefore, this therapy should be considered for patients suffering from Conn's syndrome with therapy resistant hypertension. This is especially true for patients who cannot be treated surgically.

Cushing's syndrome

Hypertension is a common characteristic of patients with Cushing's syndrome. Up to now the pathogenesis of hypertension has been controversial (41,42). The following factors are dicussed: mineralocorticoid action of glucocorticoid hormones; altered pressure response to catecholamines, especially to noradrenaline on the vasculature; an increased concentration of the plasma renin substrate and changes of the renin-angiotensin system. The patients suffering from Cushing's syndrome may be divided into two groups, one with normal plasma renin activity and an other with increased plasma renin activity. Patients with increased plasma renin activity show a more marked change in blood pressure after administration of ACE inhibitors (36,41).

HYPERTENSION OF PREGNANCY

Animal experiments have shown a significantly higher rate of stillbirths under captopril administration (43). A possible explanation is that the synthesis of prostaglandin E in utero is suppressed during ACE inhibitor therapy, and therefore the utero-placental perfusion is decreased (44).
In humans one case of severe fetal malformation after Captopril application in early pregnancy has been reported (45). Furthermore a floppy infant with renal insufficiency has been reported after captopril in the 28th week of pregnancy (43). This indicates that

ACE inhibitors should not be used during pregnancy.

HYPERTENSION IN THE ELDERLY

Treatment of hypertension in the elderly has been shown to reduce both morbidity and mortality even if the treatment is started when the patient is over 65 years of age. The treatment of hypertension in patients of this age group is known to be associated with a higher rate of side effects. Considering the good subjective tolerance of ACE inhibitors, the use of these agents in this group of patients seems to be rational, particularly when signs of heart failure are present. A placebo-controlled double-blind study in patients with a mean age of 72 years showed an excellent antihypertensive effect. The medication consisted of 50 mg captopril and 25 mg hydrochlorothiazide in a single daily dose and no serious side effects were registered (46).

HYPERTENSION AND METABOLIC DISORDERS

Long-term therapy with beta-blockers or diuretics can occasionally cause an increase in the serum cholesterol level (47). It is known that thiazides may worsen an existing diabetes mellitus and cause an increase in uric acid level (48,49). In contrast these effects are lacking during monotherapy with captopril or enalapril (50,51). During combination therapy with captopril and hydrochlorothiazide, serum potassium and uric acid level decreased to normal values after having increased during diuretic monotherapy (52). These explanations make clear that ACE inhibitors should be regarded as antihypertensive agents of the first choice for patients suffering from diabetes mellitus and/or hyperuricemia.

ACE INHIBITORS AND QUALITY OF LIFE

A controlled double-blind crossover trial of captopril against placebo , on a fixed background of betablocker plus diuretic, showed a mild , but significant diminution of mood with the ACE inhibitor (53). A large multicentre study of quality of life conducted in hypertensive middle-aged persons, showed that captopril was superior in several aspects to both propranolol and methyldopa (54).
Our group evaluated the antihypertensive efficacy of and tolerance to enalapril and atenolol in a double-blind crossover study of mild to moderate hypertensive patients.

After two weeks of therapy, the incidence of adverse effects was similar in the enalapril (38%) and atenolol (36%) groups (Tab.1). Although the doses used at four weeks were doubled those used at two weeks, in more than 50% of patients, the incidence of

	Enalapril		Atenolol	
	week 2	week 4	week 2	week 4
Dizziness	16	7	5	4
Stomachache	2	0	4	2
Weakness, fatigue	14	5	5	0
Reduced efficacy	9	4	5	4
Dyspnoea	5	0	4	2
Sleep disturbance	9	5	11	5
Vivid dreams	0	0	5	2
Pruritus	4	0	5	2
Exanthema	2	0	4	0
Palpitations	4	2	0	0
Nausea	4	0	0	0
Restlessness	2	2	2	0
Cold extremities	4	0	5	2
Headache	2	2	7	0
Diarrhoea	0	0	2	0
Obstipation	0	0	7	4
Increased appetite	0	0	2	2
Dry mouth	0	0	2	0
Psychological problems	5	5	4	2
Patients with side effects	38	13	36	16

Table 1. List of side effects and patients with side effects (all values in %)

side effects had decreased in both the enalapril (13%) and atenolol (16%) groups (55).These improvements achieved in the face of increased dosage may reflect the additional 'tender loving care' associated with participation in a clinical trial. A decreasing incidence in side effects during the course of antihypertensive therapy has been observed not only in earlier trials by our group but also by other investigators (56).

SIDE EFFECTS

The most common problem related to the administration of ACE inhibitors is a dry, irritant cough. An early report suggested that this occured in about 6 % of patients and that this figure represents a good estimate of its frequency (57). Withdrawal of the ACE inhibitor relieves this symptom. The pathogenetic mechanism remains uncertain, but may involve accumulation of kinins in the respiratory mucosa.

Urticarial rashes and morbilliform eruptions have been seen with most ACE inhibitors (58). A rare but serious side effect is angio-edema under ACE inhibitors, usually occuring in the early days of therapy (59).

The two major side effects reported initially of captopril are: leukopenia (in approx. 0.3 % of the cases) and proteinuria (0.4 % of patients without preexisting renal disease) (60). All instances of granulocytopenia and most instances of proteinuria were reversed when the drug was discontinued. Two cases of pancytopenia, however, proved fatal (61,62). One other side effect of captopril therapy may be related directly to its physiological action. Since inhibition of angiotensin converting enzyme will reduce angiotensin II and aldosterone, one should anticipate hyperkalemia if potassium is prescribed with captopril therapy or potassium sparing diuretics are in use.

References

1) Frohlich, E.D. Antihypertensive therapy: newer concepts and agents. Cardiol. 72: 349 - 365, 1985

2) Ondetti M.A., Rubin B., Cushman D.W. Design of specific inhibitors of angiotensin-converting enzyme: new class of orally active antihypertensive agents. Sience 196: 441, 1979

3) Currie W.J.C., Cooper W.D. Safety of angiotensin-converting enzyme inhibitors. Lancet 1: 580, 1985

4) Atkinson A.B., Brown S.J., Cumming A.M.M., Fraser R., Lever A.F., Leckie B.J., Morton J.I., Robertson J.I.S., Davies D.L. Captopril in the management of hypertension with renal artery stenosis: its long term effect as a predictor of surgical outcome. Am. J. Cardiol. 49: 1460, 1982

5) Salvetti A., Arzilli F., Nuccorini A., Simonini N., Glorioso N., Dessi-Fulgheri P., Madeddu P., Rappelli A. Acute response to captopril as a predictive test for surgery in renovascular hypertension. Nephron 44: suppl.1 87, 1986

6) Biollaz J., Waeber B., Brunner H.R. Hypertensive crisis treated by orally administered captopril. Eur. J. Clin. Pharmacol. 25 : 145, 1983

7) Bertel O., Marx B.E. Hypertensive emergencies. Nephron 47: suppl. 1, 51, 1987

8) Croog S.H., Levine S., Testa M.A., Brown B., Bulpitt C.J., Jenkins D., Klerma G.L., Williams G.H. The effects of antihypertensive therapy on the quality of life. N. Engl. J. Med. 314: 1657-1664, 1986

9) Moncloa F., Sromovsky J.A., Walker J.F., Davies R.O. Enalapril in hypertension and congestive heart failure. Overall review of efficacy and safety. Drugs 30 (Suppl. 1)

82-89, 1985
10) Yodfat Y., Fidel J., Bloom D.S. Captopril as a replacement for multiple therapy in hypertension: a controlled study. J. Hypertension 3 (Suppl. 2): 155-158, 1985
11) Morgan T.O., Sabto J., Anavekar S.N., Louis W.J., Doyle A.E. A comparison of beta adrenergic blocking drugs in the treatment of hypertension. Postgrad. Med. 50: 253-259, 1974
12) Edmonds D., Knorr M., Greminger P., Walger P., Frielingsdorf J., Vetter H., Vetter W. ACE inhibitors versus beta-blocker in the treatment of essential hypertension. Nephron 47: 90, 1987
13) Bergstrand R., Herlitz H., Johansson S., Berglund G., Vedin A., Wilhelmson C., Gomez H.J., Crillo V.J., Bolognese J.A. Effective dose range of enalapril in mild to moderate essential hypertension. Br. J. Clin. Pharmac. 19: 605-611, 1985
14) Brunner H.R., Waeber B. Nussberger J., Schaller M.D., Gomez H.J. Long-term clinical experience with enalapril in essential hypertension. J. Hypertension 1 (Suppl. 1): 103-107, 1983
15) Ayers C.R., Baker K.M., Weaver B.A., Lehman M.R. Enalapril maleate versus captopril. A comparison of the hormonal and antihypertensive effect. Drugs 30 (Suppl.1): 70-73, 1985
16) Atkinson A.B., Lever A.F., Brown J.J., Robertson J.I.S. Combined treatment of severe intractable hypertension with captopril and diuretic. Lancet 2: 105-108 1980
17) Case D.B., Atlas S.A., Sullivan P.A., Laragh J.H. Acute and chronic treatment of severe and malignant hypertension with the oral angiotensin-converting enzyme inhibitor captopril. Circulation 64: 765-771, 1981
18) Atkinson A.B., Brown J.J., Cumming A.M.M., Fraser R., Lever A.F., Leckie B.J., Morton J.J., Robertson J.I.S., Davies D.L. Captopril in the management of hypertension with renal artery stenosis: its long term effect as a predictor of surgical outcome. Am. J. Cardiol. 49: 1460-1466, 1982
19) Smith S.J., Markandu N.D., Mac Gregor G.A. Optimal dose of captopril in hypertension. Lancet 2: 1460, 1982
20) Veterans Administration Cooperative Study Group on Antihypertensive Agents: Low-dose captopril for the treatment of mild to moderate hypertension. Hypertension 5 (Supp. 3): 139-144, 1977
21) Greminger P., Foerster E., Vetter H., Baumgart P., Vetter W. Minoxidil and captopril in severe hypertension. Klin. Wochenschr. 64: 327-332, 1986
22) Gavras H., Brunner H.R., Turini G.A., Kershaw G.R., Tift C.P., Cuttelod S., Gavras I., Vukovich R.A., McKinstry D.N. Antihypertensive effect of the oral angiotensin-converting enzyme inhibitor SQ 14.225 in man. N. Engl. J. Med. 298; 991-995, 1978
23) Grüntzig A., Kuhlmann U., Vetter W., Lütolf U., Meier B., Siegenthaler W. Treatment of renovascular hypertension with percutaneous transluminal dilatation of a renal artery stenosis. Lancet 1: 801-802, 1978
24) Forster J.H., Maxwell M.H., Franklin S.S., Bleifer K.H., Trippeö O.H., Julian O.C., De Camp P.T., Varady P.T. Renovascular occlusive disease: results of operative treatment. J. Am. Med. Ass. 231: 1043-1048, 1983
25) Largiader F. Operative techniques in renovascular hypertension. Nephron 44 (Suppl. 1): 32-35, 1986
26) Grim C.E., Luft F.C., Yune H.Y., Klatte E.C., Weinberger M.H. Ann. Percutaneous transluminal dilatation in the treatment of renal vascular hypertension. Intern. Med. 95: 439-442, 1981
27) Hunt C.J., Strong C.G. Renovascular hypertension: mechanisms, natural history and treatment. Am. J. Cardiol. 32: 562-574, 1973
28) Case D.B., Atlas S.A., Laragh J.H. Long-term efficacy of captopril in renovascular and essential hypertension. Am. J. Cardiol. 49: 1440-1446, 1982
29) Coulie P., De Plaen J.F., van Yepersele de Strihou C. Captopril-induced acute reversible renal failure. Nephron 35, 108-111, 1983
30) Hricik D.E., Broening P.J., Kopelman R., Goorno W.E., Madias N.E., Dzau

V.J. N. Captopril-induced functional renal insufficiency in patients with bilateral renal-artery stenosis in a solitary kidney. Engl. J. Med. 308: 373-376, 1983
31) Greminger P., Vetter H., Steurer J., Siegenthaler W., Vetter W. Captopril and kidney function in renovascular and essential hypertension. Nephron 44 (Suppl. 1): 91-95, 1986
32) Watson M.L., Bell G.M., Muir A.L., Buist T.A.S., Kellet R.J., Padfield P.L. Captopril/diuretic combinations in severe renovascular disease. Lancet 2: 404-405, 1982
33) Brunner D.B., Desponds G., Biollaz J., Keller I., Ferber F., Gavras H., Brunner H.R., Schelling J.L. Effect of a new angiotensin-converting enzyme inhibitor MK-421 and its lysine analogue on the components of the renin system in healthy subjects. Br. J. Clin. Pharmac. 11: 461-467, 1981
34) Vaughan E.D. Jr., Carey R.M., Ayers C.R., Peach M.J. Hemodialysis-resistant hypertension: control with an orally active inhibitor of angiotensin-converting enzyme. J. Clin. Endocrinol. Metab. 48: 869-871, 1979
35) Wauters J.P., Waeber B., Brunner H.R., Guignard J.P., Turini G.A:, Gavras H. Uncontrollable hypertension in patients on hemodialysis: long-term treatment with captopril and salt subtraction. Clin. Nephrol. 16: 86-92, 1981
36) Davies D.L., Schalenkamp M.A., Beevers D.G., Brown J.J., Briggs J.D., Lever A.F., Medina A.M. Morton J.J., Robertson J.I.S., Tree M. Abnormal relation between exchangeable sodium and the renin-angiotensin system in malignant hypertension and in hypertension with chronic renal failure. Lancet 1: 683-686, 1973
37) Textor S.C., Bravo E.L., Fouad F.M., Tarazi R.C. Hyperkalemia in azotemic patients during angiotensin-converting enzyme inhibition and aldosterone reduction with captopril. Am. J. Med. 73: 719-725, 1982
38) Brunner H.R., Gavras H., Waeber B., Textor F.C., Turini G.A., Wauters J.P. Clinical use of an orally acting converting enzyme inhibitor: captopril. Hypertension 2: 558-566, 1980
39) Mantero F., Fallo F., Opocher G., Armanini D., Boscaro M., Scaroni C. Effect of angiotensin II and converting enzyme inhibitor (captopril) on blood pressure, plasma renin activity and aldosterone in primary aldosteronism. Clin. Sci. 61: 289s-293s, 1981
40) Stimpel W., Vetter W., Groth H., Greminger P., Vetter H. Captopril before and after spironolactone therapy in primary aldosteronism. Klin. Wochenschr. 63: 361-363, 1985
41) Greminger P., Vetter W., Groth H., Lüscher T., Tenschert W., Siegenthaler W., Vetter H. Captopril in Cushing's syndrome. Klin. Wochenschr. 62: 855-858, 1984
42) Krakoff L., Nicolis G., Amsel B. Pathogenesis of hypertension in Cushing's syndrome. Am.J.Med. 58: 216-220, 1975
43) Broughton Pipkin F., Symonds E.M., Turner S.R. The effect of captopril upon mother and fetus in the chronically cannulated ewe and in pregnant rabbit. J. Physiol. 323: 415-422, 1980
44) Ferris T.F., Weir E.K. Effect of captopril on uterine blood flow and prostaglandin E synthesis in the pregnant rabbit. J.Clin. Invest: 71: 809-815, 1983
45) Duminy P.C., Burger P.D. Fetal abnormality associated with the use of captopril during pregnancy. S. Afr. Med. J. 60: 805, 1981
46) Creisson C., Baulac L., Lenfant B. Captopril/hydrochlorothiazide combination in elderly patients with mild - moderate hypertension. A double blind, randomized, placebo controlled study. Postgrad. Med. J. 62 (Suppl. 1): 139-141, 1986
47) Weidmann P., Gerber A., Mordasini R. Hypertension 5 (Suppl.3): 120-131, 1983
48) Bulpitt C.J. Serum uric acid in hypertensive patients. Br. Heart J. 37: 1210-1215, 1975
49) Perez- Stable E., Caralis P.V. Thiazide-induced disturbances in carbohydrate, lipid, and potassium metabolism. Am. Heart J. 106, 245-251, 1983
50) Groel J.T., Tadros S.S., Dreslinski G.R., Jenkins A.C. Long-term antihypertensive treatment with captopril. Hypertension 5 (Suppl. 3): 145-151,1983
51) Malini P.L., Strocchi E., Ambrosini E., Magnani B. Long-term antihypertensive,

metabolic and cellular effects of enalapril. J. Hypertension 2 (Suppl. 2): 101-105, 1984
52) Weinberger M,H. Influence of an angiotensin-converting enzyme inhibitor on diuretic-induced metabolic effects in hypertension. Hypertension 5: suppl. 3, 132-138, 1983
53) Callender J.S., Hodsman G.P., Hutcheson M.J., Lever A. F., Robertson J.I.S. Mood changes during captopril therapy for hypertension: a double-blind pilot study. Hypertension 5 : suppl. 3, 90-93, 1983
54) Croog S.H., Levine S., Testa M.A., Brown B., Bulpitt C.J., Jenkins C.D., Klerman G.L., Williams G.H. The effects of antihypertensive therapy on the quality of life. N. Engl. J. Med. 314: 1657 -1664, 1986
55) Edmonds D., Vetter H., Vetter W. Angiotensin-converting enzyme inhibitors in the clinic: quality of life. J. Hypertension 5 suppl.3: 31 -35, 1987
56) Mann A.H. Hypertension: psychological aspects and diagnostic impact in a clinical trial. Psychol. Med. suppl.5 Monog., 1977
57) Havelka J, Vetter H, Studer A, Greminger P, Luscher T, Wollnik S, Siegenthaler W, Vetter W. Acute and chronic effects of the angiotensin-converting enzyme inhibitor captopril in severe hypertension. Am J Cardiol 49: 1467 - 1474, 1982
58) Ball SG, Robertson JIS. A need for new converting enzyme inhibitors? Br Med J 290: 180 -181, 1985
59) Robertson JIS, Tillman DM. Treatment of hypertension with converting enzyme inhibitors. J Cardiovasc Pharmacol (in press)
60) Captopril: benefits and risks in severe hypertension (editorial). Lancet 2: 129, 1980
61) Gavras I., Graff L.G., Rose B.D. et al. Fatal pancytopenia associated with the use of captopril. Ann. Intern. Med. 94: 58, 1981
62) Matri A.E., Larabi M.S., Kechrid C. et al. Fatal bone-marrow suppression associated with captopril. Br. Med. J. 283: 277, 1981

THE KIDNEY IN PREGNANCY

7

PREVENTION OF PREECLAMPSIA

A. DAL CANTON, G. ROMANO*, P. VENIERO*.
Division of Nephrology, University of Reggio Calabria, Faculty of Medicine at Catanzaro, via T. Campanella, 88100 Catanzaro; * Department of Nephrology, II Faculty of Medicine, University of Naples, via S. Pansini, Naples, Italy.

IS IT POSSIBLE TO PREDICT PREECLAMPSIA ?

Ideally, treatment to prevent preeclampsia should be limited to patients in whom the disorder can be accurately predicted. Unfortunately, in most cases prediction is impossible since the typical preeclamptic patient is a young primipara with no previous evidence of disease, in whom a sudden rise in blood pressure develops in association with proteinuria and edema. Efforts have been made, however, to find PREDICTIVE TESTS that are of help in anticipating the occurrence of preeclampsia.

Some pathologic conditions, either preceding or complicating pregnancy, are associated with increased incidence of preeclampsia. Patients that are affected by these disorders are, therefore, AT RISK for developing preeclampsia.

PREDICTIVE TESTS

Angiotensin Sensitivity Test.

Pregnant women with preeclampsia have an increased sensitivity to infused angiotensin II (1). Gant suggested that this hypersensitivity precedes preeclampsia, and proposed a predictive test consisting of the i.v.

infusion of progressively increasing doses of angiotensin II, up to the dose able to raise BP by 20 mm Hg (Effective Pressor Dose, EPD). The test is positive (i.e. predictive of preeclampsia) in subjects at 28 to 32 weeks'gestation in whom the EPD is lower than 8 ng/kg body weight/min (2). The validity of this test has been questioned, however, due to the high incidence of false-positive results (3,4). It seems clearly established that the predictive value of a negative test is higher than that of a positive test (5). In addition, the test is cumbersome. Thus, we suggest that this test is performed only in patients enrolled in a controlled study aimed to define either the validity of the test or the effects of a preventive treatment. The risk of a sudden increase in blood pressure mandates that the test be performed under careful monitoring.

Measurement of Plasma Volume.

Plasma Volume (PV) increases during normal gestation. In contrast, a decrease in PV is a well know feature of preeclampsia. There is evidence that a reduction of PV precedes the onset of preeclampsia (6) and that PV depletion is predictive of severe preeclampsia (7). Serial measurements of PV may be useful, therefore, for monitoring selected patients known to be at special risk for preeclampsia, for example patients with chronic hypertension in pregnancy (see below, PATIENTS AT RISK).

Serum Uric Acid.

Serum Uric Acid concentration decreases in the first half of pregnancy. Then it rises slowly till the end of

gestation, remaining lower then in normal non-pregnant women (8). A rise in serum uric acid concentration above the limit of normal for a given point in gestation has been considered as pathognomonic of preeclampsia (9). The rise in serum uric acid occurs very early and precedes the decrease of GFR in preeclamptic patients (10); thus hyperuricemia is an early diagnostic clue of preeclampsia. Redman et al. (11), however, have emphasized that the level of serum uric acid is predictive of the severity of preeclampsia; in their study of 332 women with pregnancy-induced hypertension, perinatal mortality rate rose steeply when serum uric acid concentration was higher than 0.36 mmol/liter (6.0 mg/100 ml) . The relation of severe preeclampsia with high serum uric acid has been confirmed by Ferris et al. (12), who set the critical level at 5.5 mg/100 ml (0.33 mmol/liter), and Riedel et al. (13) who suggest special care in fetal monitoring when serum uric acid exceeds 0.315 mmol/liter after 32 weeks' gestation. The level of serum uric acid, therefore, is useful to anticipate the risk for development of a severe preeclampsia.

Roll-Over Test.

Gant et al. (14) described the "roll-over test"in primigravid women between 28 and 32 weeks' gestation. The subject is placed in the left lateral recumbent position and blood pressure is measured every 5 minutes until a constant diastolic value is established. Then the subject is turned to the supine position and the blood pressure is measured immediately and again 5 minutes later. An increase in the diastolic blood pressure of at least 20 mmHg is considered a positive pressure response. In

Gant's original work, there was an excellent correlation between the roll-over test and the angiotensin sensivity test. Twenty of the 22 subjects with a negative roll-over test (91%) remained normotensive throughout pregnancy.

Fifteen of 16 subjects with positive test (93%) later developed preeclampsia. The roll-over tests reported by Gudson et al (15) Marshall and Newmann (16) and Karbhari et al (17) demonstrated false-positive rates of 15%, 16% and 7%, respectively and false-negative rates of 7.5%, 9% and 7% respectively. More recently, Tunbridge and Donnai (18) performed the test in 100 primigradae, with much less satisfactory results; of the 10 women with positive tests, in fact, only 2 later developed hypertension. Of the 90 patients with a negative test, 17 subsequently developed diastolic blood pressures > 90 mmHg. The reasons for these discrepancies are not evident.

Simplicity makes this test very attractive; thus, further studies should be done in a large population to define its real predictive validity.

Other signs of potential use in prediction of Preeclampsia.

Preeclampsia may be associated with and is perhaps preceded by a fall in platelet count (19). Recently, however, Fay et al (9) have given evidence against the utility of monitoring platelet count to predict preeclampsia.

Fibronectin is a glycoprotein contained in endothelial cells and in alpha granules of platelets. Lazarchick et al (20) have shown that plasma fibronectin levels increase before the onset of preeclampsia, suggesting that an endothelial abnormality is the

earliest process in preeclampsia. These authors have suggested that a plasma fibronectin level higher than 400 microg/ml predicts preeclampsia some weeks before the onset of clinical symptoms.

Erskine et al. (21) have recently shown that the ratio of 18:2 [9,11] to 18.2 [9,12] linoleic acid in plasma phospholipids at 28 weeks' gestation is increased in women destined to develop preeclampsia. This alteration would reflect an increased free-radical activity occuring before the onset of symptoms of preeclampsia. This interesting phenomenon, however, was observed in a very limited number of patients and further studies are necessary to assess its clinical utility.

PATIENTS AT RISK.

Chronic Hypertension in Pregnancy.

There is no doubt that chronic hypertension in pregnancy (CHP), i.e. pregnancy occuring in a patient suffering from preceding hypertension, predisposes to preeclampsia (22). The onset of preeclampsia in a patient with CHP is signaled by a further rise in BP, the appearance of proteinuria and/or edema. The mechanisms by which CHP predisposes to preeclampsia are not well understood. CHP may cause ischemia of the feto-placental unit and this has been supposed to have a pathogenic role in preeclampsia (23). CHP may be associated with urinary loss of salt and hypovolemia (24, 25) and a reduction in plasma volume precedes the onset of preeclampsia (6).

Renal Disorders.

Leppert et al. (26) have shown that the incidence of complications of pregnancy -including preeclampsia- is increased in patients with active renal disease, especially when serum creatinine exceeds 1.6 mg/100 ml.

The increased risk of preeclampsia in nephropatic patients has been confirmed by others (22,27,28). The reasons for this negative effect of renal disorders include CHP and, possibly, alterations in the immune-system and activation of intravascular coagulation.

Bacteriuria.

The association of bacteriuria with preeclampsia was first noted many years ago (29). Recently, Hill et al. have confirmed that preeclampsia occurs with increased frequency in patients with asymptomatic bacteriuria (30); Sack et al. (31) have examined a population of women in whom asymptomatic bacteriuria had been previously documented during childhood, and have concluded that preeclampsia occurs with increased frequency only in patients in whom bacteriuria is associated with renal scarring.

Preeclampsia-Eclampsia in previous pregnancies.

Bryons and Torpin reported 40 years ago that 36% of 243 women affected by eclampsia had at least one recurrence in subsequent pregnancies (32). Sibai et al (33) recently reported on the subsequent pregnancy outcome of 406 women having severe preeclampsia or eclampsia in their first pregnancy; 46.8 % had recurrent preeclampsia in the second pregnancy; preeclampsia occurred in an additional 20.7% in successive pregnancies after the second.

Genetic Factors

In 1961, Chelsey (34) and Adams and Finlay (35) separately studied the incidence of preeclampsia in daughters, daughters in law and grand-daughters of preeclamptic women and concluded that preeclampsia is a highly hereditable disorder with a single gene transmission modality. In 1979 , Cooper and Lister (36)

suggested that the susceptibility to preeclampsia depends on trasmission of a single recessive gene. The influence of genetic factors is also supported by the association of preeclampsia with fetal genetic disorders (37).

Paternal Factors.

Preeclampsia occurs more frequently in women mated with men of different race (38); a role of paternal factors is also suggested by anecdotal reports of different women who developed preeclampsia when bearing sons of the same man (39).

Other Risk Factors.

Diabetes Mellitus, severe Rh immunization, twin pregnancies and molar pregnancies increase the incidence of preeclampsia (40, 41).

WHEN ARE PREVENTIVE MEASURES INDICATED ?

Prevention of preeclampsia requires repeated laboratory examinations and the use of drugs. Thus, prevention is not costless and causes risk (from drug assumption) and discomfort to the patient. As discussed above, we are still looking for a safe and simple test by which to predict with high probability the development of preeclampsia in otherwise healthy women. In these, the probability of carrying out unnecessary procedures and the inherent costs and risks counterbalance the potential benefit of avoiding preeclampsia. Therefore, we currently believe that it is not justified to include patients in a program of prevention unless (a) this is made in the spirit of and with the cautions of a controlled clinical study or (b) we are dealing with patients at special risk of preeclampsia. Unfortunately, the definition of "special risk" is still largely subjective.

Tentatively, we suggest that a patient is considered

at special risk when she is affected by at least 1 of the main risk factors that have been discussed above (CHP, renal disease, preeclampsia in previous pregnancies) or a combination of 2 or more of the other risk factors (bacteriuria with renal scars, partner of different race, diabetes mellitus, Rh immunization, molar pregnancy, twin pregnancy). In these patients a program of prevention may be started independently of the results predictive tests; studies investigating the validity of the predictive tests in patients at risk, however, are lacking and are badly needed.
A special type of prevention consists of ensuring that mild preeclampsia does not worsen to become a severe preeclampsia. Clearly in this case, prevention largely coincides with treatment. This, however, is the kind of prevention that the physician is most often faced with.

PREVENTIVE TREATMENT.

Antiplatelet and Anticoagulation Treatment

It is well known that preeclampsia is associated with signs of platelet activation and intravascular coagulation (42, 43). It is not clear whether these changes have a primary pathogenic role, or they are complications occurring after preeclampsia has already been established (19, 44). Recently, it has been suggested that preeclampsia results from imbalanced production of thromboxane A2 and prostacyclin in the fetal and maternal circulations (45). Excessive synthesis of thromboxane A2 relative to that of prostacyclin would account for vasoconstriction, platelet hyperactivity and intravascular coagulation (46). Based on these premises, Beaufils and coworkers were the first to try to prevent preeclampsia by early antiplatelet therapy (47). These

authors selected 102 patients judged to be at particularly high risk for preeclampsia, either on the basis of their obstetrical history (several previous complicated pregnancies) or because they had vascular risk factors (e.g., known essential hypertension, familial hypertension). Patients were randomly allocated to treatment with 300 mg dipyridamole and 150 mg aspirin daily from 3 months' gestation onwards, or no treatment. In the treated group (48 women) no case of preeclampsia , or major fetal complications occurred. In contrast, preeclampsia developed in 6 patients of control group (45 women); in addition, in the control group there were 6 fetal losses and 4 cases of severe growth retardation. These results, therefore, support the utility of antiplatelet therapy in selected patients judged to be at special risk on a clinical basis.

Almost simultaneously with Beaufils' paper, another paper was published by Wallenburg and coworkers (48). The approach of these authors to prevention of preeclampsia differed from that of Beaufils in two respects: first, patients were selected among primigravid women judged to be at risk because of a positive angiotensin sensitivity test at 28 weeks' gestation and second, that only low-dose aspirin (60 mg daily) was administered. The choice of low-dose aspirin regimen was based on evidence that this dose is able to reduce platelet thromboxane A2 synthesis while not affecting vascular prostacyclin production (49). In the control (placebo) group (23 women) pregnancy-induced hypertension (PIH), pre-eclampsia and eclampsia developed in 4, 7, and 1 cases, respectively; in contrast, in the aspirin group only 2 out of 23 women developed mild PIH. These results suggest that low-dose aspirin restores prostacyclin/ thromboxane imbalance and prevents the development of

preeclampsia in patients in whom the risk for the disorder is not predictable on a simple clinical basis.

Both Beaufils' and Wallenburg's studies have raised great interest. Concern, however, has been expressed for the possible adverse effects of aspirin in pregnancy, including prenatal closure of the ductus arteriosus, hemorragic complications, retardation of spontaneous delivery and alteration of surfactant synthesis (50, 51). Clearly, further studies are recommended to arrive at definite conclusions about the risk/benefit ratio of antiplatelet therapy to prevent preeclampsia. In the meantime, we feel that treatment is justifiable in patients at high risk for preeclampsia, as judged on a clinical basis (see above for the definition of "high risk"). A low-dose regimen may be preferable to reduce the risk of complications.

Maintaining normal Plasma Volume expansion.

Preeclampsia is associated with a reduction of plasma volume, a rise in hematocrit due to hemoconcentration, and blood hyperviscosity (52, 53). The reduction of plasma volume occurs early in preeclampsia (7) and there is evidence that a fall in plasma volume precedes the onset of the disorder (6). Goodlin, in fact, has suggested that preeclampsia results from the inability of the pregnant women to "appriopriately increase her blood volume commensurate with the increase in size of her uterus" (7). Even if others have considered the decrease of plasma volume in preeclampsia as a merely secondary phenomenon (54), there is little doubt that the severity of the disorder is related with the degree of plasma volume contraction (55). Thus, maintaining plasma volume expansion during gestation is at least

useful to reduce the risk of severe preeclampsia . During pregnancy, therefore, liberal fluid and salt intake should be allowed and protein consumption should be encouraged to help maintaining adequate plasma protein concentration.

Diuretic treatment is contraindicated, with the exception of severe congestive heart failure. Actually, even in patients with chronic hypertension in pregnancy (e.g., essential hypertension) the use of diuretics has been shown to have either deleterious or no beneficial effects (56, 57). Restriction of salt intake, or diuretic treatment are inappropriate in healthy, pregnant women if there is only a mild edema of the legs. This condition may be considered normal in many pregnant women, especially in the last trimester (58).

Debatable questions are whether plasma volume should be activelely expanded (e.g. by intravenous fluid infusion) and in which patients, when, and how this should be done (7, 22, 59). At present, there are no definite guidelines acceptable by general consent. Personally, we feel that repeated plasma volume measurements are useful in patients at high risk for preeclampsia, especially in patients with chronic hypertension in pregnancy. In these patients, in fact, plasma volume is inversely related to blood pressure (6) and hypertension is associated with a salt-losing disposition (24,25). The first plasma volume measurement should be done in the first trimester; the regular increase in plasma volume should then be checked at approximately 26 weeks' and 36 weeks' gestation. Finding a decreased or even constant plasma volume should alert the physician to the fact that preeclampsia is probably developing. The state of fluid and salt balance should then be appropriately investigated and, if balance is

negative, an adequate oral fluid and salt intake should be restored. Daytime bed rest should be prescribed, because this is a simple way to increase circulating blood volume (7). Finally, cautious expansion by i.v. infusion of Albumin (50-100 ml of a 20% solution daily) may be be carried out for 3 days a week for 2-3 weeks. Afterwards, plasma volume should be checked again. In some patients, preeclampsia may occur after the last measurement of plasma volume had indicated a normal increase. In these patients, plasma volume should be checked again immediately and, if it is decreased, the procedure mentioned above should be carried out.

Maintaining normal Blood Pressure.

Treatment of chronic hypertension in pregnancy has been recently reviewed (60). Here we emphasize that the treatment of CHP may reduce the occurrence of superimposed preeclampsia. Methyldopa is still thought of as the drug of choice, mainly because it has been widely employed and a vast knowledge of this drug has accumulated (61). Hydralazine has long been used, and its use is preferred in association with beta-blockers. This last cathegory of drugs has been intensively investigated in the last years: promising results have been obtained especially with beta-blockers possessing intrinsic sympathomimetic activity, like Pindolol. Despite previous concerns these drugs seem not to reduce uterine blood flow despite effectively decreasing blood pressure (62,63). Selective beta-blockers (atenolol, metoprolol) have been preferred by others because they should not interfere with uterine activity (61, 64). Converting enzyme inhibitors and calcium channel blocking agents have not yet been adequately investigated in pregnant women. Caution should be used especially with ACE

inhibitors, because in a study of pregnant animals (ewes and rabbits) treatment with captopril resulted in a high incidence of intrauterine fetal death (65).

Prevention of complications of severe Preeclampsia.

Severe preeclampsia has been defined as the association of a blood pressure of 160/110 mm Hg with either generalized edema or proteinuria (at least 3+ on dipstick examination) (66, 67). This definition, however, is not universally accepted. The criteria followed by Moore and Redman, for example, were a rise in systolic and diastolic BP of at least 30 and 15 mm Hg respectively, an antenatal BP exceeding 140/90, and a persistent proteinuria of 2+ on Albustix, or 1.0 g or more per litre (68). Others stress the concept that severe preeclampsia is characterized by the onset of complications such as oliguric renal failure (69), increased serum transaminases (70), the HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelet count) (71), or Diffuse Intravascular Coagulation (42). Independently of the criteria used to define severe preeclampsia, these maternal complications and the high incidence of perinatal morbidity and mortality are the reasons that make preeclampsia "severe". Bed rest, normalization of blood pressure by antihypertensive treatment and prevention of plasma volume contraction are the basic principles to prevent complications of severe preeclampsia. (59). A further rise in serum uric acid concentration, a rise in hematocrit, a fall in plasma volume and platelet count are early signs indicating worsening of preeclampsia and the need for more vigorous treatment. A problem raised by severe preeclampsia is whether the patient should be delivered early, to prevent serious maternal morbidity, or whether conservative

treatment should be instituted to reduce the problems of prematurity of the infant. Sibai et al reported on the effects of conservative treatment in 60 patients in whom severe preeclampsia developed between 18-27 weeks' gestation, i.e. at a time of high fetal immaturity (22). Management included bed rest, sedation, aggressive antihypertensive therapy and intensive antepartum fetal surveillance by means of ultrasonography, antepartum fetal heart rate testing, and assessments of fetal pulmonary maturity. In these patients, maternal morbidity was frequent and, occasionally, life-threatening. Abruptio placentae was the most frequent complication, followed by thrombocytopenia, diffuse intravascular coagulation, the HELLP syndrome, and acute renal failure. The 60 pregnancies resulted in 31 stillbirths and 21 neonatal deaths, for a perinatal mortality of 87% . In addition, 28 of the live-born infants (97%) had an Apgar score of 4 or less at 1 minute. These results confirm other reports that the attempt to delay delivery in patients with severe preeclampsia expose the mother to severe morbidity and even mortality (71, 72, 73), and the increased risk for the mather is not associated with any benefit to the neonate (7, 74).

In contrast to the poor or absent benefits of conservative management in midtrimester patients, prolongation of pregnancy may improve fetal outcome in patients of 26 weeks' gestation onwards (75). Fetal outcome is improved especially in patients at more than 29 weeks' gestation (66). Steroids can be used to accelerate fetal lung maturity (76). Thus, it seems reasonable to delay delivery in patients at 29 weeks' gestation or more until fetal lung maturity is obtained, provided that acute maternal and fetal distress are absent. An exception to this rule may be represented by

patients in whom preeclampsia is superimposed on chronic hypertension; Sibai et al., in fact, have shown that prolongation of pregnancy is particularly hazardous in these patients (66).

Conclusions.

In conclusion, the prevention of preeclampsia is still mostly experimental. New studies are necessary both to understand the real predictive value of available tests and to confirm the utility of treatment. Patients enrolled in a program of prevention should be considered as part of a controlled investigation. The only exception may consist of patients judged to be at high risk for the disorder either because of their obstetric history or due to the existance of a serious predisposing disease. In these selected cases, low-dose aspirin and careful monitoring and maintenance of plasma volume expansion are indicated.

REFERENCES

1. Talledo, O.E., Chelsey, L.C., Zuspan, F.P. Renin-Angiotensin system in normal and toxemic pregnancies. Am. J. Obstet. Gynecol. 100:218-221,1968.
2. Gant, N.F., Daley, G.L., Chand, S., Whalley, P.J., Mac Donald, P.C. A study of Angiotensin II pressor response throughout primigravid pregnancy. J. Clin. Invest. 52:2682-2689,1973.
3. Morris, J.A., O'Grady, J.P., Hamilton, C., Davidson, E.C. Vascular reactivity to Angiotensin II infusion during gestation. Am. J. Obstet. Gynecol. 130:379-384, 1978.
4. Orozco, J.Z., Pinsker, V.S., Hernandez, J., Karchmer, S. Valor de la preuba de la Angiotensina II y del " Roll Over Test" como metodos predictivos de la enfermedad hipertensiva aguda del embarazo (preeclampsia/eclampsia). Ginecol. Obstet. Mex. 46:235,1979.
5. Oney, T.,Kaulhausen, H. The value of the Angiotensin sensitivity test in the early diagnosis of hypertensive disorders in pregnancy. Am. J. Obstet. Gynecol. 142:17-20,1982.
6. Gallery, E.D.M., Hunyor, S.N., Gyory A.Z. Plasma volume contraction: a significant factor in both pregnancy-associated hypertension (pre-eclampsia) and chronic hypertension in pregnancy. Quart. J. Med. 192: 593-602, 1979.
7. Goodlin,R.C. Severe pre-eclampsia: another great imitator. Am. J. Obstet. Gynecol. 125:747-752,1976.
8. Lindt, E., Godfrey, K.A., Otun, H., Philips, P.R. Changes in serum uric acid concentration during normal pregnancy. Br. J. Obstet. Gynecol. 91:128-132,1984.
9. Fay, R.A., Bromham, D.R., Brooks, J.A., Gebski, V.J. Platelets and uric acid in prediction of preeclampsia. Am. J. Obstet. Gynecol. 152:1038-1039, 1985.
10. Seitchik, J. Observations on the renal tubular reabsorbtion of uric acid. Normal pregnancy and abnormalpregnancy with and without preeclampsia. Am. J. Obstet. Gynecol. 65:981-985,1953.
11. Redman, C.W.G., Beilin, L.J., Bonnar, J., Wilkinson, R.H. Plasma-urate measurements in predicting fetal death in hypertensive pregnancy. Lancet 1:1370-73,1976.
12. Burrow, G.N., Ferris, T.F. Medical complication during pregnancy. W.B. Saunders Company, Phyladelphia,1982.
13. Riedel, H., Eisenbach, G.M., Haeckel, R., Buttner, J. The importance of monitoring uric acid concentrations to evaluate the risk from gestosis. In: Pregnancy Hypertension. M.B. Samour Editor Ain Shams University press, Cairo 83,1982.

14. Gant, N.F., Chand S., Worley, R.J., Whalley, P.J., Crosby, V.D., Donald, P.C., A clinical test for predicting the development of acute hypertension in pregnancy. Am. J. Obstet. Gynecol. 120:1-7,1974.
15. Gudson, J.P., Anderson, S.G., May, W.S. A clinical evaluation of the roll-over test for pregnancy induced hypertension. Am J. Obstet. Gynecol. 127:1-3,1977
16. Marshall, J.W., Newman,R.L. Roll over test. Am. J. Obstet. Gynecol. 127:623-625,1977.
17. Karbhari, D., Harrigan, J.T., La Magra, R. The supine hypertension test as a predictor of incipient preeclampsia. Am. J. Obstet. Gynecol. 127:620-622,1977.
18. Tunbridge, R.D.G., Donnai, P. Pregnancy-associated hypertension, a comparison of its prediction by "Roll-Over Test" and plasma Noradrenaline measurement in 100 primigravidae. Brit. J. Obstet. Gynecol. 90:1027-1032,1983.
19. Redman, G.W.G., Bonnar, J., Beilin, L. Early platelet consumption in Preeclampsia. Br. Med. J. 1:467-469,1978.
20. Lazarchick, J., Stubbs, T.M., Romein, L., Van Dorsten, J.P., Loadholt, C.B. Predictive value of fibronectin levels in normotensive gravid women destined to became preeclamptic. Am. J. Obstet. Gynecol. 154:1050-1052,1986.
21. Erskine, K.J., Iversen, S.A., Davies, R. An altered ratio of 18:2(9,11) to 18:2(9,12) linoleic acid in plasma phospholipids as a possible predictor of preeclampsia. Lancet 1,554-555,1985.
22. Sibai, B.M., Taslini, M., Abdella, T.N., Brooks, T.F., Spinnato, S.A., Anderson, G.D. Maternal and perinatal outcome of coservative management of severe preeclampsia in midtrimester. Am. J. Obstet. Gynecol. 152:32-37,1985.
23. Anonimous. Hypertension in pregnancy. Lancet 2:487-489,1975.
24. Dal Canton, A., Altomonte, M., Conte, G., Esposito, C., Fuiano, G., Romano, G., Russo, D., Sabbatini, M., Uccello, F., Veniero, P., Andreucci, V.E. Glomerular dynamics and salt balance in pregnant rats with renal hypertension. Am. J. Physiol. in press
25. Conte, G., Dal Canton, A., Terribile, M., Fuiano, G., Esposito, C., Andreucci, V.E. Exaggerated natriuresis in chronic hypertension in pregnancy. Proc. EDTA-ERA 22:493-497,1985.
26. Leppert, P., Tisher, C.C., Cheng, S-C.S., Harland, W.R. Antecedent renal disease and the outcome of pregnancy. Ann.Intern.Med. 90:747-751,1979.

27. Dal Canton, A., Dell'Aglio, P., Olivetti, G., Gardini, F., Benassi, L., Migone, L. EPH-Gestosis isolated and complicating a pre-existing renal disease. Panminerva Medica 19:415-422,1977.
28. Hayslett, J.P. Interaction of renal disease and pregnancy. Kidney Int. 68:579-587,1984.
29. Peters, J.P., Lavietes, P.H., Zimmerman, H.M. Pyelitis in toxemias of pregnancy. Am. J. Obstet. Gynecol. 32:911,1936.
30. Hill, J.A., Devoe, L.D., Iverson Bryans jr, C. Frequency of asymptomatic bacteriuria in preeclampsia. Obstet. Gynecol. 67:529-532,1986.
31. Sacks, S.H., Roberts, R., Verrier Jones, K., Asscher, A.W., Ledingham, J.G.G. Effect of symptomless bacteriuria in childood on subsequent pregnancy. Lancet 2:991-994,1987.
32. Bryans, C.L., Torpin, R. A follow up study of two hundred forty-three cases of eclampsia for an average of twelve years. Am. J. Obstet. Gynecol. 58:1054,1949.
33. Sibai, B.M., El-Nazer, A., Gonzales-Ruiz, A. Severe preeclampsia-eclampsia in young primigravid women : subsequent pregnancy outcome and remote prognosis. Am. J. Obstet. Gynecol. 155:1011-1016,1986.
34. Chelsey, L.C., Cosgrove, R.A., Annitto, J.E. Pregnancy in the sisters of daughters of eclamptic women. Path. Microbiol. 24:662-666,1961.
35. Adams, E.M., Finlayson, A. Familial aspects of preeclampsia and hypertension in pregnancy. Lancet 2: 1375-1378,1961.
36. Cooper, D.S., Liston, W.A. Genetic control of severe preeclampsia. J. Med. Genet. 16:409-416,1979.
37. Bower, C., Stanley, F., Walters, B.N.J. Pre-eclampsia and trisomy 13. Lancet 2:1032,1987.
38. Alderman, B.W., Sperling, R.S., Daling, J.R. An epidemiological study of the immunogenetic aetiology of preeclampsia. Br. Med. J. 292:372-374,1986.
39. Astin, M., Scott, J.R., Worley, R.J. Preeclampsia/ eclampsia: a fatal father factor. Lancet 2:533,1981
40. McMullan, P.F., Norman, R.J., Marivate, M. Pregnancy-induced hypertension in twin pregnancy. Brit.J. Obstet. Gynecol. 91:240-243,1984.
41 Symonds, E.M. Genetics of hypertension in pregnancy. Brit. J. Obstet. Gynecol. 93:897,1986.
42. Mc Kay, D.G. Chronic intravascular coagulation in normal pregnancy and preeclampsia. Contrib. Nephrol. 25:108-119,1981.
43. O'Brien, W.F., Saba, I., Knuppel, R.A., Scerbo, J.C., Choen, G.R. Alterations in platelet concentration and aggregation in normal pregnancy and preeclampsia. Am. J.Obstet. Gynecol. 155:486-490,1986.

44. Bonnar, J., McNicol, G.P., Douglas, A.S. Coagulation and fibrinolytic sistems in preeclampsia and eclampsia. Brit. Med. J. 2:12-16,1971.
45. Wallenburg, H.C.S., Rotmans, N. Enhanced reactivity of the platelet thromboxane pathway in normotensive and hypertensive pregnancies with insufficient fetal growth. Am. J. Obstet. Gynecol. 144:523-528,1982.
46. Lindheimer, M.D., Kats, A.I. Pathophysiology of preeclampsia. Ann. Rev. Med. 32:273-289,1981.
47. Beaufils, M., Uzan, S., Donsimoni, R., Colav, J.C. Prevention of preeclampsia by early antiplatelet therapy. Lancet April 13:840-842,1985.
48. Wallenburg, H.C.S., Dekker, G.A., Makovitz, J.W., Rotmans, P. Low-dose aspirin prevents pregnancy-induced hypertension and preeclampsia in angiotensin-sensitive primigravidae. Lancet 1:1-3,1986.
49. Masotti, G., Galanti, G., Poggesi, L., Abbate, R. Differential inhibition of prostacyclin production and platelet aggregation by aspirin. Lancet 2:1213-1216,1979
50. Rennie, J. Aspirin and preeclampsia. Lancet 1:328,1986.
51. Stuard, M.J., Gross, S.J., Elrad, J., Graeber, E. Effects of Acetylsalicilic-acid ingestion on maternal and neonatal hemostasis. N. Engl. J. Med. 307:909-912, 1982.
52. Buchan, P.C. preeclampsia: a hyperviscosity syndrome. Am. J. Obstet. Gynecol. 142:111-113,1982.
53. Matthews, J.D., Mason, T.M. Plasma viscosity and preeclampsia. Lancet 2:409,1974.
54. Assali, N.S., Vaughn, D.L. Blood volume in preeclampsia: fantasy and reality. Am. J. Obstet. Gynecol. 129:355-359,1977.
55. Goodlin, R.C. In defense of conservative management of severe preeclampsia. Am. J. Obstet. Gynecol. 156:924,1987.
56. Sibai, M., Grossman, R.A., Grossman, H.G. Effects of diuretics on plasma volume in pregnancies with long-term hypertension. Am. J. Obstet. Gynecol. 150:831-835,1984.
57. Collins, R., Yusuf, S., Peto, R. Overview of randomised trials of diuretics in pregnancy. Brit. Med. J. 290:17-23,1985.
58. Chelsey, L. Diagnosis of pre-eclampsia. Obstet. Gynecol. 65:423-425,1985.
59. Fliegner, J.R. Correction of hypervolemia and central venous pressure monitoring in the management of severe preeclampsia and eclampsia. Am. J. Obstet. Gynecol. 156:1041-1042,1987.

60. Andreucci, V.E., Dal Canton, A., Russo, D. Treatment of chronic hypertension in pregnancy. In " The kidney in pregnancy", V.E. Andreucci Editor. Martinus Nijhoff Boston,1986.
61. Liedholm, H., Melander, A. Drug selection in the treatment of pregnancy hypertension. Acta Obstet. Gynecol. Scand. Suppl. 118:49-55,1984.
62. Lundgren, Y., Karlsson, K., Ljungblad, U. Acute haemodynamic effects of pindolol during pregnancy in experimental renal hypertension. Acta Obstet. Gynecol. Scand. suppl. 118:85-90,1984.
63. Lunell, N.O., Nyulund, L., Lewander, R., Sarby, B., Wager, J. Uteroplacental blood flow in pregnancy hypertension after the administration of a beta-adrenoceptor blocker, pindolol. Gynecol. Obstet. Invest. 18:269-274,1984.
64. Sandstrom, B. Clinical trials of adrenergic antagonist in pregnancy hypertension. Acta Obstet. Gynecol. Scand. suppl. 118:57-60,1984.
65. Broughton Pipkin, Turner, F. The effect of angiotensin converting enzyme inhibition in pregnant animals . In: Pregnancy Hypertension ed. M.B. Samour Ain Shams University press , Cairo : 507,1982.
66. Sibai, B.M., Spinnato, J.A., Watson, D.L., Hill, G.A., Anderson, G.D. Pregnancy outcome in 303 cases with severe preeclampsia. Obstet. Gynecol. 64:319-325,1984.
67. Martin, T.R., Tupper, W.R.C. The management of severe toxemia in patients at less than 36 weeks' gestation. Obstet. Gynecol. 54:602-605,1979.
68. Moore, M.P., Redman, C.W.G. Case control study of severe preeclampsia of early onset. Brit. Med. J. 287:580-583,1983.
69. Clark, S.L., Greenspoon, J., Aldahl, D., Phelan, J.P. Severe preeclampsia with persistent oliguria: management of hemodynanic subsets. Am. J. Obstet. Gynecol. 154:490-494,1986.
70. Gleicher, N., Theofilopoulos, A.N. Immunecomplexes in pregnancy. Lancet 1:216,1979.
71. Weinstein, L. Symdrome of hemolysis, elevated liver enzyme and low platelet count: a severe consequence of hypertension in pregnany. Am. J. Obstet. Gynecol. 142:159-167,1982.
72. Hibbard, L.T. Maternal mortality due to acute toxemia. Obstet. Gynecol. 42:263-270,1973.
73. Andersen, W.A., Harbert, G.M. Conservative management of preeclamptic and eclamptic patients:a reevalutation. Am. J. Obstet. Gynecol. 129:260-267,1977.
74. Lin, C.C., Lindheimer, M.D., River, P., Moawad, A.H. Fetal outcome in hypertensive disorders of pregnancy. Am. J. Obstet. Gynecol. 142:255-260,1982.

75. Dillon, W.P., Egan, E.A. Aggressive obstetric management in late second-trimester deliveries. Obstet. Gynecol. 58:685-690,1981.
76. Ricke, P.S., Elliot, J.P., Freeman, R.K. Use of corticosteroids in pregnancy-induced hypertension. Obstet. Gynecol, 55:206-210,1980.

PEDIATRIC NEPHROLOGY

8

CYCLOSPORIN IN THE THERAPY OF IDIOPATHIC NEPHROTIC SYNDROME IN CHILDREN

P. NIAUDET and M. BROYER

Service de Nephrologie Pédiatrique and INSERM U 192, Hôpital Necker-Enfants Malades, 149 rue de Sèvres, 75015 Paris, France

INTRODUCTION

Idiopathic nephrotic syndrome, which is the most frequent glomerular disease in children, is defined by the combination of nephrotic syndrome and minimal change glomerular disease, with foot process fusion on electron microscopy. No immunoglobulin or complement fraction deposits are seen on immunofluorescent examination. However, in some cases, diffuse mesangial proliferation or focal and segmental glomerulosclerosis may be seen on light microscopy. In addition, immunofluorescent examination sometimes reveals mesangial immunoglobulin deposits found either in isolation or in association with C_{1q} and/or C_3 deposits. The most frequently found immunoglobulin is IgM, leading some authors to consider IgM nephropathy as a disease entity (1). IgA deposits have also been found in some patients (2, 3) as well as granular C_3 deposits.

There have been many retrospective and prospective studies devoted to the clinical significance of these various morphological features. Many authors use the term of nephrosis synonymously with minimal change disease and consider nephrotic syndrome with focal and segmental glomerulosclerosis, diffuse mesangial proliferation or IgM deposits as distinct entities. The main arguments are that the response to treatment and the clinical course can be different. There is nevertheless a clinical overlap between the different anatomical entities (4). For example, focal and segmental glomerular sclerosis can occur in patients whose first biopsy showed minimal change lesions or diffuse mesangial proliferation. Although the

morphological anomalies do indeed carry prognostic significance, they in no way allow distinct and specific diseases to be identified. It thus seems preferable to think of idiopathic nephrotic syndrome or nephrosis as a syndrome with different clinical and histological variants.

Experience has shown that response to steroid therapy carries greater prognosis weight than the histological features seen on the initial renal biopsy. Thus, two types of nephrosis can be described in function of the clinical response to steroid therapy: steroid-responsive nephrosis, in which proteinuria rapidly resolves and steroid-resistant nephrosis, in which the nephrotic syndrome persists despite treatment.

In the vast majority of childhood cases, nephrosis is steroid responsive. There are several possible outcomes after the first remission. The original episode remains unique and remission is definitive (20 to 30% of cases). In 10 to 15% of cases, relapse occurs several months after stopping therapy and cure takes place in most cases after two to three such episodes. However, most cases relapse as soon as steroid therapy is withdrawn or when the dosage is decreased after the first month of daily steroid therapy. This constitutes steroid-dependent nephrosis, which has a mean course of five to ten years. The severity of the condition lies less in the risk of developing end-stage renal failure which is an extremely rare outcome, than in the complications of treatment. When the level of steroid therapy required to maintain remission is too high, the side-effects force one to resort to other drugs, particularly immuno-suppressive agents. Immunosuppressive agents, mainly alkylating agents, have been used in such situations and have been shown effective in several controlled studies. However, the potential toxic effects from these drugs have led to avoid them unless the cost-benefit analysis is positive, i.e., when maintaining steroid therapy is contraindicated. Cyclophosphamide is the drug most frequently prescribed in this situation at the dose of 2.5 to 3 mg/kg BW for six to eight weeks. Chlorambucil, which is easier to manage, may also be used, below a total dose of 8 mg/kg BW. The duration of remission after this type of treatment depends on the severity of

the nephrosis. Some patients relapse again but the disease may be more easily controlled by low-dose steroids. The limitation on the longer use of alkylating agents lies on their long-term toxic effects, in particular the risks of cancer and leukemia and the gonadal complications, particularly in boys.

In 10% of cases, the nephrotic syndrome persists unchanged after the initial course of steroid therapy. In such cases of steroid-resistant nephrosis, the severity of the condition lies essentially in the risk of developing end-stage renal failure. This occurs in one-third to one-half of cases, whatever the histopathologic pattern observed on initial renal biopsy. Some children progress to cure with slowly decreasing proteinuria. The efficacy of alkylating agents in this situation is open to question as the percentage of full or partial remissions after treatment is fairly similar to that of the patients who remit without any treatment. Nevertheless, there have been case reports in which full remission has occurred on treatment with alkylating agents.

IMMUNOSUPPRESSIVE ACTION OF CYCLOSPORIN

Cyclosporin is a new immunosuppressive drug (5) which has been introduced in clinical organ transplantation a decade ago (6). The drug, isolated from fungi, is a cyclic endecapeptide of 11 amino acids with a molecular weight of 1200 (7). Cyclosporin acts selectively on helper T lymphocytes. B lymphocytes, macrophages and granulocytes are not affected by the drug. Cyclosporin does not affect myeloid or erythroid proliferation.

Cyclosporin suppresses T lymphocyte responses. The drug inhibits the in vitro proliferation response of T lymphocytes to polyclonal activators and to allogeneic cells in the mixed lymphocyte reaction. It also inhibits the generation of cytotoxic T lymphocytes in the mixed lymphocyte reaction but, once generated, it does not affect the cytotoxic activity of T lymphocytes. The action of cyclosporin on helper T lymphocytes can be explained by its capacity to block the release of interleukine 2 (IL_2) (8). However the expression of IL_2 receptors and the response of activated lymphocytes to exogenous IL_2 are not affected by the drug. Cyclosporin

also blocks the release of other lymphokines such as interleukine 1 and gamma interferon. Cyclosporin has a sparing effect on T suppressor lymphocytes (9). The major site of action seems to be the inhibition of lymphokine gene transcription, thus preventing the elaboration of interleukines, which are essential messengers of the immune response.

In experimental animals, cyclosporin has been shown to be very effective in preventing allograft rejection and in suppressing spontaneous or induced autoimmune diseases.

IMMUNOLOGIC ABNORMALITIES IN IDIOPATHIC NEPHROTIC SYNDROME

Cyclosporin has been used in patients with idiopathic nephrotic syndrome following several observations suggesting that immunological abnormalities may be implicated in the disease. Indeed, several abnormalities in both humoral and cellular immunity have been reported. An impaired immunoglobulin production in vivo and in vitro has been found (10-13). Alterations of cellular immunity have also been reported: decreased skin reactivity to common antigens in patients in relapse (14-15), toxicity of lymphocytes from patients with minimal change disease to renal tubular epithelial cells (16), decreased lymphoblast transformation (17). Several studies have also shown an increased lymphokine production in particular for the monocyte migration inhibitory factor (18), the soluble immune response suppressor factor (19) and the vascular permeability factor (20). However, some of these abnormalities have been found also in patients with other forms of the nephrotic syndrome suggesting that they could be secondary to the nephrotic syndrome rather than the cause of proteinuria. Nonetheless, indirect evidence of an immune basis for nephrosis remains compelling as suggested by Shalhoub (21). This author suggested that lymphokines could render the glomerular basement membrane more permeable to proteins.

CYCLOSPORIN IN STEROID-SENSITIVE IDIOPATHIC NEPHROTIC SYNDROME

Among the children with idiopathic nephrotic syndrome who initially respond to prednisone therapy, approximately 60% of them have either frequent relapses or are steroid-dependent. Cyclosporin

has been used in those patients who had developed serious steroid side-effects.

Hoyer et al. (22) have treated five steroid responders who had frequent relapses despite cytotoxic therapy. Cyclosporin was given at a daily dose of 150 to 200 mg/m^2 in order to maintain trough levels between 200 and 400 ng/ml. The treatment was started after the remission had been obtained with prednisone 100 mg/m^2/day. Alternate day prednisone was then given for eight weeks and the dose was decreased. All five patients responded to cyclosporin with fewer relapses (mean 4.2 relapses during the six months before cyclosporin and one relapse per patient during the six months of treatment) and reduced prednisone requirements (mean 113 to 48 mg/kg).

Capodicasa et al. (23) have treated six frequently relapsing children with cyclosporin at an initial dose of 150 mg/m^2. The dosage was adjusted to obtain trough blood levels of 200 to 400 ng/ml. Methylprednisolone was given initially at a dose of 60 mg/m^2/day and after the remission had been obtained at a dose of 35 mg/m^2 every other day. Cyclosporin and steroids were withdrawn after six months. This treatment induced a long-lasting remission of 12 to 14 months after initiation of cyclosporin in five children. The remaining patient relapsed one month after cyclosporin withdrawal.

Niaudet et al. (24) gave cyclosporin to 20 steroid-dependent children who had suffered serious side-effects of steroid therapy. The initial daily dose was 6 mg/kg and this was adjusted to obtain trough plasma levels of 50 to 150 ng/ml. Cyclosporin was given for at least three months before tapering. Seventeen out of the 20 patients either went into remission or did not relapse despite the fact that prednisone was withdrawn. At the final examination, 10 of the 12 children in whom cyclosporin had been tapered off and who had initially responded to cyclosporin had relapsed: seven while receiving cyclosporin at doses varying between 0.7 to 5 mg/kg, two as soon as cyclosporin was withdrawn and the remaining patient two months after cyclosporin withdrawal. Prednisone could be lowered but not stopped in one patient and the remaining two patients relapsed when prednisone was tapered off.

Tejani et al. (25, 26) treated 13 steroid-dependent nephrotic children with cyclosporin starting at 7 mg/kg/day. The dose was adjusted to maintain trough HPLC whole blood levels between 100 and 200 ng/ml. Cyclosporin was given for eight weeks and discontinued. Prednisone, 5 to 10 mg every day, was given during the first 10 to 14 days. Among the 13 patients, 11 achieved remission. Four of these 11 patients had remained in remission for over nine months after discontinuation of therapy. The other seven patients had relapsed following cyclosporin therapy.

Table 1. Response of steroid-responders to cyclosporin

Author	Number of patients	Dose of cyclosporin	Duration of treatment	Responders to cyclosporin
Hoyer et al. (22)	5	150-200 mg/m^2	6 months	5
Capodicasa et al. (23)	6	150 mg/m^2	6 months	6
Niaudet et al. (24)	20	6 mg/kg	3 months	17
Tejani et al. (26)	13	7 mg/kg	2 months	11
Total	44			39

In conclusion, as shown on Table 1, of 44 steroid-dependent children treated with cyclosporin at doses varying between 5 to 7 mg/kg/day, 89% responded to the treatment. The duration of the remission varies. Most patients have relapsed during the tapering phase of cyclosporin treatment or at cyclosporin withdrawal while few patients have had a sustained remission.

CYCLOSPORIN IN STEROID-RESISTANT IDIOPATHIC NEPHROTIC SYNDROME

Around 10% of children with idiopathic nephrotic syndrome fail to respond to steroid therapy. Cyclosporin has been given to such patients in small uncontrolled trials.

Capodicasa et al. (23) have treated four steroid non-responsive children with a combination of cyclosporin and steroids over a six-month period. Cyclosporin was started at a dose of 150 mg/m^2 and adjusted to maintain trough blood levels between 200 and 400 ng/ml.

Two of the four patients went into remission and were still protein-free five and six months after the end of the treatment.

Brandis et al. (27) gave cyclosporin alone at a dose of 100 to 300 mg/m^2 to four steroid non-responders over a six-month period. The four patients went into complete remission within eight weeks. One patient experienced a relapse four months after cyclosporin withdrawal but came again into remission after cyclosporin was reintroduced.

Waldo and Kohaut (28) treated with cyclosporin for six weeks six patients who had failed to respond to prednisone. Cyclosporin was given at a dosage of 300 mg/m^2 and then adjusted to maintain trough levels between 100 and 300 ng/ml. Only one patient had a significant reduction of proteinuria. However, in this patient, proteinuria returned to pretreatment levels one month after cyclosporin withdrawal. In the five other patients, proteinuria remained unchanged despite cyclosporin therapy.

Table 2. Response of steroid non-responders to cyclosporin

Author	Number of patients	Dose of cyclosporin	Responders to cyclosporin	
			Partial	Complete
Capodicasa et al. (23)	4	150 mg/m^2		2
Brandis et al. (27)	4	100-300 mg/m^2		4
Waldo and Kohaut (28)	6	200-400 mg/m^2	1	
Niaudet et al. (24)	10	6 mg/kg	2	1
Brodehl et al. (29)	7	100-200 mg/m^2	2	
Tejani et al. (26)	7	7 mg/kg		3
Total	38		5	10

Niaudet et al. (24) treated with cyclosporin ten children with steroid-resistant idiopathic nephrotic syndrome. The initial daily dose was 6 mg/kg. The dosage was adjusted to maintain trough plasma levels between 50 and 150 ng/ml. The duration of treatment varied between two and seven months. One patient went into complete remission within the first month of treatment and remained in

remission three months after cyclosporin withdrawal. Two patients had a partial and transient response to the treatment and, in the remaining seven patients, cyclosporin was without any effect on the nephrotic syndrome.

Brodehl et al. (29) gave cyclosporin to seven steroid non-responders starting at a dose of 100 mg/m^2/day, followed by an increase to achieve trough blood levels of 200-400 ng/ml. Patients were treated for periods of 6 to 29 months. No patient went into complete remission but two patients had a partial remission with normalization of serum albumin and four patients had a significant reduction of proteinuria.

In conclusion, as shown on Table 2, among the 38 steroid non-responsive patients, only 26% went into complete remission and in most cases, the remission has been long-lasting. A partial response was observed in 13% of cases, but this response was usually transient.

RESPONSE TO CYCLOSPORIN ACCORDING TO MORPHOLOGIC CLASSIFICATION

Among the children treated with cyclosporin, 39 were classified as minimal change disease by histological examination (22-26). Twenty-eight of them (72%) responded to cyclosporin. Thirty-seven patients had lesions of focal and segmental glomerulosclerosis on renal biopsy (23, 24, 29-29) and only 13 of them (35%) responded to cyclosporin whereas 6 had a partial and transient response to therapy. Tejani et al. (26) reported on six patients who were classified as IgM nephropathy. Five of them responded to cyclosporin. Niaudet et al. (24) found mesangial IgM deposits on renal biopsy of seven patients, five of whom responded to cyclosporin.

These data show that the response of patients with idiopathic nephrotic syndrome is better correlated to the initial steroid responsiveness than to the histological category. Indeed, 89% of steroid responders and only 26% of steroid non-responders reacted to cyclosporin whereas 72% of patients with minimal change disease and 35% of those with focal and segmental glomerulosclerosis did so.

Table 3. Response to cyclosporin according to histologic pattern

Histologic pattern	Number of patients	Responders to cyclosporin	
		Partial	Complete
Focal and segmental glomerulosclerosis			
Capodicasa et al. (23)	2	-	1
Brandis et al. (27)	3	-	3
Waldo and Kohaut (28)	6	1	-
Niaudet et al. (24)	9	3	3
Brodehl et al. (29)	7	2	-
Tejani et al. (26)	10	-	6
Total	37	6	13
IgM nephropathy			
Niaudet et al. (24)	7		5
Tejani et al. (26)	6		5
Total	13		10
Minimal change disease			
Hoyer et al. (22)	5		5
Capodicasa et al. (23)	8		7
Niaudet et al. (24)	23		14
Tejani et al. (26)	3		2
Total	39		28

SIDE-EFFECTS OF CYCLOSPORIN IN IDIOPATHIC NEPHROTIC SYNDROME

The main unwanted effect of cyclosporin is nephrotoxicity (30), which is generally evidenced by deteriorating renal function. However, in idiopathic nephrotic syndrome, renal insufficiency may occur either in relapsing steroid-sensitive idiopathic nephrotic syndrome or as end-stage renal failure develops in steroid-resistant idiopathic nephrotic syndrome. Therefore, it is not always possible in patients with idiopathic nephrotic syndrome treated with cyclosporin to determine to what extent deterioration of renal function is due to drug-induced nephrotoxicity or to renal insufficiency due to the renal disease itself, especially as the two events can, at least in theory, be superimposed on one another.

An impairment of renal function has been reported in 26 cases out of 83 patients treated with cyclosporin. In 19 of them, the rise of serum creatinine was transient with a rapid return to pretreatment values at the end of cyclosporin therapy. Some of these patients experienced a transient increase of serum creatinine during a relapse of a steroid-sensitive nephrotic syndrome. Impairment of renal function was partially reversible or non-reversible in seven patients, all of them with a steroid-resistant nephrotic syndrome. In such cases, the deterioration of renal function could be related to the natural course of the disease. Most patients who experienced nephrotoxicity had persistent nephrotic syndrome or were in relapse when the glomerular filtration rate was noted to be decreased, which suggests that factors other than cyclosporin nephrotoxicity may have been operative.

Changes in renal histology following cyclosporin have been documented in two studies. Tejani et al. (25) reported on three patients with repeat renal biopsy after eight weeks of cyclosporin therapy and noted no changes in two and tubular atrophy in one. Niaudet et al. (24) performed repeat renal biopsies in 11 patients. They noted no significant changes in six patients and vacuolization of the cells lining the proximal convoluted tubules in two patients with moderate interstitial fibrosis and few atrophic tubules in one. Marked changes were noted in three patients. The first, steroid-sensitive, case with deteriorating renal function during a relapse on cyclosporin, had biopsy evidence of focal and segmental glomerulosclerosis in two-thirds of the glomeruli, moderate interstitial fibrosis and vacuolization of some convoluted tubules. The second, steroid-resistant, case whose renal function remained normal throughout the duration of the treatment, developed, within an 8-month period, diffuse interstitial fibrosis with focal aggregates of inflammatory cells, groups of atrophic tubules and vacuolization of convoluted tubules. The severest deterioration was seen in a patient with renal insufficiency that was partially reversible after cyclosporin was stopped. There were many areas of calcified tubular necrosis with interstitial fibrosis that were most probably related to cyclosporin treatment.

The other side-effects give less cause for concern. Moderate elevation of blood pressure has been reported in 13 patients, hyperkalemia in 3 patients, hypertrichosis in 27 patients, gum hypertrophy in 11 patients and finally hypomagnesemia in 32 patients.

COMPARISON WITH THE EFFICACY OF CYCLOSPORIN IN ADULT IDIOPATHIC NEPHROTIC SYNDROME

Several authors have reported their experience with cyclosporin treatment in adults with idiopathic nephrotic syndrome. Meyrier et al. (31) treated six adult patients, including three with minimal change disease who went into remission within 12 to 42 days of treatment but became cyclosporin-dependent and three patients who responded only partially to cyclosporin. Lagrue et al. (32) treated 13 patients, 10 of whom were steroid-resistant. A remission was observed in seven cases, all with minimal change disease, three with steroid-dependent and four with steroid-resistant nephrotic syndrome. Five steroid-resistant patients, two with minimal change disease and three with focal and segmental glomerulosclerosis, had a partial remission. The 12 patients who responded to cyclosporin relapsed after the end of the treatment. Chan and Cheng (33) reported on eight steroid-dependent adults with minimal change disease treated for eight to ten weeks with cyclosporin at doses of 7.5 to 10 mg/kg BW. They observed a transient remission in only one patient. Meyrier and Simon (34) recently reported the preliminary results of a cooperative study of the French Society of Nephrology concerning 45 patients treated with cyclosporin for at least three months. Of the 22 patients with minimal change disease, 11 were in total remission and 4 in partial remission. Conversely, among the 23 patients with focal and segmental glomerulosclerosis, only 4 were in total remission and 9 in partial remission. Unfortunately, the authors did not correlate the results of cyclosporin treatment with the response to steroids.

CONCLUSIONS

Cyclosporin is effective in most cases of steroid-responsive idiopathic nephrotic syndrome. It may be of help in patients who

develop serious side-effects of steroid therapy as an alternative to alkylating agents. However most of the patients relapse when cyclosporin is decreased or withdrawn. Further studies are needed to know if low doses of cyclosporin or an association of low doses of cyclosporin and prednisone may be effective and safe for long periods in these patients.

Conversely, cyclosporin seems to be less effective in steroid-resistant patients. The discrepancies observed between the different trials may be explained in part by different definitions of steroid resistance. Most authors define steroid resistance as the failure to respond to daily prednisone (2 mg/kg BW) given for one month. Other authors give the treatment for eight weeks or give methyl-prednisolone pulses following four weeks of daily prednisone therapy. In adult patients, the daily prednisone dose varies between 0.33 to 2 mg/kg BW. Cyclosporin may be effective in steroid-resistant patients if given early in the course of the disease. A cooperation study of the French Club of Pediatric Nephrology using cyclosporin in association with prednisone in children with steroid-resistant idiopathic nephrotic syndrome is in progress. In this trial, only patients who have had the disease for less than two years are included.

Nephrotoxicity is the main side-effect. Impairment of renal function occurs mainly in patients with steroid-resistant idiopathic nephrotic syndrome. Cyclosporin should be cautiously prescribed to patients with nephrotic syndrome.

REFERENCES

1. Cohen, A.H., Border, W.A. and Glassock, R.J. Nephrotic syndrome with glomerular mesangial IgM deposits. Lab. Invest. 38: 610-619, 1978.
2. Katz, A., Walker, J.F. and Landy, P.J. IgA nephritis with nephrotic range proteinuria. Clin. Nephrol. 20: 67-71, 1983.
3. Mustonen, J., Pasternack, A. and Rantala, I. The nephrotic syndrome in IgA glomerulonephritis: response to corticosteroid therapy. Clin. Nephrol. 20: 172-176, 1983.
4. Habib, R. and Churg, J. Minimal change disease, mesangial proliferation glomerulonephritis and focal sclerosis: individual entities or a spectrum. IN: Nephrology (Ed. R.R. Robinson) Springer Verlag, New York, 1984, pp. 634-644.

5. Borel, J.F., Gubler, H.U. and Stahelin, H. The biological effects of Cyclosporine A: A new antilymphocyte agent. Agents Actions. 6: 468-475, 1976.
6. Cohen, D.J., Loertscher, R., Rubin, M.F., Tilney, N.L., Carpenter, C.B. and Strom, T.B. Cyclosporine: A new immunosuppressive agent for organ transplantation. Ann. Intern. Med. 101: 667-682, 1984.
7. Nelson, P.W. Cyclosporine. Surg. Gynecol. Obstet. 159: 297-308, 1984.
8. Bunjes, D., Hardt, C., Rollinghoff, M. and Wagner, H. Cyclosporine A mediates immunosuppression of primary cytotoxic T-cell responses by impairing the release of interleukine 1 and interleukine 2. Eur. J. Immunol. 11: 657-661, 1981.
9. Hess, A.D., Tutschka, P.J. and Santos, G.W. Effect of Cyclosporine A on human lymphocyte responses in vitro: II induction of specific alloantigen unresponsiveness mediated by nylon wool adherent suppressor cell. J. Immunol 126: 961-968, 1981.
10. Brouhard, B.H., Goldblum, R.M., Bunce, H. and Cunningham, R.J. Immunoglobulin synthesis and urinary IgG excretion in the idiopathic nephrotic syndrome of children. Int. J. Pediatr. Nephrol. 2: 163-169, 1981.
11. Giangiacomo, J., Cleary, T.G., Cole, B.R., Hoffsten, P., Robson, A.M. Serum immunoglobulins in the nephrotic syndrome. A possible cause of minimal change nephrotic syndrome. N. Engl. J. Med. 293: 8-12, 1975.
12. Heslan, J.M., Lautie, J.P., Intrator, L., Blanc, C., Lagrue, G. and Sobel, A.T. Impaired IgG synthesis in patients with the nephrotic syndrome. Clin. Nephrol. 18: 144-147, 1982.
13. Dall'Aglio, P. Minimal change glomerulonephritis and focal glomerulosclerosis: markers and in vitro activity of peripheral blood mononuclear cells. Proc. Eur. Dial. Transplant. Assoc. 19: 673-678, 1982.
14. Fodor, P., Saitua, M.T., Rodriguez, E., Gonzales, B. and Schlesinger, L. T-cell dysfunction in minimal-change nephrotic syndrome of childhood. Am. J. Dis. Child. 136: 713-717, 1982.
15. Matsumoto, K., Osakabe, K., Harada, M. and Matano, M. Impaired cell-mediated immunity in lipoid nephrosis. Nephron 29: 190-194, 1981.
16. Eyres, K., Mallick, N.P. and Taylor, G. Evidence for cell-mediated immunity to renal antigens in minimal-change nephrotic syndrome. Lancet 1: 1158-1159, 1976.
17. Minchin, M.A., Turner, K.J. and Bower, G.D. Lymphocyte blastogenesis in nephrotic syndrome. Clin. Exp. Immunol. 42: 241-246, 1980.
18. Mallick, N.P., Williams, R.J., McFarlane, H., Orr, W.M., Taylor, G. and Williams, G. Cell-mediated immunity in nephrotic syndrome. Lancet 1: 507-509, 1972.
19. Schnaper, H.W. and Aune, T.M. Identification of the lymphokine soluble immune response suppressor in urine of nephrotic children. J. Clin. Invest. 76: 341-349, 1985.

20. Lagrue, G., Branellec, A. and Blanc, C. A vascular permeability factor in lymphocyte culture supernatants from patients with nephrotic syndrome. II Pharmalogical and physicochemical properties. Biomedecine 23: 73-75, 1975.
21. Shalhoub, R.J. Pathogenesis of lipoid nephrosis: a disorder of T-cell function. Lancet 2: 556-559, 1974.
22. Hoyer, P.F., Krull, F. and Brodehl, J. Cyclosporin in frequently relapsing minimal change nephrotic syndrome. Lancet 2: 335, 1986.
23. Capodicasa, G., De Santo, N.G., Nuzzi, F. and Giordano, C. Cyclosporin A in nephrotic syndrome of childhood: a 14 month experience. Int. J. Pediatr. Nephrol. 7: 69-72, 1986.
24. Niaudet, P., Habib, R., Tete, M.J., Hinglais, N. and Broyer, M. Cyclosporin in the treatment of idiopathic nephrotic syndrome in children. Pediatr. Nephrol. 1: 566-573, 1987.
25. Tejani, A., Butt, K., Trachtman, H., Suthanthiran, M., Rosenthal, C.J. and Khawar, M.R. Cyclosporine-induced remission of relapsing nephrotic syndrome in children. J. Pediatr. 111 (6, part 2): 1056-1062, 1987.
26. Tejani, A., Butt, K., Trachtman, H., Suthanthiran, M., Rosenthal, C.J. and Khawar, M.R., Cyclosporine A induced remission of relapsing nephrotic syndrome in children. Kidney Int. 33: 729-734, 1988.
27. Brandis, M., Burghard, R., Leititis, J., Zimmerhackl, B., Hildebrandt, F. and Helmcher, U. Cyclosporin A for treatment in nephrotic syndrome. Pediatr. Nephrol. 1: C42, 1987.
28. Waldo, F.B. and Kohaut, E.C. Therapy of focal segmental glomerulosclerosis with Cyclosporine A. Pediatr. Nephrol. 1: 180-182, 1987.
29. Brodehl, J., Ehrich, J.J.H., Hoyer, P.F., Lee, I.J., Oemar, B.S. and Wonigeit, K. Cyclosporin A treatment of minimal change nephrotic syndrome and focal segmental glomerulosclerosis in children. Korean J. Nephrol. 6: 26-33, 1987.
30. Myers, B.D. Cyclosporine nephrotoxicity. Kidney In 30: 964-974, 1986.
31. Meyrier,A., Simon, P., Perret, G. and Condamin-Meyrier, M.C. Remission of idiopathic nephrotic syndrome after treatment with Cyclosporine A. Br. Med. J. 292: 789-792, 1986.
32. Lagrue, G., Laurent, J., Belghiti, D. and Robeva, R. Cyclosporin and idiopathic nephrotic syndrome. Lancet 2: 692-693, 1986.
33. Chan, M.K. and Cheng, I.K.P. Cyclosporin A in steroid-sensitive nephrotic syndrome with frequent relapses. Postgrad. Med. J. 63: 757-759, 1987.
34. Meyrier, A. and Simon P. Treatment of cortical resistant idiopathic nephrotic syndrome in the adult: minimal change disease and focal segmental glomerulosclerosis. In: Advances in Nephrology (Eds. Grunfeld, Maxwell, Bach, Crosnier, Funk Bruntano) Year Book Medical Publishers, Inc. 1988, pp. 127-150.

DRUG NEPHROTOXICITY

9

CYCLOSPORINE A NEPHROTOXICITY

V.E. ANDREUCCI, G. FUIANO

Department of Nephrology, Second Medical School, University of Naples, Naples, Italy.

INTRODUCTION

Despite the many studies performed both in humans and in experimental animals during the decade which has elapsed since the introduction of Cyclosporine A (CyA) into clinical practice, the mechanisms by which CyA damages the kidneys is still poorly defined. The main problem faced in the past years in studying CyA nephrotoxicity is related to the almost exclusive clinical use of CyA in renal transplant recipients, i.e. in patients who initially (soon after transplantation) exhibit, in the transplanted kidney, the consequences of ischemic injury, and then undergo acute and/or chronic renal allograft rejection; these conditions make CyA-induced renal impairment difficult to isolate. Only in recent years has clinical experience been gained in humans with previously healthy native kidneys, i.e. in heart, liver or bone marrow transplant recipients or in patients treated with CyA for extrarenal diseases (1).

ACUTE CYCLOSPORINE NEPHROTOXICITY

Histopathological evidence of injury

It is well known that CyA administration causes acute renal insufficiency in many renal transplant recipients that is readily reversed upon withdrawal or

dosage reduction. Similar renal dysfunction has been observed in patients treated with CyA for extrarenal diseases.

Experimental studies in rats have demonstrated that CyA causes tubular necrosis only when given at very high dosage: necrosis is observed already with 50 mg/kg b.w./day (small areas of necrosis, after one week), but extensively with 100 mg/kg b.w./day (focal necrosis after less than a week) and even more with 150 mg/kg b.w./day (severe diffuse necrosis, after 5 days) (2). At a dosage of 20 mg/kg b.w./day proximal tubular changes are subtle and can be detected only after a week and only by electron microscopy (3). The described proximal tubular lesions as well as the demonstration of some biochemical mechanisms underlying CyA nephrotoxicity (such as CyA-induced inhibition of DNA and RNA synthesis and Na-K-ATPase activity in tubular cells) (4), have suggested a direct toxic effect of the drug on proximal tubular cells (where CyA has been demonstrated to accumulate) through initiation of calcium-dependent intracellular processes which may lead to toxic lesions. Calcium channel blockers (verapamil, diltiazem), in fact, have been reported to inhibit both calcium and CyA uptake, thereby exerting a protective effect (5). A recent study, however, failed to show verapamil inhibition of the cellular uptake of CyA; verapamil potentiation of CyA immunosuppression seems to be due to interference with the second messanger cascade necessary for lymphocyte activation (6). Renal vascular injury has also been related to acute CyA nephrotoxicity, since plasma level of Factor VIII-related antigen, one of the proteins synthesized by the vascular endothelium and usually increased in blood during diseases associated with vascular injury, is increased in renal transplant recipients during CyA nephrotoxicity (7,8).

The lack of early histopathologic lesions clearly associated with CyA therapy even after 90 days of CyA treatment (9) and the complete reversibility (within 2 weeks) of renal dysfunction upon discontinuation of CyA after 90 days (or even more) of treatment (10,11) have supported the hypothesis that acute renal function impairment is due to reversible changes in renal hemodynamics, a form of "prerenal" failure (12). On the other hand a great body of evidence in favour of a CyA-induced increase in fractional proximal tubular reabsorption (13,14) and, therefore, of the ability of the kidney to conserve sodium, argues against a tubulotoxic effect, such as that caused by gentamicin, which impairs proximal tubular reabsorption and usually causes morphologic changes when GFR is still normal (15). Furthermore, electron microscopy studies have excluded the presence of the typical aminoglycoside-induced myeloid bodies in lysosomes of proximal tubular cells of rats treated with CyA; the lysosomes in CyA-treated rats are sometimes enormously enlarged up to the size of the nucleus, a shape never observed in aminoglycoside-treated animals (16).

Urinary excretion of tubular enzymes

The behaviour of urinary excretion of lysosomal and brush border enzymes in laboratory animals under CyA is still controversial. Some authors have found no increase in urinary N-acetyl-p glucosaminidase (NAG) (lysosomal marker) and gammaGT (brush border marker) in rats, even at moderately high doses of CyA (40-50 mg/kg b.w./day for up to 14 days) (3,17,18). Others have observed urinary leakage of enzymes, not only at very high doses of CyA (100 mg/kg b.w./day), but also at 25 and 50 mg/kg b.w./day before any functional and structural deterioration of the kidneys (19). However, this enzymuria may be secondary to the CyA-induced

vasoconstriction rather than the result of a direct toxic effect of the drug on proximal tubular cells; renal ischemic injury itself would cause an increase of gamma-GT enzymuria according to some authors (19), significant elevation of urinary NAG (but not of gammaGT) according to others (20).

Acute effects of cyclosporine on renal hemodynamics in rats

In recent years renal hemodynamics under the acute effect of CyA has been studied in laboratory animals. The acute i.v. infusion as well as the daily intraperitoneal injection for one week of 20 mg/kg b.w. of CyA in rats, caused a fall of renal blood flow (evaluated by microspheres) and a rise in renal vascular resistance; the rapidity by which these changes occurred suggested that a renal vasoconstriction was a primary effect of CyA (21). Similarly the oral daily administration of CyA for 13 days to rats at doses of 12.5 to 50 mg/kg b.w./day caused a fall in RPF (PAH clearance) and GFR (inulin clearance, Cin), and a decrease of the ratio lithium clearance (CLi) to inulin clearance, indicative of proximal tubular overreabsorption, also suggesting a renal vasoconstriction (13,14,18,22).

A double-blind study performed acutely in Munich-Wistar rats by micropuncture technique, in our laboratory, has demonstrated that the acute i.v. infusion of CyA (20 mg/kg b.w.) caused significant alterations in glomerular hemodynamics: decrease of afferent and efferent arteriole blood flow; fall of whole kidney GFR and GFR in single nephron (SNGFR); no change in filtration fraction; marked and significant decrease of glomerular ultrafiltration coefficient, Kf; significant increase both in afferent and especially efferent arteriole resistance,

reflecting a marked glomerular vasoconstriction in both pre- and post-glomerular vessels and possibly in glomerular capillaries (as mirrored by the fall in Kf); no changes were observed in glomerular, tubular and effective filtration pressures (23). The same results have been obtained with 50 mg/kg b.w./day (24). When dopamine was added to CyA by i.v. infusion at dopaminergic dosage (1.2-2 microg/100 g b.w./min), all the above changes were reversed (23,25). That hemodynamic factors play a major role in acute CyA nephrotoxicity is supported by scanning electron microscopy observations: rats given CyA (50 mg/kg b.w./day) by gavage for 3 to 14 days showed a progressive decline in afferent arteriole lumen diameter and vasoconstriction (17).

The behaviour of Kf (=kS, where k:effective hydraulic permeability and S:glomerular basement membrane surface) under the effects of CyA has been studied also in the isolated perfused kidney of untreated rats (controls) and rats treated with CyA (10-15 mg/kg b.w./day); 4 weeks after unilateral nephrectomy a rise of SNGFR was observed in controls because of an increased Kf due to a significant increase of both S and k; in CyA-treated rats, on the contrary, the compensatory rise of SNGFR did not occur, despite the significant increase of k, because S had a slight (although not significant) reduction (26).

Pathogenetic mechanisms in acute cyclosporine nephrotoxicity

(a) Role of angiotensin II (AII)

The renal vasoconstriction caused acutely by CyA has been considered non AII-mediated since, in rats, captopril neither prevented nor reversed the decrease of renal blood flow associated with CyA administration (14,21). More recent studies have demonstrated that

acute CyA-induced changes in renal blood flow and GFR were blunted by captopril (24,27) and by saralasin. Taken together these studies suggest an important, but not exclusive, role of AII in CyA-induced renal dysfunction. The AII involvement, however, does not occur through the activation of the tubuloglomerular feedback system (27-29).

(b) Role of sympathetic nervous system

Renal denervation prevented and phenoxibenzamine or prazosin (α-adrenergic agents) reversed the impairment of renal blood flow and the increase of the renal vascular resistance caused by CyA in rats, suggesting that renal vasoconstriction by CyA is mediated by an increase of either renal sympathetic nerve activity or circulating levels of catecholamines (21,30). The beneficial effect of phenoxibenzamine in reversing CyA-induced renal vasoconstriction in rats has not been confirmed by others (14). Should the sympathetic nervous system be involved, only circulating catecholamines could mediate early CyA-induced renal vasoconstriction in renal transplant recipients since renal allograft are initially denervated (21). There is some evidence, however, that the grafts begin to innervate within a month (31).

(c) Role of thromboxane (TX) and vasodilating prostaglandins (PGs)

It has been suggested that alterations in the synthesis of TX and PGs might contribute to the CyA-induced renal hemodynamic changes. Conflicting results have been reported on this matter (32-35). The differences in the behaviour of TX in experimental studies may be related to difference in duration of CyA treatment. Thus, apparently acute or short-term (up to 7 days) administration of CyA does not, while long-term

treatment does increase TX synthesis by the kidney.

Single i.v. infusion or daily administration over 7 days of 20 mg/kg b.w. of CyA caused an increase of urinary excretion of 6-cheto-$PGF_{1\alpha}$, similar to that usually observed in conditions of renal hypoperfusion and increased renin secretion (21). On the contrary, no increase of urinary PGs was observed after 3 months of therapy (34).

These observations have suggested that: (a) TX may contribute to the CyA-induced renal vasoconstriction at least after several days of therapy; after single or short-term administration, other factors (AII? catecholamines?) may be involved in causing renal vasoconstriction; (b) PGs may have protective effects against this vasoconstriction; (c) inhibition of PGs may enhance renal dysfunction by CyA; (d) inhibition of TX may ameliorate the CyA-induced renal function impairment. Surprisingly, in recent studies, indomethacin failed to modify CyA nephrotoxicity (14,24); a possible explanation is that nonsteroidal antiinflammatory drugs, while capable of decreasing platelet TX, do not affect intrarenal TX synthesis (35).

Acute and short-term effects of cyclosporine in humans with normal native kidneys.

Studies on CyA effects on renal hemodynamics have been performed in humans by our group (36,37). When CyA was given orally (12 mg/kg b.w.) to 8 healthy volunteers during maximal water diuresis, the following changes were observed by clearances studies: a significant fall in renal plasma flow (PAH clearance, from 570 to 350 ml/min) and GFR (Cin, from 118 to 98 ml/min) with increase in filtration fraction; a reduction in urine output and a decrease in fractional excretion of sodium and in free-water clearance; blood

levels of CyA ranged between 1,000 and 1,500 ng/ml. The addition of dopamine (2 microg/kg b.w./min i.v.) readily reversed these changes. No changes were observed in plasma renin activity or aldosterone, nor in urinary catecholamines both after CyA alone and after CyA+dopamine (36,37). A positive effect of dopamine both on renal blood flow and GFR has been recently demonstrated, in our Unit, also in renal transplant patients from 4 to even 24 months after transplantation (38); others have observed a similar positive effect of dopamine but only on renal blood flow (39).

Long-term effects of CyA in humans with previously normal renal function have been evaluated in 11 patients given CyA as treatment of Graves ophtalmopathy (4 pts), or iridocyclitis (4 pts), or as prophylaxis for graft-vs-host disease following bone marrow transplantation (3 pts). After a mean of 41 days of daily CyA administration (range 21-133 days), when CyA dosage averaged 7.87 mg/kg b.w./day and after a mean comulative CyA dose of 22,000 mg, GFR was significantly reduced (from 83 to 73 ml/min) as was CLi (used as a measure of fluid delivery out of proximal tubules). In six of these patients, 273 days after CyA withdrawal, CLi was still significantly lower than the basal value, suggesting a persistent fractional overreabsorption in proximal tubules (40).

CURRENT OVERVIEW OF ACUTE CYCLOSPORINE NEPHROTOXICITY

The foregoing information suggests that the functional, reversible renal impairment induced by a single dose of CyA or by daily CyA administration for up to several months is a renal hypoperfusion due to renal vasoconstriction. Acute morphological changes observed by light and electron microscopy may be due to a direct toxic effect of CyA, but may also represent

the result of CyA-induced renal ischemia. This is the case with the demonstrated hypertrophy of the juxtaglomerular apparatus, the presence of focal fat deposits in the proximal tubular cells (which may indicate impaired mitochondrial metabolism of free fatty acids), (16), the structural alterations of renal mitochondria with impairment of mitochondrial respiration (16,41,42). An injury of mitochondrial energy metabolism has been proposed as mediator of CyA-induced nephrotoxicity; but this may well be due to ischemic damage of the proximal tubular cells because of renal vasoconstriction induced by CyA.

ENHANCEMENT OF ACUTE CYCLOSPORINE NEPHROTOXICITY

Cyclosporine and renal ischemia

CyA and renal ischemia mutually enhance their deleterious renal effects. This has very important clinical implication since CyA is usually given to renal transplant recipients immediately after, during or even before renal transplantation, so that the ischemic graft is immediately challanged by CyA. It has been suggested that even acute allograft rejection may enhance CyA nephrotoxicity because of its ischemic renal effect (43). Rejection and CyA nephrotoxicity may occur simultaneously.

Studies in laboratory animals have clearly demonstrated the interaction between CyA administration and renal ischemia (44-46). When the effects of CyA (10 to 25 mg/kg b.w./day for 14-28 days) alone or associated with 30 to 60 min ischemia (clamping of renal artery) were evaluated in rats after unilateral nephrectomy, which was performed to mimic the condition of the single transplanted kidney, the drug exhibited adverse effects on the initiation or progression of compensatory hyperthrophy and the repair of the ischemic insult (47,48).

It has been observed that renal damage by ischemic injury was particularly exacerbated by CyA when the drug was given after rather than before the ischemic insult (46). On the basis of this observation it was suggested that the administration of CyA too soon after renal transplantation may have deleterious effects (46).

Taken together the mentioned studies demonstrate that (a) ischemic kidney is more vulnerable to CyA nephrotoxicity; (b) CyA interferes with the processes involved in the compensatory hypertrophy that is expected to occur in transplanted kidney; presumably the renal vasoconstriction induced by CyA prevents the renal vasodilation necessary for compensatory adaption (48).

Cyclosporine and other drugs

CyA is metabolized by the hepatic cytocrome P450 mixed-function oxidase system. Thus drugs, such as ketaconazole (antifungal drug) and cimetidine, that inhibit this system may increase blood concentration of CyA and consequentely its nephrotoxicity (49). Recently erythromycin has been shown to increase serum levels of CyA and serum creatinine in renal and cardiac transplant recipients (50-52) and in CyA-treated patients with type I diabetes (53). Even nicardipine, a calcium channel blocker, has been reported to greatly increase plasma levels of CyA in renal transplant patients (54).

Many other drugs have been shown to increase CyA nephrotoxicity (19,51,55-57). A list of them is given in Table 1.

Since CyA is metabolized in the liver, abnormalities in hepatic function may rise blood levels of the drug and increase the probability of nephrotoxicity.

Table 1. Drugs known to potentiate cyclosporine nephrotoxicity.

(A) by increasing cyclosporine concentration:

- -Calcium channel blockers: verapamil, nicardipine, diltiazem
- -Antibiotics: erythromycin, doxyciclin, ticarcillin, imipenem (?), josamycin
- -Anti-fungal agents: ketoconazole
- -Quinolone derivatives: norfloxacin
- -H_2-antagonists: cimetidine, ranitidine
- -Androgenic steroids: levonorgestrel, danazol, methyltestosterone

(B) by adding their nephrotoxicity:

- -Antibiotics: aminoglycosides (gentamicin), amphotericin B
- -Antimitotic agents: melphalan
- -Sulphonamides: trimethoprim
- -Diuretics: furosemide (?), metazolone (?)
- -Osmotic agents: mannitol

Other potentiating factors

Advanced age, preexisting hypertension and (for non-renal transplant patients) preexisting impairment of renal function, have been shown to represent risk factors for CyA nephrotoxicity (58). The impairment of renal blood flow and GFR by acute CyA administration has been demonstrated to be greater in patients with nephrotic syndrome and reduced basal values of renal blood flow and GFR than in normal controls (59).

CLINICAL ASPECTS OF CYCLOSPORINE NEPHROTOXICITY

Blood levels of Cyclosporine and renal function

Considering that episodes of CyA-induced renal dysfunction usually occur after a few days of a too high blood concentration of CyA, frequent measurements of the drug have been suggested to plan changes in

dosage for avoiding the high concentrations associated with CyA nephrotoxicity as well as too low values which may lead to graft rejection (60,61); 200 ng/ml of predose whole-blood concentration of CyA (RIA) has been suggested as a sort of threshold value for graft rejection for renal transplant patients treated with CyA and steroids (62); considering that many factors may influence the relation between blood levels of CyA and graft rejection or CyA nephrotoxicity (preservation longer than 24 hrs and/or surgical anastomosis time in excess of 45 minutes undoubtedly enhance CyA nephrotoxicity) (63), it has been suggested to avoid predose whole-blood concentration of CyA lower than 400 ng/ml, to prevent rejection, and higher than 800 ng/ml, to avoid CyA nephrotoxicity (61); others, however, have proposed to maintain whole-blood concentration of CyA between 200 and 500 ng/ml (RIA), bearing in mind that 300 ng/ml would afford a better protection against graft rejection when low-dose steroids (e.g. methylprednisolone 20 mg/day) are used early post-transplant (60,62).

Cyclosporine nephrotoxicity and renal allograft rejection: Differential diagnosis

Differentiation between CyA-induced renal dysfunction and acute rejection in renal transplant patients on a clinical basis is often impossible, since both conditions are characterized by a decrease in urine output, salt retention and increase in serum creatinine concentration. The traditional clinical signs of renal allograft rejection, such as fever and graft tenderness and swelling, are less common in CyA-treated patients; this may increase the difficulties of diagnosing rejection in CyA-treated renal transplant patients. Even on a needle renal biopsy, acute CyA nephrotoxicity is a diagnosis of

exclusion, i.e. when the histopathologic features of acute rejection are absent (64). Some morphologic changes, observed by light and electron microscopy in proximal tubular cells (mainly in S2 and S3 segments), such as tubular inclusion bodies corresponding to enlarged lysosomes (autolysosomes) which may contain mitochondrial fragments, giant mitochondria, vacuolization of cytoplasm (Fig. 1) (due to dilation of endoplasmatic reticulum), focal fat deposits in late proximal (S3) segments, focal loss of brush border (mainly in S3 segments), thickening and breaks of the basement membrane have been associated with CyA nephrotoxicity (4,16,17,34,65-67).

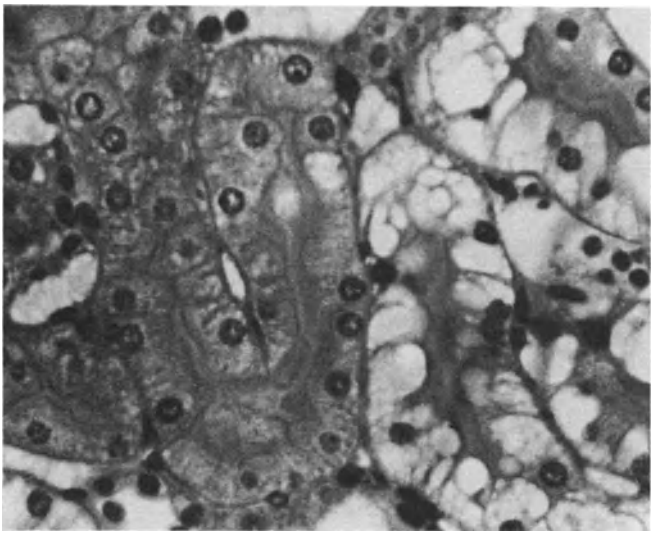


Fig. 1. Tubular vacuolization, with vacuoles of variable size, in the straight part of the proximal tubule (on the right of the photograph) of a rat treated for five days with the very high dosage of 100 mg/kg b.w./day of cyclosporine A by gavage. Initial mild vacuolization is observed also in a loop of a convoluted part of the proximal tubule (on the left of the photograph), in which the brush border appears well preserved.

However, these reversible changes are not specific and

therefore are of limited value (43). The accumulation of PAS-positive material (glycogen) within the cells of early distal tubules in rats treated for 5 months with 40 mg/kg b.w./48 hrs of CyA is also a non specific finding (67).

In order to distinguish graft rejection from acute CyA nephrotoxicity, indirect immunofluorescence and immunoperoxidase techniques using polyclonal antibodies directed against CyA have been applied to needle aspirates and renal biopsies from renal allograft recipients treated with CyA and exhibiting renal function impairment; CyA was found in tubular epithelial cells and renal interstitium in cases of CyA nephrotoxicity (68,69). Diagnostic limits of the technique are the frequent false-positive and false-negative results (43).

In a recent study (70), venous blood samples for T cell subset counts were collected from renal transplant patients every week during hospitalization and every 1-4 weeks after discharge, up to 6 months after renal transplantation, in the attempt to correlate T cell subset counts with acute CyA nephrotoxicity and acute rejection episodes: total lymphocyte, T cell and subset counts increased significantly in the week preceding each episode of acute CyA nephrotoxicity; reduction of CyA dosage was followed by decrease of both serum creatinine and cell counts. In contrast, all cell counts decreased significantly in the week preceding acute rejection episodes. No significant changes were observed in Helper T cells/Suppressor T cells ratios. This finding is very important for early diagnosis of acute rejection and CyA nephrotoxicity (70).

Acute arteriolopathy induced by cyclosporine

An acute arteriolopathy resembling Hemolytic-Uremic Syndrome, with hypertension, azotemia,

microangiopathic hemolytic anemia, red blood cell fragmentation, thrombocytopenia, associated with glomerular thrombosis and arteriolar hyaline deposition has been rarely reported, initially in bone marrow transplant recipients receiving CyA to prevent graft-vs-host disease (71,72), and later in liver transplant patients treated with CyA (73). Recently a similar thrombotic microangiopathy and glomerulopathy has been observed in a renal allograft recipient treated with CyA, which was rapidly reversed by drug withdrawal (74). In vitro studies have demonstrated that CyA has a direct toxic effect on endothelial cells which may account for the CyA-induced vascular damage (75).

Other side effects related to cyclosporine nephrotoxicity

Hypertension

Hypertension is a frequent side effect of CyA, occurring, within a few weeks of therapy, not only in renal transplant patients, but also in patients with normal native kidneys (i.e. after heart, liver and bone marrow transplantation or during CyA therapy of extrarenal diseases) (11,43,58,76-78). The mechanism of such hypertension is poorly understood. Some authors have attributed it to CyA-induced salt retention with suppression of plasma renin activity (PRA) (79). Others have considered it as renin-dependent, on the basis of increased PRA observed in experimental animals. Actually it may be due to a primary effect of CyA on the systemic vasculature. CyA, in fact, has been reported to increase the contractility of vascular smooth muscle. Pretreatment of rat vascular smooth muscle cells with CyA caused an increase in amplitude and duration of AII-induced rise in cytosolic free calcium, that was not blocked by nifedipine (80); since the increase in cytosolic free calcium is a

prerequisite of smooth muscle contraction, this might be the mechanism by which CyA causes hypertension in transplanted patients. Alternatively hypertension is secondary to the CyA-induced chronic renal injury.

Sodium Excretion

Acute i.v. CyA administration in normal rats (24) and in healthy humans (36,37), causes a significant reduction of both absolute (UNaV) and fractional urinary excretion of Na (FENa), a behaviour that is typical of renal hypoperfusion ("functional" ARF) (15). This Na retention is associated (both in animals and in men) with an increase in proximal tubular reabsorption (13,14,18,36,40).

Short-term CyA administration both in humans and animals has also a salt-retaining effect (13,14,18,27,40), which is mainly due to a decrease in filtered Na, with no change in FENa (40). Thus, after a short-term administration, CyA may cause hypertension because of salt retention and the consequent ECV expansion.

But in rats treated for 5 months with 40 mg/kg b.w./48 hrs of CyA, enhanced urinary Na excretion, polyuria and renal insufficiency have been observed which were associated with cellular accumulation of glycogen in early distal tubules (67).

Plasma renin activity (PRA)

Morphological studies in rats and rabbits, already after 7 days of CyA treatment, have demonstrated hypertrophy and hyperplasia of the juxtaglomerular apparatus (increase of both total cells and granular cells per juxtaglomerular apparatus) that were dose-dependent (16) and are consistent with the demonstrated stimulatory effect of acute CyA administration on renin-angiotensin system in rats

(21,23). Usually, after long term treatment with CyA, PRA in humans is normal, despite systemic hypertension; it has been found even reduced in heart transplant recipients treated with CyA as compared to those treated with azathioprine (43,76), and in renal transplant recipients with associated reduced plasma aldosterone levels (79).

After long-term (1-2 years) treatment with CyA, cardiac transplant patients have demonstrated a chronic stimulation of the renin-angiotensin system, as mirrored by the hyperplasia of the juxtaglomerular apparatus and the high levels of plasma inactive renin (prorenin) and total plasma renin; PRA, however, was normal despite systemic hypertension. A relative block in the intrarenal conversion of prorenin into active renin may account for the limited release of renin in these patients (81).

Potassium retention

Hyperkalemia with mild hypercloremic metabolic acidosis has been observed in CyA-treated renal transplant patients even with preserved renal function. When renal transplant recipients treated with CyA were compared with patients treated with azathioprine three months after renal transplantation, a defect in K excretion was observed in CyA-treated patients which could not be accounted for by the reduced GFR, but was associated with a suppression of PRA and a reduced sensitivity to aldosterone (82). Higher serum levels of potassium in CyA-treated patients, as compared to azathioprine-treated allograft recipients, have also been observed six months after renal transplantation; no differences in serum concentration of chloride and bicarbonate and in creatinine clearance (that averaged 52 ml/min) were found between CyA-treated patients with

hyperkalemia and those with normokalemia (83). The exact mechanism of CyA-associated hyperkalemia is not yet elucidated.

These observations suggest that patients receiving CyA should avoid high dietary potassium intake, potassium-sparing diuretics as well as potassium-containing medications (82).

Hyperuricemia

Hyperuricemia has been reported after treatment with CyA both in adults (10,84) and in children (85), in renal transplanted patients and in patients with normal native kidneys (77). This hyperuricemia is caused not only by a reduction of GFR but also by a functional and readily reversible impairment in tubular handling of uric acid (10,84,85).

Hypomagnesemia

Hypomagnesemia (with minimum value of 0.9 mg/dl) has been observed in renal transplant patients treated with CyA, but not in those treated with azathioprine. It occurs by the second to third week after renal transplantation (depending upon allograft function) and has been attributed to Mg wasting (increased fractional excretion of Mg) requiring oral Mg oxide supplementation (750 mg daily) (86).

LIMITATION OF CYCLOSPORINE NEPHROTOXICITY. EFFECTS OF CALCIUM CHANNEL BLOCKERS ON CYCLOSPORINE NEPHROTOXICITY

Concomitant treatment of normal rats with CyA (25 mg/Kg b.w./day) and nifedipine (50 mg/ kg b.w./day) for 13 days partially prevented the observed changes of renal plasma flow, GFR and proximal tubular reabsorption (evaluated by CLi) induced by CyA alone (13). Similar beneficial effects were observed with verapamil in rats acutely receiving CyA i.v. (50 mg/ kg

b.w.) (24) and in rats undergoing 20 min. renal artery clamping and acute intraperitoneal administration of CyA (60 mg/kg b.w.) (87). Thus calcium channel blockers in rats appeared to be nephroprotective against CyA nephrotoxicity, even though the amelioration of renal function was only partial (14,24). Acute i.v. infusion of nifedipine, on the contrary, was ineffective on renal functional impairment induced by 13 days administration of CyA (14). In vitro studies of rat kidney perfusion have demonstrated that CyA treatment causes mitochondrial calcium accumulation and that pretreatment with verapamil and cotreatment with ATP-$MgCl_2$ can significantly reduce CyA nephrotoxicity by preventing this accumulation and by preserving mitochondrial respiratory function (88), As far as we know, no clinical trial has been performed on the effects of calcium channel blockers on CyA nephrotoxicity. Only in a retrospective study on renal transplant patients serum creatinine was lower, despite higher whole blood levels of CyA, in patients treated with nifedipine for CyA-induced hypertension than in non-treated patients (89). Should verapamil be confirmed an efficient drug in preventing CyA nephrotoxicity, its clinical use would be quite desirable because of its recently demonstrated potentiating effect on CyA immunosuppressive properties (6) (that would reduce the dose of CyA required for adequate immunosuppression, with a consequent reduction in nephrotoxicity).

CHRONIC CYCLOSPORINE NEPHROTOXICITY

A large body of clinical evidence has demonstrated that long-term treatment with CyA of renal transplant recipients is associated with values of serum creatinine (usually 2 mg/dl or more) significantly greater than those of patients treated with

conventional immunosuppressive agents (43) and that conversion of patients from CyA is associated with improvement of renal perfusion (90) and even decrease of serum creatinine (10,58,77). This suggests that functional impairment by CyA may last very long. On the other hand after 3 or 6 months of CyA therapy no histologic findings specific of CyA can be observed on renal biopsies (9,21).

But, while clinical and experimental studies have demonstrated that acute and short-term CyA administration has a salt-retaining effect (13,14,24,36,40), long-term administration of the drug has been shown to cause different handling of sodium and water by the kidney. Thus, when 11 liver transplant patients were evaluated, 6 to 26 months after transplantation and CyA administration, GFR and renal blood flow were reduced to about 53-54% of control (preoperative) values; under such circumstances, during water diuresis, a significant decrease (to 88%) in fractional tubular sodium reabsorption was observed (FENa averaged 12%). This sodium excretion appeared to be mainly due to a decrease (to about 75%) in the fraction of glomerular filtrate reabsorbed in the proximal tubules with the consequent increase in delivery of sodium and water to the diluting segment; a minor functional impairment of the diluting segment was also present (91). Fractional excretions of phosphate (that is reabsorbed mainly in the proximal tubule) and potassium were significantly increased, further demonstrating the impairment of proximal tubular reabsorption. In the same patients, however, renal biopsies demonstrated arterial and arteriolar nephrosclerosis, with patchy interstitial fibrosis, separation of the tubules and tubular atrophy; these morphological lesions poorly correlated with the corresponding renal function (91). These results

suggest that (a) a renal functional impairment can be observed even after long-term treatment with CyA, although these late functional changes are different from acute changes; (b) chronic renal lesions occur after prolonged CyA administration.

In 37 heart transplant recipients who were evaluated after 1-2 years of therapy with CyA, GFR (47 ml/min) and renal plasma flow (284 ml/min) were significantly reduced as compared to 24 azathioprine-treated patients (GFR: 94 ml/min; renal plasma flow: 450 ml/min); increase of renal vascular resistance, proteinuria, systemic hypertension and impairment of conversion of prorenin to renin were also observed in CyA-treated patients; renal biopsies exhibited striped interstitial fibrosis, tubular atrophy, hyalinosis of small arteries and arterioles affecting mainly the afferent glomerular arteriole, hyperplasia of the juxtaglomerular apparatus and even focal, segmental glomerulosclerosis or ischemic glomerular collapse (with enlargement of remaining glomeruli), suggesting chronic, irreversible renal damage (43,76,81). A primary tubular injury was considered responsible for the CyA-induced chronic nephropathy: according to this hypothesis, nephrons with severely damaged tubules would cease functioning and become obsolete; this will cause hyperfiltration in remaining nephrons thereby leading to glomerulosclerosis which is further aggravated by persistent CyA-induced systemic hypertension (76). A longitudinal study of 15 patients examined every year up to 4 years demonstrated heavier proteinuria, increasing renal vascular resistance, and further histopathological deterioration, despite reduction in dosage or even withdrawal of CyA, and improving cardiac performance, with 3 of these patients reaching end stage renal failure (ESRF) (81). Considering all

cardiac transplant recipients of this study, while no ESRF was observed in the 148 patients treated with azathioprine, 7% of CyA-treated patients reached ESRF then undergoing either dialysis or renal transplantation (81).

Patients treated with CyA (at doses of 7.5 to 10 mg/kg b.w./day) for diseases other than renal transplantation (e.g. demyelinating polyradiculo-neuropathy, sight-threatening uveitis, choroiditis, ocular cicatricial pemphigoid, corneal transplantation) exhibited, after a period of therapy ranging between 6 months and 4 years, renal function impairment associated with morphological renal lesions, mainly represented by tubular atrophy and separation of the tubules, interstitial fibrosis (usually striped or band-like), sometimes corresponding to the distribution of vascular channels, and arteriolar lesions compatible with those observed in hypertensive nephrosclerosis (77,91-94).

Similar morphological renal lesions by CyA, including arteriolar medial hypertrophy and hyalinosis, have been reported also in renal transplant recipients. But in these patients the chronic morphological lesions are not specific; they are found, in fact, (although less frequently) also in patients treated with azathioprine (62). Furthermore the association of the renal effects of rejection episodes makes it difficult to distinguish CyA nephrotoxicity (64).

The persistence of renal arteriolar vasoconstriction (that may be reversed by CyA withdrawal) (90) and the occurrence of chronic lesions of small arteries and arterioles (with intimal proliferation, luminal narrowing and medial hypertrophy and sclerosis) after long-term therapy with CyA (64,81) suggest that the irreversible arteriolar damage is the result of the CyA-induced vasospasm (81). The

progressive luminal obliteration of the arterioles will result in persistent cortical ischemia particularly in the zone of renal cortex supplied by the damaged vessels which may account for the tubular (atrophy), interstitial (fibrosis) and glomerular (sclerosis) lesions observed in renal biopsies after prolonged (one year or more) CyA administration even in non renal transplant recipients (43,94). CyA-induced hypertension will undoubtedly aggravate the progression of the renal lesions. Thus, after 6 months or more of CyA therapy an irreversible renal damage seems to have occurred, even when renal function improves after drug withdrawal; such improvement, in fact, may be due to reversal of renal vasoconstriction and/or to compensatory mechanism; but it does not exclude that irreversible damage has already occurred (78).

CONCLUSIONS

Studies performed in humans and animals suggest that, when given acutely, CyA causes functional renal impairment through a persistent renal vasoconstriction: a "functional" ARF ("prerenal azotemia") is manifested as decreases of renal blood flow and GFR and salt retention; no histopathologic lesions can be detected on renal biopsy. Under such circumstances, renal functional impairment can be reversed either by drug withdrawal or reduction in dosage, or by the use of vasodilating agents (e.g. dopamine). Normalization of renal perfusion and GFR may be obtained after a duration of treatment no longer than 6 months. Several authors suggest that a prolonged renal vasoconstriction first induced by and then maintained by long-term CyA therapy might cause arteriolar and tubular damage on a ischemic base. Eventually, fibrosis and chronic nephron loss occur (81,90). Consistent with this hypothesis is the morphologic evidence of

"ischemic" tubular damage reported in laboratory animals after treatment with CyA. To date, however, such a transition from acute haemodynamic changes induced by CyA and CyA-induced chronic renal damage has not been demonstrated. Undoubtedly, however, after a long-term treatment (12 months or more) renal effects of CyA are different: renal blood flow and GFR exhibit a non-proportional decline with decrease in filtration fraction; renal function seems to progressively decrease with time; renal biopsy shows arteriolar, tubulointerstitial and glomerular lesions; these observations suggest chronic, irreversible and possibly progressive renal damage.

On this basis the prolonged use of CyA is hazardous. The benefit of reduced incidence of rejections in transplant recipients is, in fact, offset by the severity of CyA-induced renal injury (76,81). Several non-renal transplant recipients have been reported to have reached end stage renal failure (entering dialysis or undergoing renal transplantation) because of long standing therapy (43,63,81). Presumably CyA-induced chronic nephropathy may have been responsible for the late loss of some renal allografts attributed to rejection (43,81).

A recent study of chronic autoimmune diseases (SLE, rheumatoid arthritis, Sjiogren syndrome, systemic hypersensitivity vasculitis) utilized a low-dose of CyA (5 mg/Kg b.w./day in two daily doses for three months, followed by introduction of 1-2 free days per week. After 6 to 12 months of therapy, CyA was alternated with azathioprine on a monthly basis together with steroids. This study has demonstrated no deterioration of renal function, no systemic hypertension, but reduction in proteinuria, improvement of the systemic disease and, in some patients, of renal function (95). On the contrary, treatment of autoimmune diseases

(polychondritis, Behcet's syndrome and chronic uveitis) with larger amounts of CyA has caused severe renal toxicity, with hypertension and, at renal biopsy, tubular atrophy, interstitial fibrosis, arteriolar hyalinization and even glomerular sclerosis (78). Thus, the use of reduced CyA doses is less hazardous and can be accepted.

Adequate CyA dosage must be based on blood concentration of Cya. Despite the limited consensus in the literature on the relation between blood, plasma or serum concentration of CyA and CyA nephrotoxicity, a recent study has demonstrated an association between mean predose blood concentration of CyA in the week preceding an episode of renal dysfunction and CyA nephrotoxicity (61).

In order to avoid the severe renal lesions of CyA, it has been suggested that CyA be withdrawn after 3 to 6 (never more than 12) months of therapy, i.e. after covering the post-transplant period in which acute allograft rejection is more frequent and before the functional injury by CyA is switched to the organic damage (10,43,81) with conversion to azathioprine; azathioprine should be started 1-5 days prior to CyA withdrawal, with slow CyA dosage tapering (96). Despite the latter precaution, however, substitution of azathioprine for CyA is frequently followed by acute rejection (96,97). Alternatively the use of the so-called triple therapy (CyA in conjunction with azathioprine and prednisone) has been proposed in order to allow a reduction in CyA dosage with consequent decrease in renal injury (43,96).

REFERENCES

1. Andreucci VE, Conte G, Sabbatini M, Fuiano G, De Nicola L, Stanziale P, Sepe V, Balletta M:
Cyclosporine nephrotoxicity.
Proc. 2nd Int. Sorrento Meeting on "Current Therapy in Nephrology", Sorrento, May 22-25, 1988, (Eds. VE Andreucci and A. Dal Canton), Kluwer Academic Publ, Boston, 1988.
2. Makowka L, Lopatin W, Gilas T, Falk J, Phillips MJ, Falk R:
Prevention of cyclosporine (CyA) nephrotoxicity by synthetic prostaglandins.
Clin Nephrol, 25 (Suppl 1): S89-S94, 1986.
3. Pfaller W, Kotanko P, Bazzanella A:
Morphological and biochemical observations in rat nephron epithelia following cyclosporine A treatment.
Clin Nephrol, 25 (Suppl 1): S105-S110, 1986.
4. Suzuki S, Oka T, Ohkuma S, Kuriyama K:
Biochemical mechanisms underlying cyclosporine-induced nephrotoxicity: effect of concomitant administration of prednisolone.
Transplantation, 44: 363-368, 1987.
5. Nagineni CN, Misra BC, Lee DBN, Yanagawa N:
Cyclosporine A-calcium channel interaction: a possible mechanism for nephrotoxicity.
Transplant Proc, 19: 1358-1362, 1987.
6. McMillen MA, Baumgarten WKm Schaefer HC, Mitchnick E, Fuortes M, Holman MJ, Tesi RJ:
The effect of verapamil on cellular uptake, organ distribution, and pharmacology of cyclosporine.
Transplantation, 44: 395-401, 1987.
7. Brown Z, Neild GH, Willoughby JJ, Somia NV, Cameron SJ:
Increased factor VIII as an index of vascular injury in cyclosporine nephrotoxicity.
Transplantation, 42: 150-153, 1986.
8. McNaughton DC, White DJG:
The differential diagnosis of rejection and nephrotoxicity in renal allograft recipients treated with cyclosporin A.
Med Sci Res, 15: 307-308, 1987.
9. D'Ardenne AJ, Dunnill MS, Thompson JF, McWhinnie D, Wood RFM, Morris PJ:
Cyclosporin and renal graft histology.
J Clin Pathol, 39: 145-151, 1986.
10. Chapman JR, Griffiths D, Harding NGL, Morris PJ:
Reversibility of cyclosporin nephrotoxicity after three months treatment.
Lancet, 1: 128-129, 1985.
11. Palestine AG, Austin HA III, Nussenblatt RB:
Renal tubular function in cyclosporine-treated patients.
Am J Med, 81: 419-424, 1986.
12. Humes HD, Jackson NM, O'Connor RP, Hunt DA, White MD:
Pathogenetic mechanisms of nephrotoxicity: insights into cyclosporine nephrotoxicity.
Transplant Proc, 19: 51-62, 1985.

13. Dieperink H, Leyssac PP, Starklint H, Kemp E:
Nephrotoxicity of cyclosporin A. A lithium clearance and micropuncture study in rats.
Eur J Clin Invest, 16: 69-77, 1986.
14. Dieperink H, Leyssac PP, Starklint H, Jorgensen KA, Kemp E:
Antagonist capacities of nifedipine, captopril, phenoxybenzamine, prostacyclin and indomethacin on cyclosporin A induced impairment of rat renal function.
Eur J Clin Invest, 16: 540-548, 1986.
15. Andreucci VE:
Acute Renal Failure. Pathophysiology, prevention, and treatment.
Martinus Nijhoff Publ, Boston, 1984
16. Verpooten GA, Wybo I, Pattyn VM, Hendrix PG, Giuliano RA, Nouwen EJ, Roels F, De Broe ME:
Cyclosporine nephrotoxicity: comparative cytochemical study of rat kidney and human allograft biopsies.
Clin Nephrol, 25 (Suppl 1): S18-S22, 1986.
17. English J, Evan A, Houghton DC, Bennett WM:
Cyclosporine-induced acute renal dysfunction in the rat.
Transplantation, 44: 135-141, 1987.
18. Whiting PH, Simpson JG:
Lithium clearance measurements as an indication of cyclosporine A nephrotoxicity.
Clin Sci, 74: 173-178, 1988.
19. Whiting PH, Thomson AW, Simpson JG:
Cyclosporine and renal enzyme excretion.
Clin Nephrol, 25 (Suppl 1): S100-S104, 1986.
20. Devineni R, McKenzie N, Duplan J, Keown P, Stiller C, Wallace AC:
Renal effects of cyclosporine: clinical and experimental observations.
Tranplant Proc, 15: (Suppl 1): 2695-2699, 1983.
21. Murray BM, Paller MS, Ferris TF:
Effect of cyclosporine administration on renal hemodynamics in conscious rats.
Kidney Int, 28: 767-774, 1985.
22. Dieperink H, Leyssac PP, Kemp E, Steinbruckl D, Starklint H:
Glomerulotubular function in cyclosporine A treated rats.
Clin Nephrol, 25 (Suppl 1): S70-S74, 1986.
23. Sabbatini M, Esposito C, Uccello F, De Nicola L, Alba MM, Conte G, Dal Canton A, Andreucci VE:
Acute effects of cyclosporine A on glomerular dynamics. Micropuncture study in the rat.
Transplant Proc, 20 (N 3,Suppl 3), 1988.
24. Barros EJG, Boim MA, Ajzen H, Ramos OL, Schor N:
Glomerular hemodynamics and hormonal participation on cyclosporine nephrotoxicity.
Kidney Int, 32: 19-25, 1987.
25. Sabbatini M, Esposito C, De Nicola L, Uccello F, Altomonte M, Romano G, Veniero P, Dal Canton A, Andreucci VE:
Dopamine reverses acute cyclosporine A nephrotoxicity. Micropuncture study in the rat.
Proc. 2nd Int Sorrento Meeting on "Current Therapy in Nephrology", Sorrento May 22-25, 1988, (Eds. VE Andreucci and A. Dal Canton), Kluwer Academic Publ, Boston, 1988.

26. Schurek HJ, Neumann KH, Jesinghaus WP, Aeikens B, Wonigeit K:
Influence of cyclosporine A on adaptive hypertrophy after unilateral nephrectomy in the rat.
Clin Nephrol, 25 (Suppl 1): S144-S147, 1986.
27. Kaskel FJ, Devarajan P, Arbeit LA, Partin JS, Moore LC:
Cyclosporine nephrotoxicity: sodium excretion, autoregulation, and angiotensin II.
Am J Physiol, 252: F733-F742, 1987.
28. Gnutzmann KH, Hering K, Gutsche H-U:
Effect of cyclosporine on the diluting capacity of the rat kidney.
Clin Nephrol, 25 (Suppl 1): S51-S56, 1986.
29. Muller-Suur R, Davis SD:
Effect of cyclosporine A on renal electrolyte transport: whole kidney and Henle loop study.
Clin Nephrol, 25 (Suppl 1): S57-S61, 1986.
30. Murray BM, Paller MS:
Beneficial effects of renal denervation and prazosin on GFR and renal blood flow after cyclosporine in rats.
Clin Nephrol, 25 (Suppl 1): S37-S39, 1986.
31. Gazdar AF, Dammin GJ:
Neural degeneration and regeneration in human renal transplants.
N Eng J Med, 283: 222-224, 1970
32. Kawaguchi A,Goldman MH,Shapiro R,Foegh ML,Ramwell PW,Lower RR:
Increase in urinary thromboxane B2 in rats caused by cyclosporine.
Transplantation, 40: 214-216, 1985.
33. Duggin GG, Baxter C, Hall BM, Horvath JS, Tiller DJ:
Influence of cyclosporine A on intrarenal control of GFR.
Clin Nephrol, 25 (Suppl 1): S43-S45, 1986.
34. Perico N, Benigni A, Zoja C, Delaini F, Remuzzi G:
Functional significance of exaggerated renal thromboxane A2 synthesis induced by cyclosporin A.
Am J Physiol, 251: F581-F587, 1986.
35. Elzinga L, Kelley VE, Houghton DC, Bennett WM:
Modification of experimental nephrotoxicity with fish oil as the vehicle for cyclosporine.
Transplantation, 43: 271-273, 1987.
36. Conte G,Sabbatini M,Napodano P,De Nicola L,Gigliotti G,Fuiano G,Testa A,Russo D,Esposito C,Libetta C,Dal Canton A, Andreucci VE:
Dopamine counteracts the acute renal effects of cyclosporine in normal subjects.
Transplant Proc, 20 (N 3,Suppl 3): 563-567, 1988.
37. Conte G, Sabbatini M, De Nicola L, Gigliotti G, Fuiano G, Testa A, Sepe V, Imperatore P, Dal Canton A, Andreucci VE:
Reversibility of acute cyclosporine renal impairment by dopamine in healrhy subjects.
Proc. 2nd Int. Sorrento Meeting on "Current Therapy in Nephrology", Sorrento, May 22-25, 1988, (Eds. VE Andreucci and A. Dal Canton), Kluwer Academic Publ, Boston, 1988.
38. Papa A, Lotito MA, Rampino T, Campolo G, Pacchiano G, Imperatore P, Memoli B, Libetta C, Milone D, Fuiano G:
"Renal functional reserve" of renal transplant patients.
Proc. 2nd Int. Sorrento Meeting on "Current Therapy in Nephrology", Sorrento, May 22-25, 1988, (Eds. VE Andreucci and A. Dal Canton), Kluwer Academic Publ, Boston, 1988.

39. Kho TL, Teule J, Leunissen KML, Heidendal GAK, Lijnen PJ, Amery AK, van Hooff JP:
Nephrotoxic effect of cyclosporine-A can be reversed by dopamine.
Transplant Proc, 19: 1749-1753, 1987.
40. Dieperink H, Leyssac PP, Kemp E, Starklint H, Frandsen NE, Tvede N, Moller J, Buchler Frederiksen P, Rossing N:
Nephrotoxicity of cyclosporin A in humans: effects on glomerular filtration and tubular reabsoprtion rates.
Eur J Clin Invest, 17: 493-496, 1987.
41. Hay R, Tammi K, Ryffel B, Mihatsch MJ:
Alterations in molecular structure of renal mitochondria associated with cyclosporine A treatment.
Clin Nephrol, 25 (Suppl 1): S23-S26, 1986.
42. Fournier N, Ducet G, Crevat A:
Action of cyclosporine on mitochondrial Ca++ effluxes.
J Bioenerg Biomembranes, 19: 297-303, 1987.
43. Myers BD:
Cyclosporine nephrotoxicity.
Kidney Int, 30: 964-974, 1986.
44. Kanzai G, Stowe N, Steinmuller D, Ho-Hsieh H, Novick A:
Effect of cyclosporine upon the function of ischemically damaged kidneys in the rats.
Transplantation, 41: 782-785, 1986.
45. Coffman TM, Carr DR, Yarger WE, Klotman PE:
Evidence that renal prostaglandin and thromboxane production is stimulated in chronic cyclosporine nephrotoxicity.
Transplantation, 43: 282-285, 1987.
46. Bia MJ, Tyler KA:
Effect of cyclosporine on renal ischemic injury.
Transplantation, 43: 800-804, 1987.
47. Jablonski P, Harrison C, Howden B, Rae D, Tavanlis G, Marshall Vc, Tange JD:
Cyclosporine and the ischemic rat kidney.
Transplantation, 41: 147-151, 1986.
48. Provoost AP, Kaptein L, Van Aken M:
Nephrotoxicity of cyclosporine A in rats with a diminished renal function.
Clin Nephrol, 25 (Suppl 1): S162-S167, 1986.
49. Dieperink H, Kemp E, Leyssac PP, Starklint H, Wanscher M, Nielsen J, Jorgensen KA, Faber V, Flachs H:
Ketoconazole and cyclosporine A: combined effects on rat renal function and on serum and tissue cyclosporine A concentration.
Clin Nephrol, 25 (Suppl 1): S137-S143, 1986.
50. Gonwa TA, Nghiem DD, Schulak JA, Corry RJ:
Erythromycin and cyclosporine.
Transplantation, 41: 797-799, 1986.
51. Harnett JD, Parfrey PS, Paul MD, Gault MH:
Erythromycin-cyclosporine interaction in renal transplant recipients.
Transplantation, 43: 316-318, 1987.
52. Jensen CWB, Flechner SM, Van Buren CT, Frazier OH, Cooley DA, Lorber MI, Kahan BD:
Exhacerbation of cyclosporine toxicity by concomitant administration of erythromycin.
Transplantation, 43: 263-270, 1987.

53. Martell R, Heinrichs D, Stiller CR, Jenner M, Keown PA, Dupre J:
The effects of erythromycin in patients treated with cyclosporine.
Ann Intern Med, 104: 660-661, 1986.
54. Cantarovich M, Hiesse C, Lockiec F, Charpentier B, Fries D:
Confirmation of the interaction between cyclosporine and the calcium channel blocker nicardipine in renal transplant patients.
Clin Nephrol, 28: 190-193, 1987
55. Ryffel B, Muller AM, Mihatsch MJ:
Experimental cyclosporine nephrotoxicity: risk of concomitant chemotherapy.
Clin Nephrol, 25 (Suppl 1): S121-S125, 1986.
56. Brunner FP, Hermle M, Mihatsch MJ, Thiel G:
Mannitol potentiates cyclosporine nephrotoxicity.
Clin Nephrol, 25 (Suppl 1): S130-S136, 1986.
57. Cockburn ITR, Krupp P:
Sandimmun. An appraisal of drug interactions.
Proc. 2nd Int. Sorrento Meeting on "Current Therapy in Nephrology", Sorrento, May 22-25, 1988, (Eds. VE Andreucci and A. Dal Canton), Kluwer Academic Publ, Boston, 1988.
58. Tindall RSA, Rollins JA, Phillips JT, Greenlee RG, Wells L, Belendiuk G:
Preliminary results of a double-blind, randomized, placebo-onctrolled trial of cyclosporine in Myasthenia gravis.
N Eng J Med, 316: 719-724, 1987.
59. Fuiano G, Stanziale P, Cianfrone P, Balletta M, Conte G, Libetta C, Guida B, Bisesti V, Sepe V:
Effects of cyclosporine A on renal function and proteinuria in patients with nephrotic syndrome after a single oral administration.
Proc. 2nd Int. Sorrento Meeting on "Current Therapy in Nephrology", Sorrento, May 22-25, 1988, (Eds. VE Andreucci and A. Dal Canton), Kluwer Academic Publ, Boston, 1988.
60. Maiorca R, Cristinelli L, Scolari F, Sandrini S, Savoldi S, Brunori G, Prati E, Lojacono L, Salerni B, Tonini G:
Cyclosporine toxicity can be minimized by careful monitoring of blood levels.
Transpant Proc, 17 (Suppl 2): 54-59, 1985.
61. Holt DW, Marsden JT, Johnston A, Bewick M, Taube DH:
Blood cyclosporin concentration and renal allograft dysfunction.
Br Med J, 293: 1057-1058, 1986.
62. Niebel W, Metz K, Donhuijsen D, Albrecht KH, Windeck R, Eigler FW:
The effect of low-dose cyclosporine A on histopathologic findings in transplant biopsy specimens and function rates after cadaver renal transplantation.
Transplant Proc, 19: 1772-1775, 1987.
63. Bennett WM, Norman DJ:
Action and toxicity of cyclosporine.
Annu Rev Med, 37: 215-224, 1986.
64. Neild GH, Taube DH,Hartley RB,Bignardi L,Cameron JS,Williams DG, Ogg CS, Rudge CJ:
Morphological differentiation between rejection and cyclosporin nephrotoxicity in renal allografts.
J Clin Pathol, 39: 152-159, 1986.

65. Mihatsch MJ, Ryffel B, Hermle M, Brunner FP, Thiel G:
Morphology of cyclosporine nephrotoxicity in the rat.
Clin Nephrol, 25 (Suppl 1): S2-S8, 1986.
66. Verani R:
Cyclosporine nephrotoxicity in the Fisher rat.
Clin Nephrol, 25 (Suppl 1): S9-S13, 1986.
67. Bertani T, Perico N, Abbate M, Battaglia C, Remuzzi G:
Renal injury induced by long-term administration of cyclosporin A to rats.
Am J Pathol, 127: 569-579, 1987.
68. von Willebrand E, Hayry P:
Cyclosporin-A deposits in renal allografts.
Lancet, 2: 189-192, 1983.
69. Kolbeck PC, Wolfe JA, Burchette J, Sanfilippo F:
Immunopathologic patterns of cyclosporine deposition associated with nephrotoxicity in renal allograft biopsies.
Transplantation, 43: 218-224, 1987.
70. Shen SY, Weir MR, Revie DR, Dagher FJ, Bentley FR, Chretien PB:
Differentiation of acute rejection from acute cyclosporine nephrotoxicity in renal transplants by peripheral T cell subset counts.
Transplant Proc, 19: 1776-1779, 1987.
71. Shulmann H, Striker G, Deeg HJ, Kennedy M, Storb R, Thomas ED:
Nephrotoxicity of cyclosporine A after allogeneic marrow transplantation: glomerular thromboses and tubular injury.
N Eng J Med, 305: 1392-1395, 1981.
72. Atkinson K, Briggs JC, Hayes H, Ralston M, Dodds AJ, Concannon AJ, Naidoo D:
Cyclosporin A-associated nephrotoxicity in the first days after allogeneic bone marrow transplantation: three distinct syndromes.
Br J Hematol, 54: 59-67, 1983.
73. Bonser RS, Adu D, Franklin I, McMaster P:
Cyclosporine-induced helomytic uremic syndrome in liver allograft recipients.
Lancet, 2: 1337-1338, 1984.
74. Wolfe JA, McCann RL, Sanfilippo F:
Cyclosporine-associated microangiopathy in renal transplantation. A severe but potentially reversible form of early graft injury.
Transplantation, 41: 541-543, 1986.
75. Zoja C, Furci L, Ghilardi F, Zilio P, Benigni A, Remuzzi G:
Cyclosporin-induced endothelial cell injury.
Lab Invest, 55: 455-462, 1986.
76. Myers BD, Ross J, Newton L, Luetscher J, Perlroth M:
Cyclosporine-associated chronic nephropathy.
N Eng J Med, 311: 699-705, 1984.
77. Palestine AG, Nussenblatt RB, Chan C-C:
Side effects of systemic cyclosporine in patients not undergoing transplantation.
Am J Med, 77: 652-656, 1984.
78. Svenson K, Bohman S-O, Hallgren R:
Renal interstitial fibrosis and vascular changes. Occurrence in patients with autoimmune diseases treated with cyclosporine.
Arch Intern Med, 146: 2007-2010, 1986.

79. Stanek B, Kovarik J, Rasoul-Rockenschaub S, Silberbauer K:
Renin-angiotensin-aldosterone system and vasopressin in
in cyclosporine-treated renal allograft recipients.
Clin Nephrol, 28: 186-189, 1987.
80. Pfeilschifter J, Ruegg UT:
Cyclosporin A augments angiotensin II-stimulated rise in
intracellular free calcium in vascular smooth muscle cells.
Biochem J, 248: 883-887, 1987.
81. Myers BD, Sibley R, Newton L, Tomlanovich SJ, Boshkos C, Stinson
E, Luetscher JA, Whitney DJ, Krasny D, Coplon NS, Perlroth MG:
The long-term course of cyclosporine-associated chronic nephropathy.
Kidney Int, 33: 590-600, 1988.
82. Bantle JP, Nath KA, Sutherland DER, Najarian JS, Ferris TF:
Effects of cyclosporine on the renin-angiotensin-aldosterone system
and potassium excretion in renal transplant recipients.
Arch Intern Med, 145: 505-508, 1985
83. Foley RJ, Hammer RW, Weinman EJ:
Serum potassium concentration in cyclosporine- and azathioprine-
treated renal transplant patients.
Nephron, 40: 280-285, 1985.
84. Cohen SL, Boner G, Rosenfeld JB, Shmueli D, Sperling O, Yusim A,
Todd-Pokropek A, Shapira Z:
The mechanism of hyperuricaemia in cyclosporine-treated renal
transplant recipients.
Transplant Proc, 19: 1829-1830, 1987.
85. Hoyer PF, Lee IkJ, Oemar BS, Krohn HP, Offner G, Brodehl J:
Renal handling of uric acid under cyclosporin A treatment.
Pediatr Nephrol, 2: 18-21, 1988.
86. Barton CH, Vaziri NS, Martin DC, Choi S, Alikhani S:
Hypomagnesemia and renal magnesium wasting in renal transplant
recipients receiving cyclosporine.
Am J Med, 83: 693-699, 1987.
87. Iaina A, Herzog D, Cohen D, Gavendo S, Kapuler S, Serban I,
Schiby G, Eliahou HE:
Calcium entry-blockade with verapamil in cyclosporine A plus ischemia
induced acute renal failure in rats.
Clin Nephrol, 25 (Suppl 1): S168-S170, 1986.
88. Sumpio BE, Baue AE, Chaudry IH:
Alleviation of cyclosporine nephrotoxicity with verapamil and
ATP-MgCl2: mitochondrial respiratory and calcium studies.
Ann Surg, 206: 655-660, 1987.
89. Feehally J, Walls J, Mistry N, Horsburgh T, Taylor J, Veitch PS,
Bell PRF:
Does nifedipine ameliorate cyclosporine A nephrotoxicity?
Br Med J, 295: 310-311, 1987.
90. Curtis JJ, Luke RG, Dubovsky E, Diethelm Ag, Whelchel JD,
Jones P:
Cyclosporin in therapeutic doses increases renal allograft vascular
resistance.
Lancet, 2: 477-478, 1986.
91. Wheatley HC, Datzman M, Williams JW, Miles DE, Hatch FE:
Long-term effects of cyclosporine on renal function in liver
transplant recipients.
Transplantation, 43: 641-647, 1987.

92. Palestine AG, Austin III HA, Balow JE, Antonovych TT, Sabnis SG, Preuss HG, Nussenblatt RB:
Renal histopathologic alterations in patients treated with cyclosporine for uveitis.
N Eng J Med, 314: 1293-1298, 1986.
93. Nahman NS Jr, Cosio FG, Kolkin S, Mendell JR, Sharma HM:
Cyclosporine nephrotoxicity without major organ transplantation.
Ann Intern Med, 106: 400-401, 1987.
94. Keown PA, Stiller CR, Cameron Wallace A:
Nephrotoxicity of cyclosporin A.
In: Kidney Transplant Rejection (Eds. GM Williams, JF Burdick and K Solez), Marcel Dekker Inc., New York, 1986, pp 423-457.
95. Miescher PA, Favre H, Chatelanat F, Mihatsch MJ:
Combined steroid-cyclosporin treatment of chronic autoimmune diseases.
Klin Wochenschr, 65: 727-736, 1987.
96. Loertscher R:
Cyclosporine-associated nephrotoxicity is not intractable.
Transplant Proc, 19: 3486-3489, 1987.
97. Morris PJ, French ME, Dunnill MS, Hunnisette AGW, Ting A, Thompson JF, Wood RFM:
A control trial of cyclosporine in renal transplantation with conversion to azathioprine and prednisolone after three months.
Transplantation, 36: 273-277, 1983.

ACUTE RENAL FAILURE

10

THE CHANGING EPIDEMIOLOGY OF ACUTE RENAL FAILURE: PATTERNS IN ECONOMICALLY ADVANCED AND DEVELOPING COUNTRIES.

KIRPAL S. CHUGH, Department of Nephrology, Postgraduate Institute of Medical Education and Research, Chandigarh - 160012 India .
CARL M. KJELLSTRAND, Department of Medicine, Division of Nephrology, Karolinska Hospital, 104 01 Stockholm, Sweden.

I. INTRODUCTION

Acute renal failure (ARF) is the most common, time consuming, dramatic and lethal syndrome seen by nephrologists (1-11). Since dialysis was introduced in clinical use in the mid-1940's, acute renal failure appears to have undergone profound changes. Our purpose is to analyze these changes and try to suggest ways of avoiding acute renal failure and predict the need of conservative care and dialysis for these patients.

We will not analyze the occurrence of acute renal failure that has accompanied the only major epidemic, that of war, that has afflicted mankind from its earliest history to present day. The influence of war on the need for dialysis, the analyses of how dialysis could be improved and major prognostic factors have been carefully analyzed ever since dialysis units accompanied armies from the Korean conflict and up till the present day (12-16) Suffice to say that any major war will dramatically change the epidemiology of acute renal failure for the worse. It is probably the reason for the enormous incidence of acute renal failure in Lebanon, 177 cases per million and year reported 1983, that is more than 6 times higher than that of Europe and N.Africa (17). We are not considering post-transplantation acute renal failure. This is highly varied depending on institutional transplant policies. In some places it would not exist at all, at others it will make up as many as 30% of patients with acute renal failure (18)

In the following we will separately describe the situation in economically advantaged and developing countries.

II. ACUTE RENAL FAILURE IN DEVELOPING COUNTRIES.

A summary of reports of acute renal failures in developing countries appears in Table I.

A review of a large series comprising 1862 patients dialyzed for acute renal failure from Jan 1965 to Dec 1986 at the Postgraduate Medical Institute, Chandigarh which is a tertiary care center and deals with a homogeneous North Indian population represents a typical pattern of this disease being encountered in the developing countries (19).

Table I

COMPARATIVE INCIDENCE OF ARF IN DEVELOPING COUNTRIES

Country / ref	Year	No.of pts.	Medical %	Obstetric %	Surgical %
Singapore / 4	1975	143	60	16	24
Indonesia / 5	1975	48	63	29	8
Argentina / 6	1975	1000	58	28	14
Thailand / 7	1975	162	61	15	24
Ghana / 8	1976	50	62	24	4
India / 1	1978	325	67	22	11
S. Africa / 64	1978	150	65	25	10
India / 21	1985	816	56	23	21
India / 9	1987	187	85	9	6
India / 19	1987	1862	60	15	25

In the overall group, medical conditions had led to acute renal failure in 1124 patients (60%), obstetric in 270 (15%) and surgical causes in 468 (25%) patients. In order to assess the change in the pattern of this disease, the patient population was analyzed separately for three study periods 1965-1974, 1975-1980 and 1981-1986 (Fig 1).

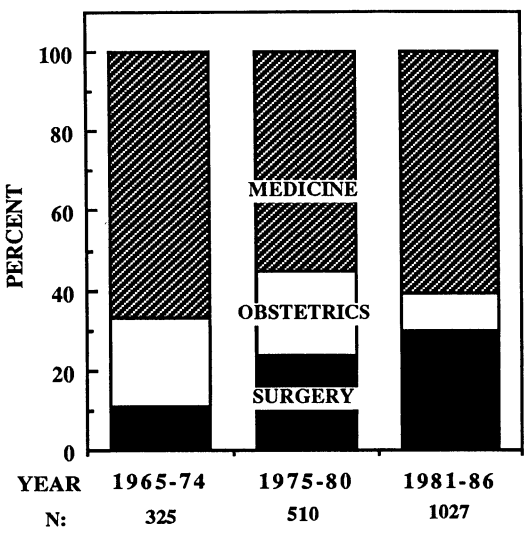


Fig 1.

MEDICAL ACUTE RENAL FAILURE

Acute renal failure occurring in the medical setting is summarized in Table II. Diarrhoeal diseases with consequent fluid and electrolyte loss constitute the leading cause of renal failure in Africa, India, Pakistan, Bangla Desh, Indonesia and many other countries in the tropics (1, 2, 3, 5, 20, 21). This entity is hardly if ever, seen in the economically rich countries today. The mortality from diarrhoeal diseases in children in the tropical countries has been assessed around 5-10 million per year (22). The persistence of this entity amongst these populations is a general reflection of poor socio-economic conditions, lack of a clean, pipe borne water supply, ignorance about personal hygiene, over-crowding and inadequate medical facilities. Though the majority of patients are in the pediatric age group, the condition is not confined to the children alone (1-3). In two recent studies of acute renal failure in children, diarrhoeal diseases were the underlying cause in 50% and 37% respectively (2, 23). More than half of the children are below the age of 4 years and renal failure is frequently of the oliguric type. Renal histology reveals acute tubular necrosis in the majority though acute cortical necrosis is occasionally seen (2). Hemolytic uremic syndrome is the

major pathogenetic factor for acute renal failure in 65% of the children with shigella dysentery in South India (24).

Table II

CAUSES OF ACUTE RENAL FAILURE IN THE MEDICAL SETTING IN DEVELOPING COUNTRIES

	1965-74	1975-80	1981-86
Diarrhoeal Diseases	23 %	12 %	10 %
Hemolysis (G-6PD Defic.)	12 %	12 %	6 %
Glomerulonephritis	11 %	9 %	9.5 %
Copper Sulphate	5 %	2 %	1 %
Chemicals & Drugs	4 %	5 %	7 %
Snakes & Insects	3 %	3 %	2.5 %
Sepsis	2 %	1 %	8 %
Transplant Related	---	3 %	4 %
Miscellaneous, Multiple & Unidentified	7 %	8 %	13 %
Percentage of Total ARF	67 %	55 %	61 %
Medical Causes	218	283	623
All Patients	325	510	1027

Though the overall incidence of renal failure due to medical causes has not changed significantly and has remained around 60%, there has been a steady decline in the in incidence of renal failure due to diarrhoeal diseases from 23% in 1965-74, to 12% in 1975-80 and to 10% in 1981-86 (Table II). The change is commensurate with a slow pace of improvement in socio-economic conditions and medical facilities in the rural health care centers in India.

Acute renal failure associated with severe hemolysis in G6PD deficient patients is another frequent condition in Africa and India and is related to interaction of genetic and environmental factors (8, 25,26). Though over 100 million persons of all races throughout the world have been estimated to be affected by erythrocyte G6PD

deficiency (27), this entity has not been reported from other parts of the world except Greece (28). The incidence of G6PD deficiency amongst Kurdish Jews has been observed to be as high as 60%, amongst African population in Ghana 22.5% (8), in oriental Jewish groups 20% (29), in Indians 2-15% (30, 31), in Chinese 2% and amongst Ashkanazee Jews 0.4% (32). Its incidence in some parts of East Africa is about 15% and among Yorubas of Nigeria 20% (33). The varying intensity of hemolysis observed in different populations is possibly determined by the type of inherited G6PD deficiency of which over 40 variants have been described, and by some unknown genetic and environmental factors (34, 35). Adu et al (8), described 55 adult patients with ARF admitted to a renal unit in Accra (Ghana), emphasizing the frequent combination of hemolysis precipitated by infections. The frequency of G6PD deficiency (22.5%) in the latter study was similar to that found in the normal population of Southern Ghana (24.3%). A high incidence of acute renal failure in G6PD deficient patients (25.8%) has also been reported from Greece, where patients have been observed to develop hemolysis following ingestion of djenkol and broad beans (28). In the Chandigarh study, 164 G6PD deficient patients comprising 14.6% of the medical group, had developed renal failure associated with intravascular hemolysis. Hemolysis followed administration of the commonly used anti-malarial drugs (primaquin, chloroquin or quinine), analgesics (acetyl-salicylic acid, acetanalide phenacetin or analgin) or a combination of these (25, 26). The condition has been reported from other parts of India also (9, 36). A variety of infections including viral hepatitis (26, 37, 38), rickettsia (39) typhoid fever (40) and urinary infection (41) have also been reported as important predisposing factors for hemolysis and renal failure in G6PD deficient patients.

Renal ischemia due to liberation of vasoconstrictor substances from the damaged erythrocytes combined with intratubular obstruction by hemoglobulin casts, dehydration, acidosis and disseminated intravascular coagulation are regarded as predisposing factors for the development of acute tubular necrosis in these patients (26). The explanation for decline in the number of patients dialyzed for hemolysis-associated renal failure from 12% to 6% is not clear since the patient population under study has not changed. It is perhaps related to the recent awareness about the existence of this condition an a more cautious use of drugs in the affected populations.

Snake bites and insect stings pose a serious health hazard in the inhabitants of the tropical and subtropical regions (42, 43). A high mortality following snake bite has been reported from Africa, India, Burma, Ceylon, Thailand, Malaysia and Brazil (44). Acute renal failure complicates the course of snake envenomation in 11-25% of

patients (42, 45, 46,, 47). The snakes which have been incriminated in the development of renal failure include Russels', viper, saw scaled viper (42, 45-49), pit viper (50), puff adder (51), rattle snake (52), boom slang (53), cobra (54) and sea snake (55, 56). Renal failure appears to be multi-factorial in origin and bleeding, hypotension, hemolysis, D.I.C. and direct nephrotoxicity acting singly or in combination appear to the significant predisposing factors (45). In 30% of patients, renal histology shows irreversible lesions of acute cortical necrosis and the remaining show acute tubular necrosis (45). No significant change in the incidence of renal failure associated with snake bites has been observed over the years (Table II).

Copper sulphate ingested accidentally or with suicidal intent has been reported as a cause of acute renal failure only from India (9, 57). Renal failure results from hemolysis, bleeding, myoglobinuria and direct nephrotoxicity. The incidence of renal failure due to copper intoxication has come down drastically from 5% in the 1970's to 1% in the 1980's (Table II) and is related to change in the pattern of poisoning over the years. Barbiturates, tranquillizers, and insecticides are now of more frequent modes of suicidal poisoning amongst Indian patients, than a decade ago (58).

Whereas no apparent change has been observed in glomerulonephritis presenting as acute renal failure, a perceptible change seems to have occurred in renal failure associated with sepsis, renal transplantation and conditions included under miscellaneous causes. The latter category has increased two-folds and amongst them, patients developing renal failure following administration of aminoglycosides, cephalosporins, rifampicin and radio contrast agents have increased six times. The presence of sepsis and failure of other organs, compounds the problem in many of these patients.

In the past fifteen years, malaria has returned to several places from where it had been eradicated. According to recent estimates, about 300 million are infected in tropical Africa alone (59). Acute renal failure associated with plasmodium falciparum infection has been reported from Thailand (7) and parts of India (60, 61). Renal failure results from a combination of heavy parasitemia, release of vascular permeability factors and intravascular hemolysis (7). Blackwater fever complicating acute plasmodium falciparum infection is now an uncommon disease and some of the cases reported in the Africans and Indians may be due to the effect of drugs and infections in individuals with G6PD deficiency (26).

Leptospirosis has been reported as a common cause of acute renal failure in Thailand (7) and Singapore (4) and recently increasing number of cases are being reported from Southern India (9, 62). Renal failure occurs during the stage of

leptospiremia in 65%, and the renal histology reveals combined changes of acute tubular necrosis and interstitial nephritis.

Acute renal failure following the use of traditional herbal remedies has been reported from Africa (63, 64). Callilepis laureola is a herb which is grown extensively in Southern Africa and its extract is prescribed for a variety of illnesses including cough, difficulty in breathing, constipation, impotence, sterility, intestinal worms and gynecological complaints. Toxic symptoms include abdominal pain, vomiting, jaundice, hypoglycemia and renal failure (63). Mortality following toxicity is around 50% in children under the age of ten years.

OBSTETRIC RENAL FAILURE.

Pregnancy related acute renal failure seems to have virtually disappeared from the economically advanced countries with readily available medical care. According to recent estimates, developing countries such as the United States, West Germany, France, Japan and the Soviet Union account for 26 million legal abortions every year. Of the 28 million abortions performed in developing countries, an estimated 20 million are illegal. Most os these are likely to be unsafe because these are performed under unhygienic conditions by self trained and unlicensed abortionists (65).

More than 6 million abortions are being performed annually in India and abortion rate is estimated around 8 per one thousand women (66). Before introduction of medical termination of Pregnancy Act in India, in 1972, a majority of these abortions were illegal. Currently the legal abortions constitute around 2.5 per thousand. Illegal abortions in India carry a mortality of 780 per 100,000 compared to 66 per 100,000 following legal abortions. The mortality after legal abortions in the developed countries is 1.4 per 100,000. In a collaborative study for evaluation of morbidity amongst patients undergoing abortion under hospitalized conditions, not a single patient developed acute renal failure (66, 67). Analysis of 270 patients dialyzed at Chandigarh, brings out some peculiarities about obstetric renal failure as seen in this part of the world. During the first trimester, acute renal failure invariably followed septic abortion whereas in late pregnancy, renal failure was precipitated by severe pre-eclampsia, eclampsia, antepartum hemorrhage, postpartum haemorrhage or puerperal sepsis. Patients of acute renal failure are equally distributed between early and late pregnancy (Table III).

Table III

PREGNANCY RELATED ARF 270 PTS. (14.5 %)

		No.	% of Obst.group	% of Total ARF
• EARLY PREGNANCY		138	51.1	7.4
Septic Abortions	(135)			
Ectopic Pregnancy	(3)			
• LATE PREGNANCY		132	48.9	7.1
Toxemia	(34)			
A.P.H.	(22)			
P.P.H.	(35)			
Puerperal Sepsis	(36)			
Postpartum	(5)			
TOTAL		270	100	14.5

The high frequency of symmetrical and patchy lesions of cortical necrosis (25%) in obstetric patients in the developing countries (65, 68) stands out prominently compared to reported studies from the West (69, 70). Moreover, cortical necrosis is regarded as of infrequent occurrence during the early pregnancy e.g. these lesions were seen only in 2 out of 136 patients (1.5%) of post-abortion renal failure and in 11 out of 52 patients (21%) with post partum renal failure at the Necker Hospital (71). None of the 52 patients with post abortion renal failure reported from Hammersmith showed cortical necrosis (70). In contrast, in the Chandigarh study, cortical necrosis has been recorded in 39% of patients with post-abortion renal failure and in 33% in association with renal failure during late pregnancy (68). Specific risk factors amongst our populations are not clear.

In the Chandigarh study, acute renal failure due to septic abortions which constituted 13.2 % of the total renal failure during 1965-1974, has declined to 3.5% during 1981-86 (Fig 2).

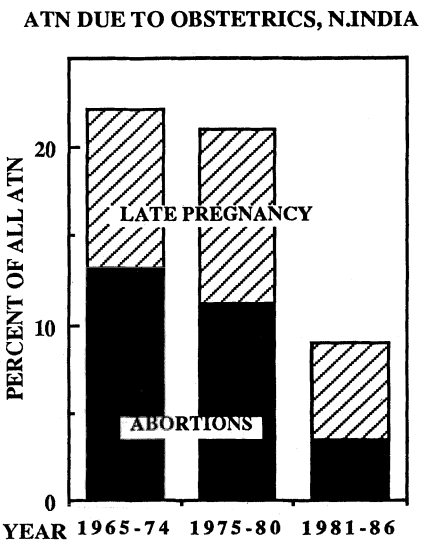


Fig 2

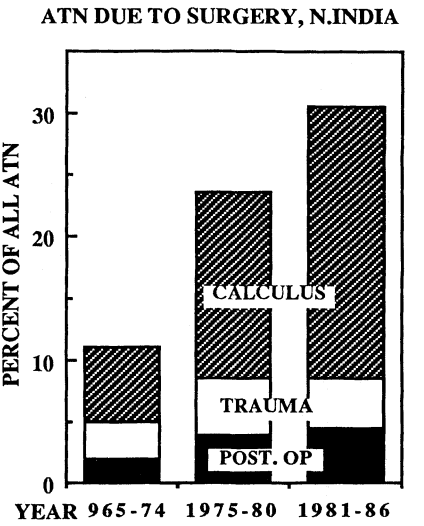


Fig 3

The decrease in the number of cases occurring during late pregnancy was less impressive. The overall incidence of obstetric cases decreased from 22% to 9% in the corresponding period. The decline in the incidence corresponds to improvement in antenatal care as well as the liberalized abortion laws.

SURGICAL ACUTE RENAL FAILURE

Surgical causes comprised 11% of total acute renal failure in 1965-74 and 30% in 1981-86 (Fig 3). The rise is attributed to increasing number of patients being taken up for advanced cardio-vascular and abdominal surgery, inclusion of high risk patients, rise in the accident rate and a four-fold increase in cases of obstructive uropathy due to stone disease. Thus, the trend observed in the surgical patients is different from the Western countries where the incidence of surgical renal failure has declined over the recent years (see later). The surgical patients now have an increasing tendency to develop medical renal failure due to frequent use of nephrotoxic drugs (10,11).

SUMMARY.

Acute renal failure is a common problem in the tropical countries and is grossly under reported. Clearly, more data are required for identifying the populations at risk and the whole range of conditions which can cause acute renal failure. Review of patients dialyzed at a tertiary care center in North India from 1965 to 1986, clearly shows the changing trends in the epidemiology of acute renal failure in the developing countries of the tropical region. At least two trends are obvious. Firstly, compared to the industrially advanced countries which have experienced a striking improvement in the socio-economic conditions and rapid expansion of medical facilities during the last two decades, the change is occurring at a much lower pace. Secondly, the pattern of change is distinctly different. Whereas the overall incidence of medical causes has remained nearly constant (around 60%) since 1965, diarrhoeal diseases which represented 23% of the total cases in 1965-1974 have shown a steady decline to 10% in 1981-86. Similarly, pregnancy related acute renal failure, which constituted 22% of the total group till 1974 have shown a decline to 9% in 1981-86. Cases of surgical renal failure have increased from 11% to 30% in the three periods. The high prevalence of acute renal failure in the tropical countries of Asia and Africa is related to poor economic development, ignorance about personal hygiene, continued prevalence of parasitic and other tropical infections, strong faith in indigenous household remedies with consequent delays in hospitalization and initiation of therapy, inadequate health care facilities in the rural medical centers and high rate of septic induced abortions. Dialysis facilities are still meagre and located only in large urban centers. The prevention and ultimate control of this potentially reversible condition is certainly a gigantic task, but acquiescence in the status quo is passing.

III. ACUTE RENAL FAILURE IN ECONOMICALLY ADVANCED COUNTRIES.

The largest survey of severe acute renal failure requiring dialysis, was performed 1983 by the European Dialysis and Transplant Association (17). Answers were obtained from 32 European, Near East and North African countries. As a mean, 29 patients per million and year required acute dialysis with the range from 0.4 (Algeria) to 177 (Lebanon). As only centers performing chronic dialysis were questioned, the true incidence is probably higher. Analyses from smaller geographic areas indicate that 30-60 patients per million and year need dialysis. These studies come from Sweden, Israel, East Germany, Hungary and England (72-76). The studies considered only patients with severe acute renal failure requiring dialysis. Three recent studies have

also included milder forms of the disease that do not need dialysis. In the late seventies, Hou et al, studied 2262 patients admitted during a 6 months period in a large teaching hospital in the USA (10). Of these, 109 patients (4.9%) developed acute renal insufficiency, in 23 (21%) due to surgery. In only 10 of 129 episodes (8%) dialysis was necessary. Kumar and his co-workers found a slightly lower incidence of acute renal failure, 2%, during a one-month analysis, but had a higher incidence of surgically acute renal failure (44%) (77). Davidman and his associates analyzed 4569 patients admitted during a 4 month period. One-hundred (2.2%) developed nephrological problems (11). It was most commonly due to acute renal failure in 59 patients. Of the 59 patients, 8 (14%) needed dialysis. At least, in large tertiary care hospitals thus, between 2% and 4% of all admitted patients will develop acute renal failure but only 10% of these need dialysis. Conversely, one can assume that for every case of severe renal failure which needs dialysis there will be approximately 9 managed conservatively (10, 11, 77).

The diseases that cause acute renal failure has not varied since dialysis was introduced four decades ago. This is summarized in Table IV. Over 80% of all cases of severe renal failure, are due to secondary renal failure that we will call ATN (Acute Tubular Necrosis). Approximately 5% were caused by obstruction, post-renal failure, and 15% by primary renal disease(PRD) and other cases. These include myeloma, acute uric acid nephropathy and others. It is obvious that the domineering cause of acute renal failure is secondary renal failure, acute tubular necrosis, and that this has not changed during four decades.

While the causes of acute renal failure remain stable there has been a marked shift in the primary diseases that lead to acute tubular necrosis. This is summarized in Table V and Fig 4. Several trends are clear. Gynecological and obstetrical causes for acute tubular necrosis have almost vanished in the 1980's, while they caused 15% of acute tubular necrosis in the early days.

Table IV

CAUSE OF ACUTE RENAL FAILURE

PERIOD	N	% DIAL	ATN	POST R.F.	PRD	OTH.
1946-70*	2952	79%	2429 (82%)	144 (5%)	301(10%)	78(3%)
1967-79**	1532	90%	1232 (80%)	91 (6%)	105(7%)	104(7%)
1977-85***	987	70%	806 (81%)	40 (4%)	131(13%)	10(2%)
	5771	80%				

*Ref:.69, 71, 72, 77-82, 91. **Ref: 10, 18, 75, 83, 84. ***Ref: 11, 85-90.

Table V

CAUSES OF ACUTE TUBULAR NECROSIS

PERIOD	N	MEDICINE	SURGERY	TRAUMA	TOXIC	GYN/OBST.
1946-70*	2429	583(24%)	1138(47%)	189(8%)	153(6%)	366(15%)
1967-79**	1227	387(31%)	622(50%)	92(8%)	93(8%)	33(3%)
1977-85***	806	294(36%)	335(41%)	52(6%)	118(16%)	4(1%)

*Ref: 69, 72, 77-81, 91. **Ref: 10, 18, 75, 83, 84. ***Ref: 11, 85-90.

To the contrary, toxic acute tubular necrosis has more than tripled from 6% to almost 20%. Trauma remains stable, but there has been a 20% decrease in surgical and a 50% increase in medical diseases as a cause of acute tubular necrosis. Table VI and Fig 5 summarizes three series that include milder cases of acute tubular necrosis as they have a low percentage of dialyzed patients, less than 25%. In these series, medical sepsis and toxic causes, domineer completely. Toxic induced tubular necrosis are as common as surgically induced acute tubular necrosis in these analyses. The two leading agents among the toxic cases are antibiotics and radiological contrast media that cause over 80% of these cases. These cases remain fairly stable through the 1960's, 70's and 80's. We conclude that milder forms of acute tubular necrosis, that do not require dialysis, are more common following medical and toxic than following surgical basic diseases.

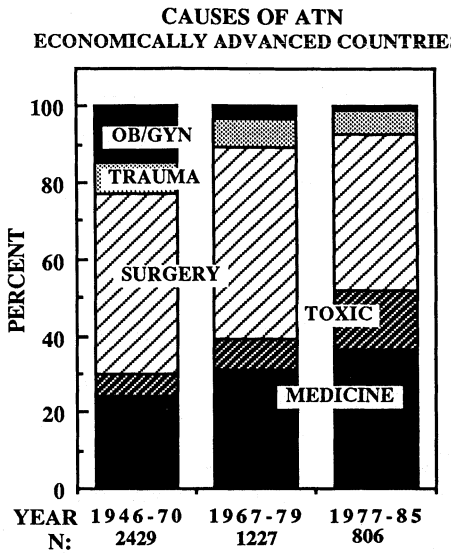


Fig 4

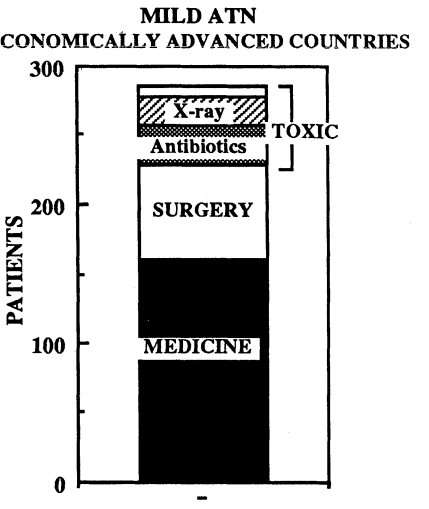


Fig.5

Table VI

CAUSES OF ATN, IN SERIES WERE FEW PATIENTS WERE DIALYZED.

AUTHOR	N	% DIALYZED	MEDICAL	SURGICAL/OTH	TOXIC		
					AB.	X-RAY.	OTH.
Ref. 77	122	25%	69	38	9	2	4
Ref. 10	112	9%	59	27	9	16	1
Ref. 11	52	15%	32	4	10	2	4
	286		160	69		57	
			56%	24%		20%	

Although it is more speculative, there has also appeared a change within the different subgroups of diseases that cause acute tubular necrosis. This seems evident when comparing the largest study from the early pioneer years, the study of Alwall

(82) 1946-1960 to the middle years,described by McMurray (84) 1967-75, to the largest most recent study by Beaman (88) from 1981-84. Approximately the same number of patients were dialyzed, 79%, 87% and 85%. The mortality was 44%, 37% and 44% respectively, while the age has increased from 50 to 52 to 57 years. Major cardiovascular surgery as a cause of ATN within the surgical group had increased from 8% to 53% to 60%. Gastrointestinal surgery decreased from 72% to 32% to 22%. While 10% of Alwall's cases had obstetrical causes for their renal failure, this was the case with only 1% in McMurray's and 3% of Beaman's cases. Also within the group of internal medical disease a gradual change towards more serious diseases occurred. While Alwall reported sepsis as the primary cause in only 21%, this had risen to approximately 50% in McMurray's and Beaman's materials. In the latter material, 24% of the patients were reported as suffering from malignancy. Cancer was not reported separately in the other materials. In at least 10% of Alwall's patients, did acute tubular necrosis occur because of dehydration secondary to gastrointestinal infections and 40% after milder gastrointestinal abdominal infections. To the contrary, this was reported in only 4% and 10% in Beaman's material. Thus, there seem no doubt that within each sub-group, more serious basic diseases now cause acute tubular necrosis than in the earlier days. Better resuscitation and earlier antibiotics have eradicated many of the milder diseases that earlier caused ATN. Paradoxically, the radiological diagnostic agents and antibiotics that have improved the care, are also the cause of many toxic cases of ATN.

There has also been some demographic changes in the patient population which undergoes acute renal failure. Whereas the mean age of the patients reported in the nine papers from before 1970 and the five papers that reported from the 1970's was 48 ± 6 years, it rose to 58 ± 3 years in the eight papers reporting from the 1980's ($p < 0.01$). There was a drop in the mortality rate. It was 48% before 1970, 51% in the 1970's and 46% as a mean in the reports from the 1980's, but the differences were not significant.

SUMMARY

In the developed countries the epidemiology of acute renal failure has remained stable over the last four decades. Acute tubular necrosis (secondary renal failure) has always been the most common cause of acute renal failure, responsible for 80% of such cases. Post-renal failure causes only 5% of all ARF and primary renal disease, and other diseases some 15% of the cases.

In the group of acute tubular necrosis marked shifts have occurred. The patients are now considerably older, and there are many more cases occurring as complications of internal medicine diseases than before, while particularly surgical disease as a cause of ATN have decreased. Obstetrical, gynecological diseases as a cause of acute tubular necrosis, has literally vanished and instead there has been a marked increase in toxic cases. These are now thought primary responsible for almost 20% of the cases, but probably contribute considerably in both internal medicine and surgical cases as well. The two leading nephrotoxins are antibiotics and radiological contrast media. The mortality rate among patients with acute tubular necrosis seems to have fallen in the 1980's in spite of an older patient population. Some of the cases of acute tubular necrosis are an unavoidable part of a laudable trend to take care of older and more sick patients, but the precipitous rise in nephrotoxic acute tubular necrosis is a source of worry as it is partially preventable and partially due to an incontinent use of antibiotics and invasive radiological methods.

REFERENCES

1. Chugh,K.S., Singhal,P.C., Nath,I.V.S., Tewari,S.C., Muthusethupathy,M.A.,Viswanathan,S., Uberoi,H.S., Pal,Y. and Sharma,L. Spectrum of acute renal failure in North India. Jr.Assoc.Phys.Ind.26: 147-154,1978.
2. Chugh,K.S., Narang,A., Kumar,L., Sakhuja,V., Narayanan Unni,V., Pirzada,R., Pereira,B.J.G. and Singhal,P.C. Acute renal failure amongst children in a tropical enviromnment. International J. Artif. Organs.10:27-31,1987.
3. Chugh,K.S. Etiopathogenesis of acute renal failure in the tropics. Natl.Acad.Med.Sci.23:88-99,1987.
4. Ku,G., Lim,C.H., Pwee,H.S. and Khoo,O.T. Review of acute renal failure in Singapore. Ann.Acad.Med. Singapore(Suppl) 4:115-120,1975.
5. Oesman,R., Markum,M.S., Rahardjo,J. and Sidabutar,R.P. Acute renal failure in General Hospital. Ann.Acad.Med. Singapore(Suppl) 4:121-123,1975.
6. Firmat,J.and Pas,R. 1000 patients with acute renal failure- Clinical and pathological observations. Abstracts of free communications. Sixth International Congress of Nephrology, Firenze. Abstract No.600,1975.
7. Sitprija,V. and Benyajati,C. Tropical disease and acute renal failure. Ann.Acad.Med. Singapore (Supp). 4:112-114,1975.
8. Adu,D., Anim-Addoy, Foli,A.K., Yeboah,E.D.,Quartey,J.K.M. and Riberio,B.F. Acute renal failure in tropical Africa. BMJ 1:890-892,1976.
9. Muthusethupathi,M.A. and Shivakumar,S Acute renal failure in South India. J.Ass.Physic.Ind. 35:504-508,1987.
10. Hou,S., Bushinsky,D.A., Wish,H., Cohen,J.J.and Harrington,J.T. Hospital-Acquired renal insufficiency: A prospective study. Am.J.Med.74:243,1983.
11. Davidman,M., Olsson,P., Kohen,J. and Kjellstrand,C.M. Renal disease in t he tertiary care hospital. Am.Soc.Nephrol.(Abstract). 19:79A,1986.
12. Teschan,P.E., Baxter,C.R., O'Brien,T.F., Freyhof,J.N. and Hall,W.H. Prophylactic hemodialysis in the treatment of acute renal failure. Annals Int.Med. 53:992-1016.
13. Barsoum,R.S, Rihan,Z.E.B., Baligh,O.K., Hozayen,A., El-Ghonaimy,EH.G ,Ramzy,M.F. and Ibrahuim,A.S. Acute renal failure in the 1973 Middle East war- Experience of a specialized base hospital:Effect of the site of injury. The J.of Trauma.20:303-307.
14. Lordon,R.E.and Burton,J.R. Post-traumatic renal failure in military personnel in Southeast Asia. Am.J.Med.53:137-147,1972.
15. Fischer,R.P. High mortality of post-traumatic renal insuffiency in Vietnam: A rewiev of 96 cases. Am.Surg.40:172-177,1974.
16. Stone,W.J. and Knepshield,J.H. Post-traumatic acute renal insufficiency in Vietnam. Clin.Neph.2:186-190,1974.
17. Wing,A.J., Broyer,M., Brunner,F.P., Brynger,H. Challa,S., Donckerwolke,R.A., Gretz,N., Jacobs,C., Kramer,P. and Selwood,N.H. Combined report on regular dialysis and transplantation in Europe, XIII. Proc.Eur.Dial.Transpl.Assoc.20:5,1983.
18. Kjellstrand,C.M., Ebben,J. and Davin,T. Time of death, recovery of renal function, development of chronic renal failure and need for chronic hemodialysis in patients with acute tubular necrosis. Trans.Am.Soc.Artif.Intern Organs.27:45,1981.

19. Chugh,K.S., Sakhuja,V. and Pereira,B.J.G. Changing trends in the spectrum of acute renal failure in the tropical countries. Abstracts of the Seventh Asian Colloquium in Nephrology, No.82,Taipei(Taiwan), Nov.25-28,1987.
20. Chugh,K.S. and Singhal,P.C. Pattern of acute renal failure in the developing countries: influence of socio-economic and environmental factors. In: Acute Renal Failure.(Ed.Eliahou) H.John Libby, London,1982,p.156-160.
21. Shah,P.P., Trivedi,H.L., Sharma,R.K., Shah,P.R. and Joshi,M.N. Acute renal failure, experience of 816 patients in tropics. Abstracts Fifteenth Annual Congress of Indian Society of Nephrology, Bangalore,1985,pp.17.
22. Okeahialam,T.C. Diarrhoeal diseases in children and oral rehydration in Nigeria. In: Childhood in the Tropics. (Eds. Eeckels,R.E., Ransome-Kuti, O. and Kronenberg, C.C.) Martinus Nijhoff Dordrecht, 1985,pp.81-88.
23. Choudhry,V.P., Srivastava,R.N., Vellodi,A., Bhuyan,U.N. and Ghai, O.P. A study of acute renal failure. Ind.Paediatr. 17:405-410,1980.
24. Raghupathy,P., Date,A., Shastry,J.C.M., Sudarsanam,A., and Jadhav,M. Hemolytic uremic syndrome complicating shigella dysentery in South Indian children. Br.Med.J. 1:1518-1521,1978.
25. Chugh,K.S., Sharma,B.K., Mathew,M.T., Bansal,V.K., Mahakur,A.C. Das,G.C., Dash,S.C., Amaresan,M.S. and Bhattacharya,K. Acute renal failure following drug induced intravascular hemolysis in G6PD deficient patients. J.Assoc.Phys.India. 21:1073-078,1973.
26. Chugh,K.S., Singhal,P.C., Sharma,B.K., Mahakur,A.C., Pal,Y., Datta,B.N.and Das,K.C. Acute renal failure due to intravascular hemolysis in the North Indian patient. Am.J.Med.Sci. 174:139-146,1977.
27. Marks,P.A. Red cell enzyme-glucose-6 phosphate dehydrogenase deficiency. Proc.XIth Cong.Int.Soc.Hematology,1966.pp.272.
28. Symvoulidis,A., Voudiclaris,S., Mountokalakis,T.H. el al. Acute renal failure in G-6PD deficiency. Lancet 2:819-820,1972.
29. World Health Organization. Technical Report Series No.338. Hemoglobinopathies and allied disorders. Geneva. p.4, 1966.
30. Jolly,J.G., Sarup,B.M., Bhatnagar,D.P. and Mani,S.C. Glucose-6-phosphate dehydrogenase deficiency in India. J.Indian Med.Assoc.58:196-200,1972.
31. Bakshi,S., Kumar,V. and Das,K.C. The clinical profile of acute hemolysis in glucose-6-phosphate dehydrogenase deficient children. Indian Pediatrics. 9:691-696,1972.
32. Allison,A.C. Glucose-6-phosphate dehydrogenase deficiency in red blood cells of East Africans. Nature 186:531-532,1960.
33. Gilles,H.M.and Ikeme,A.C. Hemoglobinuria among adult Nigerians due to glucose-6-phosphate dehydrogenase deficiency with drug sensitivity. Lancet. 2:889-891,1960.
34. Das,K.C. and Chugh,K.S. G6PD, the red cell and hemolysis. J.Assoc.Physic.India. 22:179-180,1974.
35. Motulsky,A.G. and Stamatoyannopoulos,G. Clinical implications of G-6PD deficiency. Ann.Int.Med. 65:1329,1966.
36. Metha,B.C., Mankodi,R.P., Acharya,V.N. et al. G-6PD deficiency as a cause of drug induced hemolysis with renal shutdown and kerniicterus. Ind.J.Med.Sci. 25:308-312,1971.
37. Salen,G., Goldstein,F., Haurani,F.et al. Acute hemolytic anemia complicating viral hepatitis in patients with G-6PD deficiency. Ann.Intern..Med. 65:1210-1220,1966.
38. Aggarwal,R.K., Moudgil,A., Kishore,K., Srivastava,R.N. and Tandon,R.K.

Postgrad.Med.J. 61:971-975,1985.
39. Whelton,A., Donadio,J.V.Jr.and Elisberg,B.L. Acute renal failure complicating rickettsial infections in G6PD deficient individuals. Ann.Intern.Med. 69:323-328,1968.
40. Lwanga,D.and Wing,A.J.E. Renal complications associated with typhoid fever. E.Afr.Med.J, 47:146-152,1970.
41. Owusu,S.K., Addy,J.:H., Foli,A.K. et al. Acute reversible renal failure associated with G-6PD deficiency. Lancet 1:1255-1257,1972.
42. Chugh,K.S., Aikat,B.K., Sharma,B.K., Dash,S.C., Mathew,M.T. and Das K.C. Acute renal failure following snake bite. Am.J.Trop:Med.Hyg. 24:701-705,1975.
43. Sakhuja,V., Bhalla,A. Pereira,B.J.G., Kapoor,M.M., Bhusnurmath,S.R. and Chugh,K.S. Acute renal failure following hornet stings. Nephron,1988 (In Print).
44. Minton,S.A.(Ed.) Snake venoms and envenomation. Marcel Dekker Inc., New York,1971.
45. Chugh,K-S., Pal,Y., Chakravarty,R.N., Datta,B.N., Metha,R., Sakhuja,V., Mandal,A.K. and Sommers,S.C. Acute renal failure following poisoning by snake bite. Am.J.Kidney Disease. 41:30-38,1984.
46. Visuvaratnam,M., Vinayagamoorthy,C. and Balakrishnan,S. Venomous snake bites in North Ceylon. J.Trop.Med.Hyg.73:9-14,1970.
47. Nigam,P., Tandon,V.K., Kumar,R., Thacore,V.R. and Lal,N. Snake bite -a clinical study. Ind.J.Med.Sci. 27:697-704,1973.
48. Sitprija,V., Benyajati,C. and Boonpucknavig,V. Further observations of renal insufficiency in snake bite. Nephron 13:396-403,1974.
49. Shastry,J.C.M., Date,A., Carman,R.H. and Johny,K.V. Renal failure following snake bite. Am.J.Trop.Med.Hyg. 26:1032-1038,1977.
50. Varagunam,T. and Panabokke,R.G. Bilateral cortical necrosis of the kidneys following snake bite. Postgrad.Med.J. 46:449-451,1970.
51. Seedat,Y.K., Reddy,J. and Edington,D.A. Acute renal failure due to proligerative nephritis from snake bite poisoning. Nephron 13:455,1970.
52. Danzig,L.E. and Abels,G.H. Hemodialysis for acute renal failure following rattle snake bite with recovery. J.Am.Med.Assoc. 175:136-137,1961.
53. Lakier,B. and Fritz,V.U. Consumptive coagulopathy caused by a boomslang bite. S.Afr.Med.J. 43:1052,1969.
54. Azevedo,A.P. and Teixeira,J.C. Intoxicacao por veneno de cobra.Necrose symetrica da cortex renal. Mems.Inst.Oswaldo Cruz. 13:23-28,1938.
55. Sitprija,V., Sribhibhadh,R. and Benyajati,C. Hemodialysis in poisoning by sea snake venom. Brit.Med.J. 3:218-219,1971.
56. Steinbeck,A.W. Nephrotic syndrome developing after snake bite. Med.J.Aust. 1:543-545,1960.
57. Chugh,K.S., Sharma,B.K., Singhal,P.C., Das,K.C. and Data, B.N. Acute renal failure following copper sulphate intoxication. Postgrad.Med.J. 53:18-23,1977.
58. Singh,S., Sharma,B.K., Wahi,P.L., Anand,B.S. and Chugh,K.S. Spectrum of acute poisoning in adults - 10 years experience. J.Ass.Physic.India. 32:561-563,1984.
59. Wyler,D.J. Malaria: resurgence, resistence and research. New Engl.J.Med. 308:875-878,1983.
60. Mahakur,A.C., Panda,S.N., Nanda,B.K., Bose,T.K., Sathpathy,S.R. and Misra,J. Malarial acute renal failure. J.Ass.Physic.India. 31:633-636,1983.
61. Chugh,K.S. and Sakhuja,V. Renal involbement in malaria. Internat.J.Artif.Org. 9:391-392,1986.

62. Visweswaran,K.S., Varghese,P.K. and Raveendran,M. Pattern and prognosis of acute renal failure in Weils' syndrome. Abstracts 3rd Asian Pacific Congress of Nephrology, Singapore,1986,pp.5.
63. Wainwright,J. and Schonland,M.M. Toxic hepatitis in black patients in Natal.S.Afr.A.Arf.Med.J. 51:571-573,1977.
64. Seedat,Y.K. Acute renal failure among Blacks and Indians in South Africa. S.Afr.Med.J.54:427-431,1978.
65. Chugh,K.S., Singhal,P.C., Sharma,B.K., Pal,Y., Mathew,M.T., Dhall,K. and Datta,B.N. Acute renal failure of of obsttetric origin. Obstet.Gynec. 48:642-646,1976.
66. Lahiri,D. and Konar,M. Abortion hazards. J.Ind.Med.Assoc. 66:288-294,1976.
67. Bulletin Indian Council Medical Research. 9:1-8,1979.
68. Chugh,K.S., Singhal,P.C., Kher,V.K., Gupta,V.K., Malik,G.H.,Narayan,G. and Datta,B.N. Spectrum of acute cortical necrosis in Indian patients. Am.J.Med.Sci. 286:10-20,1983.
69. Balsløv,J.T. and Jørgensen,H.E. A survey of 499 patients with acute anuric renal insufficiency. Am.J.Med. 34:753-764,1963.
70. Smith,K., Browne,J.C.M., Shackman,R. et al. Renal failure of obstetric origin. Br.Med.Bull. 24:49-58,1968.
71. Kleinknecht,D., Grunfeld,J., Gomez,P.C., Moreau,J. and Garcia-Torres,R. Diagnostic procedures and long term prognosis in bilateral renal cortical necrosis. Kid.Internat. 4:390-400,1973.
72. Lundberg,M. Dialysbehandling vid akut njurinsufficiens. Läkartidn.67:487-493,1970.
73. Eliahou,H.A., Boichis,H., Bott-Kanner,G., Barell,V., Bar-Noach,N. and Modan,B.An epidemiologic study of renal failure. Am.J.Epidemiol. 101:281,1975.23.
74. Karatso,A., Juhasz,I., Koves,S.and Balogh,F. Estimated frequency of acute and chronic renal insufficiencies in a transdanubian region of Hungary. Int.Urol.Nephrol. 7:321,1975.
75. Lachhein,L., Kielstein,R., Sauer,K., Reinschke.P., Muller,V.,Krumhaar,I., Falkenhagen,D.,Schmidt,R.and Klinkmann,H. Evaluation of 433 cases of acute renal failure. Proc.Eur.Dial.Transpl.Assoc.14:628,1977.
76. Branch,R.A., Clark,G.W., Cochrane,A.C.and Jones,H.J. Incidence of uremia and requirements for maintenance hæmodialysis. Br.Med.J. 1:249-254,1971.
77. Kumar,R., Hill,C.M. and McGeown,M.G. Acute renal failure in the elderly. Lancet.1:90-91,1073.
78. Fischer,R.P..,Griffen,W.O., Reiser,M. and Clard,D.S. Early dialysis in the treatment of acute renal failure. Surg.Gyn.& Obst.123:1019-1023,1966.
79. Kirkland,K., Edwards K.D.G. and Whyte,H.M. Oliguric renal failure: A report of 400 cases including classification, survival and response to dialysis. Austr.Ann.Med. 14:275-281,1965.
80. Kleinknecht,D., Jungers,P., Chanard,J., Barbanel,C. and Ganeval,D. Uremic and non-uremic complications in acute renal failure: Evaluation of early and frequent dialysis on prognosis. Kidney Int.1:190-196,1972.
81. Hall,J.W., Johnson,W.J., Maher,F.T. and Hunt,J.C. Immediate and long-term prognosis in acute renal failure. Ann.Intern.Med. 73:515-521,1970.
82. Alwall,N. Therapeutic and diagnostic problems in severe renal failure. In: Severe Renal Failure, Svenska Bokförlaget-Bonniers, Stockholm,1963.
83. Stott,R.B., Ogg,C.S., Cameron,J.S. and Bewick,M. Why the persistently high mortality in acute renal failure? Lancet 2:75-78,1972.

84. McMurray,S.D., Luft,F.C., Maxwell,D.R., Hamburger,R.J.,Futty,D., Szwed,J.J., Lavelle, K.J. and Kleit,S.A. Prevailing patterns and predictor variables in patients with acute tubular necrosis. Arch.Intern.Med. 138:950-955,1978.
85. Gillum,D.M., Dixon,B.S., Yanover,M.J., Kelleher,S.P., Shapiro,M.D., Benedetti,R.G., Dillinghan,M.A., Paller,M.S., Goldberg,J.P., Tomford,R.C., Gordon,J.A. and Conger,J.D. The role of intensive dialysis in acute renal failure. Clin.Neph. 25:249-255,1986.
86. Làmeire,N., Matthys,E., Vanholder,R., DeKeyser,K., Pauwels,W., Nachtergaele,H., Lambrecht,L. and Ringoir,S. Causes and prognosis of acute renal failure in elderly patients. Nephrol.Dial.Transplant. 2:316-322,1978.
87. Corwin,H.L., Teplick,R.S., Schreiber,M.J., Fang,L.S.T., Bonventre,J.V. and Coggins,C.H. Prediction of outcome in acute renal failure. Am.J.Nephrol. 7:8-12,1987.
88. Beaman,M., Turney,J.H., Rodger,R.S.C., McGonigle,R.S.J., Adu,D. and Michael,J. Changing pattern of acute renal failure. Quart.J.Med.,New Series 62,No.237:15-23,1987.
89. Lien,J. and Chan,V. Risk factors influencing survival in acute renal failure treated by hemodialysis. Arch.Intern.Med. 145:2067-2069,1985.
90. Rasmussen,H.H., Pitt,E.A., Ibels,L.S. and McNeil,D.R. Predictions of outcome in acute renal failure by discriminant analysis of clinical variables. Arch Intern.Med. 145:2015-2018,1985.
91. Kennedy, A.C., Burton,J.A., Luke,R.G., Briggs,J.D., Lindsay,R.M., Allison,M.E.M., Edward, N. and Dargie,H.J. Factors affecting the prognosis in acute renal failure.Quart.J.Med.,New Series 42, No.165:73-86,1973.

11

ACUTE RENAL FAILURE AND CONTINUOUS RENAL REPLACEMENT THERAPY

F. COSENTINO, E.P. PAGANINI

The Section of Dialysis and Extracorporeal Therapy, Cleveland Clinic Foundation, Cleveland, Ohio, USA

INTRODUCTION

Continuous renal replacement therapy has evolved into an important therapeutic modality for the management of acute renal failure. The mainstay has been continuous arteriovenous hemofiltration (CAVH) for the management of acute azotemia and slow continuous ultrafiltration (SCUF) for the management of fluid overload. A pumpless system is employed in which the patient's arterial pressure is utilized to perfuse the extracorporeal circuit. Additional variations have been developed to meet various clinical needs. These variations have improved the efficacy of the continuous treatment method and will be described in detail later.

The simplicity of the system and hemodynamic stability offered to the patient treated with CAVH are the major advantages over conventional hemodialysis in the intensive care setting. Continuous renal replacement therapy allows for the control of azotemia, correction of electrolyte and acid/base disorders, and the removal of fluid in overhydrated patients. All of these tasks are accomplished continuously avoiding the saw-toothed pattern created by the intermittent methods of azotemic control and thus creating a more physiological steady state of uremia similar to its chronic counterpart, the patient with stable chronic renal failure.

This review will serve to describe briefly the history of continuous renal replacement therapy, equipment and operational characteristics, variations on the theme, along with indications, complications, and patient selection criteria.

DEFINITIONS

Slow Continuous Ultrafiltration (SCUF): The removal of fluid, similar in composition to plasma water, by convective forces. Usually at rates of 100-300 ml/hr.

Continuous Arteriovenous Hemofiltration (CAVH): The removal of fluid and solutes via convective forces at typical rates of 500-700 ml/hr, and the simultaneous administration of a replacement solution.

Continuous Venovenous Hemofiltration (CVVH): Similar to CAVH with the exception that blood access is venous rather than arterial and venous, necessitating the use of a blood pump.

Continuous Arteriovenous Hemodialysis (CAVHD): A diffusion mode of therapy in which the ultrafiltrate side of the filter is perfused with dialysate. Solute removal occurs primarily by diffusion with a variable contribution from convective forces.

HISTORY

Perhaps the first modern report of continuous extracorporeal therapy for the support of renal failure was Scribner's presentation of continuous hemodialysis in 1960 (1). While the theory was quite plausable and valid, the equipment available at the time did not lend itself to this method. Shaldon described the use of both the femoral artery and vein for access routes by altering the Seldinger technique (2). In 1967 Henderson and colleagues reported on the technique of diafiltration in which a porous membrane was utilized to remove fluid while replacement fluid was administered simultaneously (3). This was accomplished on an intermittent basis in patients with chronic renal failure. Silverstein in 1974 described the use of a new permeable material (polysulfone) in an artificial filter design applied to patients with fluid overload (4). The authors were able to demonstrate safe removal of fluid at rates of 300-800 ml/hr in fluid overloaded chronic dialysis patients. Khanna and Nakamoto described the simultaneous ultrafiltration and diffusion as separate entities (5) while several others described the system of isolated ultrafiltration in chronic dialysis patients.

In 1977 Kramer reported on the use of arteriovenous hemofiltration in overhydrated patients resistant to diuretics (6). By placing catheters in the femoral artery and vein and using the patient's arterial pressure to perfuse the circuit, the need for an occlusive blood pump was obviated. The porous hemofilter allowed for the continuous removal of fluid while simultaneously a replacement solution similar in composition to plasma water was administered at a rate dictated by the patient's clinical status. Kramer's experience demonstrated that fluid withdrawal was better tolerated on a continuous basis compared to intermittent fluid removal with hemodialysis (7-9). Control of electrolyte balance was also demonstrated by several authors as the technique slowly began to be used predominantly in the intensive care unit setting. The hemodynamic advantage of slow continuous fluid removal (SCUF) over the usual intermittent forms of ultrafiltration was further demonstrated by Paganini and colleagues (10). While Lauer (11) described the CAVH experience in multiorgan failure patients, Bartlett stressed the ability to administer adequate fluids and total parenteral nutrition to patients with post surgical acute renal failure without the risk of overhydration (12).

CIRCUIT

The set up utilized for CAVH characterizes the simplicity of this technique. As originally described by Kramer (6), CAVH is a pumpless system which utilizes the patient's arterial venous pressure gradient to perfuse the extracorporeal circuit. Access to arterial and venous circulations is therefore required. Vascular access can therefore by obtained either percutaneously through cannulation of the femoral artery and vein or by way of a surgically placed Scribner shunt. A hemofilter is used since they usually contain membrane material with a high ultrafiltration coefficient. While there had been some use of the less porous material for hemodialysis, the ultrafiltration characteristics were not suitable for the fluid removal rates needed in these patients. The blood is brought to the hemofilter via short tubing. It must be emphasized that this tubing be as short as technically possible,

and also be positioned so as not to dissipate any pressure translation, avoiding unnecessary bending or change in internal diameters. Commercial lines are available that are 25-30 cm in length with an internal diameter of 3/16 in. The ultrafiltrate is collected in a container placed below the level of the filter so as to exert a negative hydrostatic force favoring filtration. Thus, spontaneous production of fluid filtered from the hemofilter, with a composition very similar to plasma water, is collected. Simultaneously, a replacement solution also similar in composition to plasma water is administered. The substitution fluid may be administered into the circuit either before the filter (predilution) or after the filter (postdilution). The basic setup is similar for other variations of continuous renal replacement therapy. Figures 1 - 3 depict the circuitry for SCUF, postdilution CAVH, and CAVHD respectively.

VASCULAR ACCESS

The adequacy of the vascular access is of utmost importance if the extracorporeal circuit is to be optimally perfused. Access via cannulation of the femoral artery and vein is the preferred choice since this will provide for the best transmission of the patient's arterial pressure to the hemofilter. A Scribner shunt can be used as an alternative. Since inferior blood flows are obtained with a Scribner shunt compared to femoral artery cannulation, a mean arterial pressure of at least 80mmHg is usually required(11)(13). Other disadvantages of using a Scribner shunt include the time required for shunt placement and the fact that it requires ligation of an artery. A third alternative for vascular access is an existing AV fistula. A standard 15 gauge hemodialysis needle can be inserted into the fistula and utilized as an arterial access, while the venous return must be into a separate vein or distal to an induced stenosis so as to maintain a large arterial-venous pressure gradient. This is not practiced to a great extent however because of fear of clotting the fistula.

There is a well established relationship between vascular access and blood flow (11)(14). The blood flow will directly

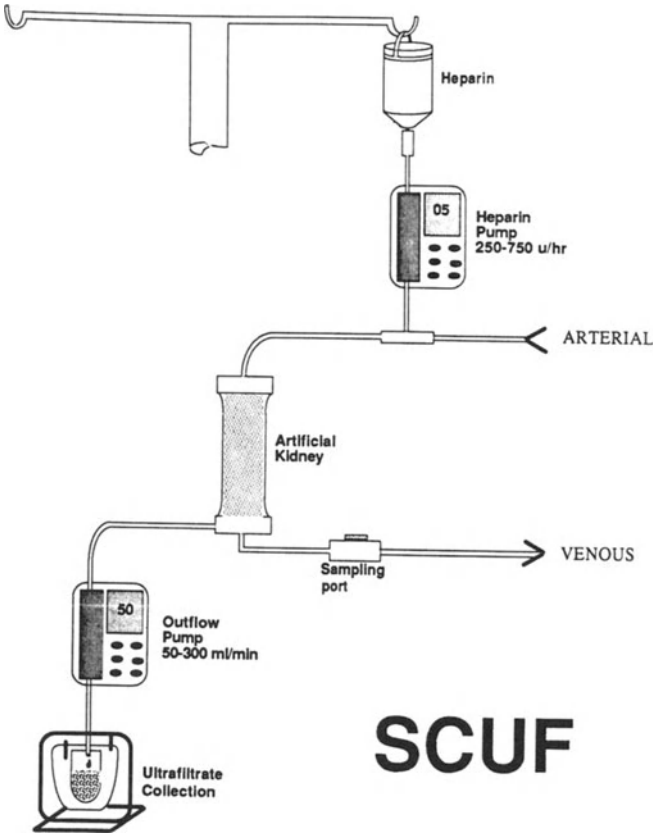


Fig. 1. Schematic of slow continuous ultrafiltration (SCUF).

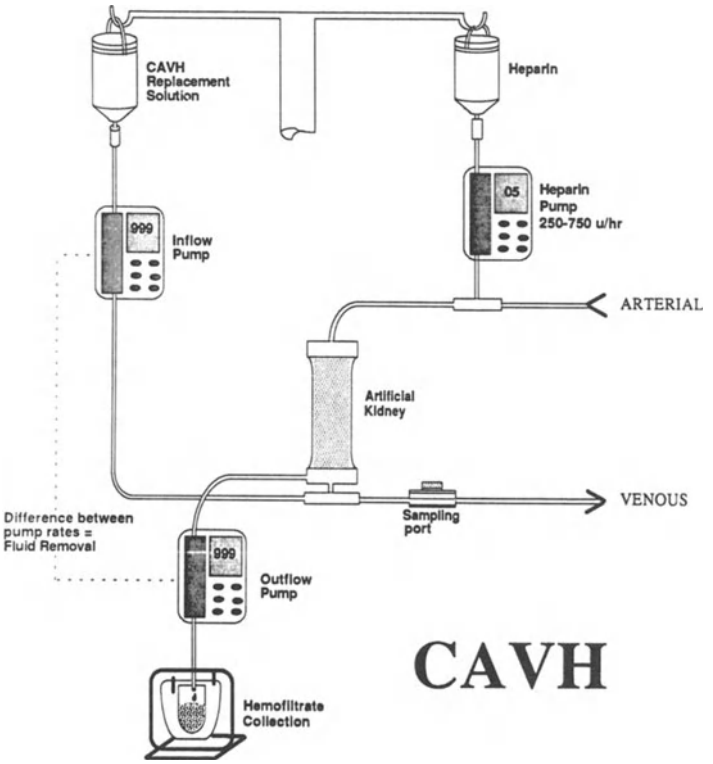


Fig. 2. Schematic of continuous arteriovenous hemofiltration (CAVH).

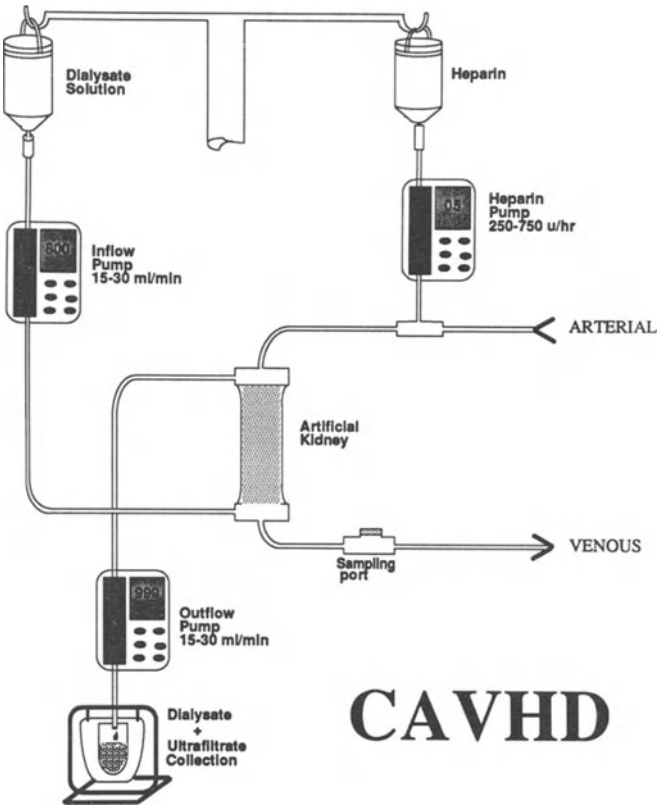


Fig. 3. Schematic of continuous arteriovenous hemodialysis (CAVHD).

influence the transmembrane pressure and ultrafiltration rate (15). Any increase in filtration will increase solute clearance. Under similar conditions and mean arterial pressure, the blood flow through a femoral arterial access will be greater than that through a Scribner shunt (11)(13). This will allow for better control of azotemia with femoral access (15).The lower blood flows obtained with Scribner shunts may be more compatible with SCUF where filtration fractions are lower compared to CAVH. Of particular interest, solute clearance in continuous arteriovenous hemodialysis (CAVHD) is not blood flow dependent, but rather is dependent on dialysate flow (16).

COMPLICATIONS OF VASCULAR ACCESS

Potential complications of femoral artery cannulation can be estimated from data on arteriographic interventions (15). Puncture site complications include bleeding and subintimal dissection (0.6-1.5%), guide wire perforation (0.44%), embolism (0.1%), arterial obstruction (0.14%), and subsequent limb amputation (0.01%). The only serious complication from femoral vein puncture is bleeding (primarily retroperitoneal) with an incidence of 0-0.3% (15). Complications due to long term cannulation include catheter related sepsis with an incidence ranging from 3% (17) to 6.2% (18). The incidence of long term complications from Scribner shunts is nearly identical to that of femoral cannulas (15).

Many of the complications listed can be avoided by careful examination of the patient, and the potential site for insertion of the femoral catheters. Any change in the distal pulse pressures or skin coloration should be noted and followed closely. Relative contraindications to femoral arterial puncture include severe atherosclerosis, risk of hemorrhage from coagulopathy, the desire for patient mobility, and the use of femoral vessels for other purposes such as intraaortic balloon pumps. The only absolute contraindications are known severe stenosis of the vessel and thus the loss of blood flow distally, and the presence of a vascular prosthetic graft or patch.

BLOOD FLOW

Under most clinical circumstances, a blood flow rate of 20-90 ml/min is obtained during CAVH (11). The rate of blood flow is dependent on the patient's mean arterial pressure, the access site, catheter dimensions, length and diameter of tubing, blood viscosity, patency of the filter, and venous resistance. The blood flow rate at the filter inlet (Q_{bi}) can be measured according to the following formula (19):

$$Q_{bi}=(Q_f \times Hct_{outlet})/(Hct_{outlet} - Hct_{inlet})$$

where Q_{bi}=blood flow at the filter inlet
Q_f=ultrafiltration rate
Hct_{outlet}= hematocrit from the venous (outlet) line
Hct_{inlet}= hematocrit from the arterial (inlet) line

The derivation of blood flow using the above formula may have limitations. A recent abstract suggests that blood flow can be more accurately assessed using an electromagnetic blood flow meter (20). Knowledge of the blood flow in the circuit is clinically useful in monitoring the circuit for early signs of filter clotting and adjusting the heparin infusion based on blood flow (11). Knowledge of flow will also define the limits of therapy, perhaps only allowing SCUF with its low fluid removal rates and thus lower filtration fraction with low access flows or CAVHD where flow is less important. High flows will allow prospective determination of the potential filtration rates and thus exchange rates when CAVH is attempted.

CATHETERS

Hemofiltration catheters can be percutaneously placed in the femoral artery and vein using the Seldinger technique (14). Surgical placement may be necessary when dealing with small children and infants (21,22), while double lumen venous catheters are usually used when applying techniques in continuous veno-venous therapy (pump assisted)(23). The arterial catheters must be able

to transmit the arterial pressure to the rest of the circuit while the venous catheter must allow free flow . Most commercially available catheters are flexible, minimally tapered, have a single opening at the end without side holes, and are non-thrombotic. It is of utmost importance to not use the standard hemodialysis venous catheters as arterial access since the presence of side holes may mislead the operator into accepting poor placement of the catheter, which may lead to significant arterial bleeding.

The internal diameter of the standard arterial catheter is usually 0.317 cm with a total length of fifteen cm. (9). An arterial catheter of smaller internal diameter will result in a smaller hydraulic pressure transmission upstream and cause a decrease in filtration as determined by in-vitro studies (24). However since the extracorporeal circuit contains several areas of resistance, the greatest of which is the hemofilter (25,26), a decrease in the internal diameter of the catheter may not add substantially to the overall resistance of the system. The hydraulic pressure has been recorded to decrease from 90 mmHg at the arterial access site to 40 mmHg at the filter inlet (27). For this reason it has more recently been proposed that catheters with an internal diameter as small as 0.20 cm (thirteen gauge) or larger would be adequate (28).

HEMOFILTERS

The artificial hemofilters utilized in continuous renal replacement therapy have several requirements: the membranes must be able to yield filtration rates of greater than 30 ml/hr/mmHg/m^2, resistance to blood flow must be as low as possible, and blood volume must be small. Although hollow fiber filters are the mainstay, parallel plate filters offer the advantage of lower resistance and less heparin requirement (29). While hollow fiber hemofilters have been used primarily for filtration techniques (CAVH, SCUF), the addition of a second "dialysate port" have made them adaptable to CAVHD. The surface area utilized during diffusion with the technique of CAVHD, however, does not require a large dialyzer since as noted earlier, the diffusion

characteristics are usually dialysate flow dependant in the range of operating parameters in play during this therapy. Resistance to blood flow across these filters can be minimized by using filters of shorter length (13-23 cm) and increasing the diameter of the individual fibers (200-280 microns) (30). The diameter of the hollow fibers must be large enough to minimize resistance, yet they must be small enough to allow a small priming volume. Surface area may play a role in the filtration techniques, and thus this must not be underestimated in the filter design. Table 1 lists some of the commercially available filters currently in use.

As noted in the table, the dialyzers are constructed with membranes made of synthetic plastics. These membranes allow the free passage of molecular weight solutes of 10,000 Daltons or less. The permeability to larger solutes progressively decreases as the solute molecular weight increases up to 50,000 Daltons, above which passage is restricted. The membranes are asymmetric and consist of two regions: the outer skin region which confers the transport properties of the membrane, and the much thicker substrate region which serves as the supporting structure (31). Polyacrylonitrile (PAN) membranes possess both the capacity for high water flux and a high diffusive permeability. Membranes of this type can provide solute removal by convection (CAVH) as well as diffusion (CAVHD) (32). Both polyamide and polysulfone filters possess high ultrafiltration capabilities so they are best utilized for hemofiltration (convection) rather than diffusion (32). Polymethyl methacrylate has a lower ultrafiltration potential so it is better suited for diffusive solute clearance (33).

Another important property of the hemofilters is their lack of complement activation and consequent leukopenia (34). Sensitive markers for complement activity do demonstrate a mild activation of complement by polysulfone, but this does not appear to be clinically significant (35). The greater degree of biocompatibility of these membranes compared to conventional cuprophane hemodialysis membranes has, however, been postulated by some to partially explain the hemodynamic stability of continuous therapy (9,10).

COMMERCIALLY AVAILABLE DEVICES FOR CAVH AND SCUF

DESIGNATION	MANUFACTURER	MEMBRANE MATERIAL	GEOMETRY				PERFORMANCE**		
			AREA M	# OF FIBERS	LENGTH cm	RADIUS microns	FILTRATION RATE cm/min	POISEUILLE RATIO mmHg-min/cm	PRIMING VOLUME cm
DIAFILTER-20	AMICON CORPORATION LEXINGTON, MA USA	POLYSULFONE	0.2	2500	13	100	11	0.83	10
DIAFILTER-30			0.6	4800	20	100	17	0.66	30
ULTRAFILTER CS	ASAHI MEDICAL CO. LTD TOKYO, JAPAN	POLYACRYLONITRILE	0.5	4300	19	100	15	0.77	26
AV-400	FRESENIUS AG OBERUSEL, FRG	POLYSULFONE	0.7	4500	23	110	19	0.56	45
AV-600			1.4	9000	23	110	21	0.28	75
FH-55	GAMBRO AB LUND, SWEEDEN	POLYAMIDE	0.6	6200	14	100	14	0.36	27
BIOSPAL 1200S	HOSPAL LTD BASLE, SWITZERLAND	POLYACRYLONITRILE	0.5	*	26	125*	15	0.13	63
RENAFLO 0.25	RENAL SYSTEMS MINNEAPOLIS, MN USA	POLYSULFONE	0.3	3000	14	140	> 10	0.19	25
RENAFLO 0.5			0.5	3000	22	140	> 20	0.30	50

* BIOSPAL 1200S employs a parallel plate configuration with 15 compartments each 6.5 cm wide, 26 cm long, and 250 microns apart.

** Filtration rates from manufacturer's literature. Poiseuille ratio is calculated as pressure drop per unit blood flow rate at a device average blood viscosity of 5 cps. Priming volume is from manufacturer's literature.

Table 1. Commercially available hemofilters (Reprinted with permission from ref. 31).

These membranes will also adsorb proteins. The resulting protein gel layer may adversely affect ultrafiltration and solute clearance over the time of therapy (24), and may also impact adversely on the life span of the filter. While individual filter life may vary from hours to days, an average lifespan of from 2.79+1.21 to 4.69+2.4 days has been reported(18). Some authors, however, recommend that the filter be changed every two days even though it may still be functioning well in order to avoid potential loss time while awaiting filter change, and to reduce the potential of infection.

SUBSTITUTION FLUID

The substitution fluid utilized for CAVH has a similar electrolyte content to that of plasma, while the buffer used may be either acetate, lactate, or bicarbonate. Table 2 summarizes various replacement solutions used in different programs. Lactated Ringer's solution has also been used as replacement fluid, however the small amount of potassium which it contains may be undesirable in patients with hyperkalemia. Variations in replacement composition may be made in order to individualize therapeutic endpoints. For example, normal saline can be substituted for more standard fluid compositions in patients with metabolic alkalosis in order to allow for the removal of bicarbonate, while higher levels of bicarbonate may be utilized in patients exibiting a severe degree of metabolic acidosis. There have been no clinical problems with lactate or acetate metabolism reported (27), however patients with lactic acidosis or hepatic failure may benefit from a bicarbonate base replacement solution.

		Acetate	Bicarbonate	Lactate
NA	MEq/L	140	138-145	140
K	MEq/L	0-2	0-2	1
Mq	MEq/L	1.5	0**	0.75
CA	MEq/L	3.5	0**	1.62
CL	MEq/L	110-120	112-125	100.75
Dext.	MEq/L	0-200	0-100	200
Base	MEq/L	35-40	26-38	45

** Added via another access

Table 2. Hemofiltration replacement solutions.

If bicarbonate is used as the base buffer, then magnesium and calcium must be removed from the replacement solution in order to avoid a calcium or magnesium bicarbonate precipitate. First described by Bartlett and later reported by Golper, this problem may be overcome by simultaneously administering the replacement solution from separate fluid containers attached to a multipronged manifold (36). In this way the magnesium and calcium containing solution remains separate from the bicarbonate until just prior to infusion. Another more practical solution has been their addition to the hyperalimentation fluid wnile deleting its base content.

The hemofiltration replacement solution may be infused either into the arterial line before the filter (predilution) or into the venous line after the filter (postdilution). These same variations were described in the intermittent hemofiltration literature, with Henderson's original report on hemodiafiltration being predilution. Kramer's first description of CAVH, however, utilized the post-dilution mode (8), since the main advantages of postdilution therapy are simplicity and lower replacement fluid requirements.

The predilution replacement described by Kaplan (37) offers several advantages. There is an increase in net urea clearance compared to postdilution CAVH (24)(38). The addition of fluid

before the filter causes dilution of plasma urea. Intraerythrocytic urea diffuses down its concentration gradient into the plasma making more urea available for filtration. However it is not clear if there is enhanced clearance of other solutes since they may not distribute across cell membranes as easily as urea (24). The dilution of blood before the filter will decrease the concentration of formed elements in the blood. The resulting decrease in blood viscosity may provide for greater filtration fractions and reduced heparin requirements as well as prolonged filter life (38). The disadvantages of predilution therapy include a higher requirement for replacement solution since some of it is immediately filtered, increased complexity of the circuit if suction is used (39), and the inability to use the ultrafiltrate to monitor plasma chemistries (9).

Electrolyte disturbances may occur if precautions are not taken. Calcium and magnesium deficits may develop if adequate replacement is not supplied. This is especially true when bicarbonate base replacement fluid is used since calcium and magnesium need to be administered in separate infusions. Hypophosphatemia is frequently found in patients treated with continuous therapies for periods of greater than four days, and will require the addition of phosphorus. Thus attention must be paid to replacement of these elements when therapy is prolonged. Lastly, hyponatremia can also occur if inadequate replacement of sodium is given. Hypotonic saline solutions may result in a true sodium deficit as sodium concentration in the ultrafiltrate is about equal to its plasma concentration.

ANTICOAGULATION

As with other types of extracorporeal systems, continuous renal replacement therapy generally requires some type of anticoagulation, usually heparin. The goal of anticoagulation is to prevent clotting of the circuit and thus maintain efficiency while minimizing systemic coagulation effects. The filter is prepared by flushing it with two liters of heparinized saline (5000 IU/liter). At the onset of therapy, a 2000 IU loading dose of heparin is

administered into the arterial sleeve of the circuit and a heparin infusion into the arterial line is initiated. The infusion is usually set at a rate of 5-10 IU/kg/hr (9). This will generally result in a PTT of about 90 seconds in the circuit and 45 seconds in the systemic circulation. The heparin infusion can also be adjusted according to the blood flow obtained in the circuit by the formula: (27)

$$\text{Heparin dose(IU/hr)} = (0.5 \text{ or } 1.0 \text{ IU}) \times Q_{bi}\text{(ml/min)} \times 60$$

$$\text{Where } Q_{bi} = \text{Blood flow at the filter inlet}$$

While blood flow and body weight are important in regulating the heparin dose, hemoconcentration from high filtration fractions will raise heparin requirements, and low platelet counts (below 100,000) will decrease heparin needs (38). It is difficult to assess the risk of bleeding from heparin in patients receiving continuous therapy since many of these critically ill patients are predisposed to coagulopathies for various reasons (25). In a series reported by Kaplan, six of fifteen patients experienced bleeding complications (38). Paganini reported a rate of eighteen percent (40). Patients who are predisposed to bleeding complications may be best managed without the added risk of heparin since it is possible to conduct continuous therapy without heparin (41,42). The filter needs to be observed frequently for signs of clotting, and it must be noted that an increased incidence of clotting will occur. The physician must be willing to change the filter before complete occlusion has occurred. Short lines and good access are of utmost importance in heparin-free therapy. When CAVHD is conducted without heparin it may be necessary to change the filters two or three times in any 24 hour period (43). The dialysate flow rate should be maintained at thirty ml/min to compensate for any decreased clearance secondary to filter clotting.

There exist potential alternatives to the use of heparin. Low molecular weight heparin has a greater anticoagulant effect but fewer bleeding complications because of an enhanced affinity for

antithrombin III (44). Regional heparinization in which protamine is infused into the venous line in an attempt to "neutralize" the heparin has also been described (45), but in practice, is quite cumbersome. Other methodologies which have been utilized in various trials have included the use of citrate to complex calcium (46), the addition of prostacycline analogues (47), and the development of membranes that bind heparin and therefore could provide a filter antithrombotic effect without systemic anticoagulation (48).

FACTORS AFFECTING FLUID REMOVAL

The formation of ultrafiltrate is dependent on a variety of factors (Figure 4). The net pressure gradient across the membrane (TMP) favoring ultrafiltration is described by the following equation (27):

$$TMP = (P_i + P_o)/2 + P_f - \pi$$

Where P_i = hydraulic pressure at the filter inlet
P_o = hydraulic pressure at the filter outlet
P_f = hydrostatic pressure on the ultrafiltrate side of the membrane
π = oncotic pressure

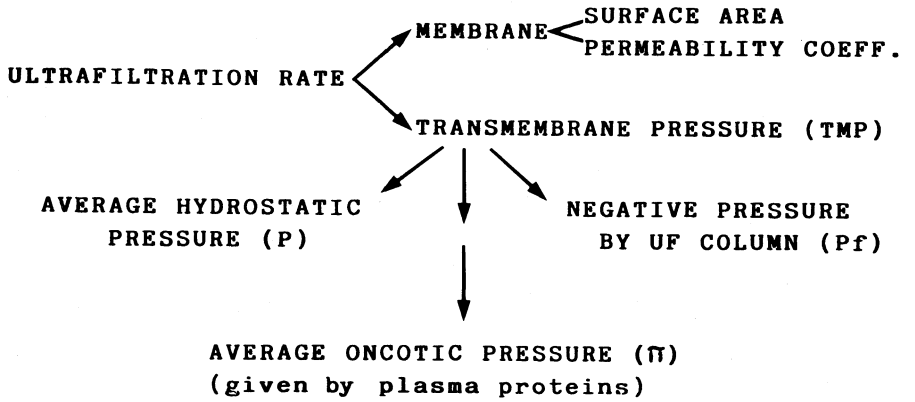


Fig. 4. Determinants of ultrafiltration. (Reprinted with permission from ref. 21).

The hydraulic pressure is the positive pressure on the blood side of the membrane favoring filtration. It is directly influenced by the site of vascular access, catheter dimensions, length and internal diameter of blood lines, filter resistance, and venous back pressure. All of these factors influence the pressure drop across the circuit. For example, at the arterial site the hydraulic pressure may be 90 mmHg. This can decrease to 40 mmHg at the filter inlet, and further decrease to 10 mmHg at the venous site (27). The blood flow at the filter inlet (Q_{bi}) can also affect the hydraulic pressure in the circuit. Lauer and colleagues have reported that ultrafiltration is only affected by blood flows between 90-250 ml/min (11), however other reports have demonstrated the influence of blood flow on ultrafiltration at a Q_{bi} less than 90 ml/min (15).

The hydrostatic pressure (P_f) is a negative pressure on the ultrafiltrate side of the membrane generated by the siphon effect of the weight of the fluid column in the ultrafiltrate line. The distance of the ultrafiltrate container below the filter will determine the P_f. This can be calculated by the equation:

$$P_f = Hgt \times 0.74 (mmHg/cm\ H_2O)$$

where Hgt = distance below filter(cm)

The hydrostatic pressure may be a major determinant of the TMP in situations in which the hydraulic pressure is low. It may be increased or decreased by lowering or raising the ultrafiltrate container respectively, unless an infusion pump is used to set the filtration rate. In this latter case, a fixed pressure will be applied to the membrane. If a syringe-type mechanism is used by the infusion pump, a significant transient negative pressure may develop at the membrane which may exceed the tolerance of the filter and lead to membrane rupture. For this reason, it is recommended to use only the peristaltic type mechanisms when applying infusion pump control to the ultrafiltrate collection.

The oncotic pressure is the major force impeding filtration across the membrane. It is generated by the plasma proteins and may be calculated by the equation: (36)

$$\text{Oncotic pressure(mmHg)} = (2.1xC) + (0.16xC^2) + (0.009x\ C^3)$$

Where C = total protein concentration (g/dl)

For a given hydrostatic pressure, ultrafiltration will decrease as the oncotic pressure rises. As blood passes through the filter and plasma water is removed the oncotic pressure will increase because of an increase in plasma protein concentration. At some point along the length of the filter the oncotic pressure will equal the hydraulic and hydrostatic pressures. This is the point of filtration pressure equilibrium where net ultrafiltration will cease. Filtration pressure equilibrium can be avoided by using pump assisted therapy to attain higher blood flow rates with a resulting increase in hydraulic pressure (see below). The Starling forces can also be altered in other ways: predilution CAVH will decrease the oncotic pressure entering the filter, so net ultrafiltration will increase (31), and the addition of suction on the ultrafiltrate side of the membrane will raise the hydrostatic pressure also increasing filtration (37).

The filtration fraction is the percentage of plasma water removed from the incoming blood. It is defined by the equation:

$$FF = 1-(TP_{inlet}/TP_{outlet})$$

Where TP_{inlet} = total protein concentration at filter inlet
TP_{outlet} = total protein concentration at filter outlet

Maximum filter efficiency is determined by a filtration fraction of 35-40% during postdilution CAVH (8). Beyond this value, there is a drammatic increase in the incidence of filter clotting. Optimum filtration fraction would be 20-25% for any of the filtration techniques and 15-20% for the diffusive methods of therapy.

SOLUTE CLEARANCE

The relationship of ultrafiltrate to plasma solute concentration can be expressed as the sieving coefficient (SC) for any given solute.

$$SC = [UF]/([Art]+[Ven])/2$$

Where [UF] = concentration in ultrafiltrate
[Art] = concentration in arterial line
[Ven] = concentration in venous line

	ART.	VEN.	U.F.	Sieving+ Coeff.
*NA	134.34	134.71	134.43	0.999
*K	4.82	4.84	4.76	0.986
*CL	95.53	92.50	103.47	1.101
$*CO_2$	21.34	20.68	23.39	1.113
**BUN	103.19	102.41	107.39	1.044
**S. Cr.	6.23	6.22	6.39	1.027
$**CA^{++}$	10.09	10.32	6.16	0.603

* Expressed as MEq/L
** Expressed as Mg/dL

Table 3. Electrolyte data. (Reprinted with permission from ref.63)

Table 3 lists the sieving coefficients for various solutes. Sodium and potassium have sieving coefficients nearly equal to unity (49). Chloride and bicarbonate are present in the ultrafiltrate at slightly higher concentrations than in the plasma (38)(49). This is because of a Gibbs-Donnan like effect created by the negatively charged plasma proteins which are not allowed to cross the membrane, and the need of the system to maintain electroneutrality.

The markers for azotemia, urea and creatinine pass easily into the ultrafiltrate as demonstrated by their sieving coefficients.

Their hemofiltration clearances can be estimated from the ultrafiltration rate (Q_f) as:

$$Cl = SC \times Q_f$$

Where Cl = clearance ml/min
SC = sieving coefficient
Q_f = ultrafiltration rate ml/min

The above formula is an approximation applicable only to postdilution CAVH and assumes total replacement of the filtered solution. It is the exchange rate that dictates the clearance. With an exchange rate of 700 ml/hr, for example, the urea clearance will be 11.6 ml/min assuming a sieving coefficient of one. For a more exact method of measuring clearance the reader is referred to reference 31. A method for evaluating solute clearance during predilution CAVH has also been reported elsewhere (50), while a discussion of solute clearance during CAVHD is presented in the following section.

One of the major advantages of CAVH is the ability to dissociate electrolyte balance from fluid balance. It is possible to remove fluid with or without concomitant sodium losses by simply adjusting the amount of sodium in the replacement solution. Conversely, by giving the patient hypotonic saline equal in volume to the ultrafiltrate, one can in essence remove sodium without changing total body water. The same principle can be applied to acid/base disturbances. In metabolic alkalosis for example, a net loss of base equivalent can be induced by providing a replacement solution that has no base buffer such as normal saline.

ENHANCING SOLUTE CLEARANCE

Solute removal during CAVH occurs by convection and is therefore determined by the ultrafiltration rate (Q_f) (51). The maximum Qf usually attained is 700 ml/hr (16.8 liters/day) yielding a clearance of 11.6 ml/min for urea and creatinine (24). In certain clinical situations the patient's catabolic rate may exceed the clearance capability of CAVH such that a satisfactory steady state level of azotemia cannot be obtained (52)(53). For this reason, methods of enhancing solute clearance with continuous renal replacement therapy have been developed.

As noted by Olbricht (53), the first step in controlling azotemia is the control of urea production. This involves the proper management of underlying disease processes, especially sepsis, and adequate nutrition to meet the patients requirements and maintain positive nitrogen balance. Kaplan has described two methods of increasing urea clearance during CAVH. Suction assisted CAVH will augment urea clearance by increasing the Qf by as much as a factor of two (39). The patient's blood pressure must be intensely monitored since fluid removal will occur in spite of hypotension (54). The increased filtration obtained with suction assisted postdilution CAVH may render therapy less optimal because of increased clotting. This can be overcome by using the predilution mode with suction assist (37). As noted above, predilution CAVH will augment urea clearance with or without suction assist (24)(37)(54)(55). The reasons for this have already been discussed.

In 1960 Scribner described the technique of continuous hemodialysis (1). The technique was then modified by Geronemus and Schneider (56) utilizing the basic circuitry of CAVH for continuous arteriovenous hemodialysis (CAVHD). The major difference is the use of diffusion dialysis in which the non-blood side of the membrane is perfused with dialysate at a rate of 15-30 ml/min in a countercurrent fashion. Usually peritoneal dialysate (1.5%) with potassium (0-4 meq/liter) is used. Solutes are removed by diffusive forces with a variable contribution from convective clearances (16)(57)(58). The system is unique in that the dialysate flow is

much less than the blood flow. Solutes in the plasma water will completely equilibrate with the dialysate. So the diffusive clearance can be estimated from the dialysate flow and is described by the relationship: (16).

$$Cl_d = Q_{di}[(C_{do}-C_{di})/C_{bi}]$$

Where Cl_d = diffusion clearance
Q_{di} = dialysate inflow rate
C_{do} = solute concentration at dialysate outlet
C_{di} = solute concentration at dialysate inlet
C_{bi} = blood solute concentration at filter inlet

For metabolic wastes, C_{di} is zero and C_{do} is equal to C_{bi}, so diffusion clearance (Cl_d) is equal to the dialysate flow rate (Q_{di}) (16). Therefore diffusive solute clearance is dialysate flow dependent. This relationship is linear until it reaches a plateau at a dialysate flow rate of 30 ml/min. At this point solute clearance will no longer increase as Q_{di} increases (16). Under most circumstances, a dialysate flow rate of one liter/hr (16.65 ml/min) is adequate to satisfactorily control azotemia (43). This will yield a urea clearance of 16.53+1.48 ml/min (16),a significant increase over that attainable with postdilution CAVH (11.6 ml/min). The complete equilibration of plasma solutes with the dialysate ($C_{do} = C_{bi}$) will persist despite the addition of convective forces (ultrafiltration).

Ultrafiltration during CAVHD is under the influence of the same hydrostatic, hydraulic, and oncotic forces as described for CAVH. Ultrafiltration and convective clearance can be adjusted by altering the distance of the ultrafiltrate container below the filter or by using an IV infusion pump to set the rate of ultrafiltration. The convective clearance for metabolic wastes with a sieving coefficient of one is equivalent to the ultrafiltration rate:

$$Cl_c = (Q_f)(C_{do})/C_{bi}$$

Where Cl_c = convective clearance
Q_f = ultrafiltration rate
C_{do} = dialysate solute concentration out
C_{bi} = blood solute solute concentration in

For a sieving coefficient of unity, C_{do} will equal C_{bi}, and therefore convective clearance will be equal to the filtration rate. Total urea clearance during CAVHD is described by the relationship: (16).

$$Cl = Q_{do} = Q_{di}+Q_f$$

Where Cl = total clearance (diffusion and convection)
Q_{do} = dialysate flow rate out
Q_{di} = dialysate flow rate in
Q_f = ultrafiltration rate

It is possible to obtain a total urea clearance of 25.3+4.4 ml/min using a Q_{di} of 16 ml/min and Q_f of 9 ml/min (16). This is a markedly substantial improvement over urea clearances attainable with CAVH.

Another method of enhancing solute clearance is the use of pump assisted continuous therapy. This may be applied to the usual CAVH circuit (59), but is more often applied to continuous venovenous hemofiltration (CVVH) in which there is no access to the arterial circulation (60)(23)(61). The addition of a blood pump with the attendant increase in blood flow rates will alter the starling forces acting on the filter so as to increase convective clearance. Although CVVH can be used to support hemodynamically unstable patients with acute renal failure, its precise role is not well defined. The disadvantage of any pump assisted system is the added complexity and need for additional personnel and alarms.

PATIENT SELECTION

From the original description of the use of continuous techniques in patients, those who failed to respond to the usual therapeutic maneuvers were subjected to treatment. Kramer's original description of continuous filtration was applied to diuretic resistant patients (6), while Paganini applied continuous ultrafiltration to dialysis resistant patients with acute renal failure (10). Later studies applied all of the various techniques to those patients who were considered the most unstable and thus the most in need of the gentle fluid, electrolyte and azotemic management afforded by these continuous methods in a consistently hemodynamically stable manner.

The results of patient outcome were encouraging and mortality in this sub-set of patients was noted to parallel that of the more stable group. Not all investigators were convinced of this superiority. When patients were allowed support with carefully done hemodialysis and this was compared to the initial experience with CAVH, Kohen (62) found that if efficacy of treatment were equalized, patients on CAVH seemed to exhibit more complications, particularly bleeding. Thus the units who are particularly adept at using standard hemodialysis have been reluctant to enter into continuous therapy for acute renal failure except in patients who fail hemodialysis attempts. Even among these patients, however, outcome was improved dramatically from virtually 100% mortality for hemodialysis resistant patients to 68% for those patients subsequently supported on CAVH(63).

Preliminary results showing positive patient outcome and increasing caloric intake following parallel lines (12) have made the delivery of optimal nutritional support to the patient a priority. Thus the limitation of fluid intake and its removal, even with daily hemodialysis sessions, as well as the increased catabolism of the intermittent hemodialysis session could both be avoided with the use of continuous methods of support.

Thus the patient characteristics which described a potential candidate for continuous therapy support was expanded to include patients who had oliguria and were receiving hyperalimentation, patients who exhibited fluid disturbances but still had some residual renal function and patients who had non-renal problems who might be helped with the addition of CAVH, such as congestive heart failure (64) or adult respiratory distress syndrome (65-66). Table 4 depicts the various conditions in which continuous therapy may be utilized.

PATIENT DIAGNOSIS	HEMODYNAMIC STATUS	STATE OF CATABOLISM	Rx Type INTER	CONTIN	BOTH
ARF	Stable	Low	X	or X	
		High	X	or	X
	Unstable	Low		X	
		High		X or	X
CHF	Stable	Low/High	X	or X	
	Unstable	Low/High		X	
ARDS	Stable	Low/High	X	or X	
	Unstable	Low/High		X	

Table 4. Various conditions in which continuous therapy has been used. INTER = Intermittent; CONTIN = Continuous; ARF = Acute Renal Failure; CHF = Congestive Heart Failure; ARDS = Adult Respiratory Distress Syndrome.

CONCLUSION

With the advent of the various forms of continuous renal therapies for the patients with acute renal failure, there has been a slight decrease in the mortality and morbidity of patients with severe hemodynamic instability. The application of these methods to the less compromised patient may also be rewarded with an improvement in survival, perhaps not as a direct effect of the therapy itself, but rather as a consequence of what the therapy allows. Unlike its dramatic ability to control azotemia in the unstable patient who was undialyzable, the less complicated patient will benefit more from being able to receive the appropriate amounts of nutrition without having to be subjected to a fluid restriction.

While only theoretical, the avoidance of the significant fluid shifts induced by intermittent modalities, as well as the stable state of azotemia, and optimal electrolyte balance afforded by the continuous methods, may well lead to a more physiological state in which patient progress will be enhanced.

With the development of bio-artificial units for such disease states as diabetes, certainly the use of biotechnology may bring to pass an artificial tubule. Coupled with the already functioning artificial glomerulus of continuous therapy, the first truly artificial kidney may be constructed. This pass toward that end has already started and only time will bring it to its natural conclusion .

REFERENCES

1. Scribner, B.H., Caner, J.E.Z., Buri. The techniques of continuous hemodialysis. Am. Soc. Artif. Intern. Organs 6:88, 1960.
2. Shaldon, S., Chiandussi, L. and Higgs, B. Hemodialysis by percutaneous catheterization of the femoral artery and vein with regional heparinization. Lancet 2:857-859, 1961.
3. Henderson, L.W., Besarab, A., Michaels, A. and Bluemle, L.W. Blood purification by ultrafiltration and fluid replacement (diafiltration). Trans. Am. Soc. Artif. Intern. Organs 13:216-226, 1967.
4. Silverstein, M.E., Ford, C.A., Lysaght, M.J. and Henderson, L.W. Treatment of severe fluid overload by ultrafiltration. New Eng. J. Med. 291:747-751, 1974.
5. Khanna, R., Popowniak, K.L., Magnusson, M. and Nakamoto, S. Control of ascites in patients with chronic hemodialysis by modified ultrafiltration using a Dow Hollow Fiber Capillary Kidney. (abstract), Trans Am Soc Artif Intern Organs 2:31, 1973.
6. Kramer, P., Wigger, W., Rieger, J., Matthaei, D. and Scheler, F. Arteriovenous haemofiltration: A new and simple method for treatment of over-hydrated patients resistant to duiretics. Klin Wschr. 55:1121-1122, 1977.
7. Kramer, P., Kaufhold, G., Grone, H.J., Wigger, W., Rieger, J., Matthaei, D., Stokke, T., Burchardi, H. and Scheler, F. Management of anuric intensive care patients with arteriovenous hemofiltration. Intern. J. Artif. Organs 3:225-230, 1980.
8. Kramer, P., Schrader, J., Bohnsack, W., Grieber, G., Grone, H.J. and Scheler, F. Continuous arteriovenous hemofiltration. A new kidney replacement therapy. Proc. EDTA 18:743-749, 1981.
9. Kramer, P., Bohler, J., Kehr, A., Grone, H.J., Schrader, J., Matthaei, D. and Scheler, F. Intensive care potential of continuous arteriovenous hemofiltration. Trans. Am. Soc. Artif. Intern. Organs 28:28-32, 1982.
10. Paganini, E.P. and Nakamoto, S. Continuous slow ultrafiltration in oliguric acute renal failure. Trans. Am. Soc. Artif. Intern. Organs 26:201-204, 1980.
11. Lauer, A., Saccaggi, A., Ronco, C., Belledonne, M., Glabman, S. and Bosch, J. Continuous arteriovenous hemofiltration in the critically ill patient. Annals Intern. Med. 99:455-460, 1983.
12. Bartlett, R.H., Mault, J.R., Dechert, R.E., Palmer, J., Swartz, R.D. and Port, F.K. Continuous arteriovenous hemofiltration: Improved survival in surgical acute renal failure? Surgery, 100:400-408, 1986.
13. Olbricht, C., Schurek, H.J., Tytul, S., (Abstract), Effeciency of CAVH in acute renal failure: Influence of blood pressure, blood flow, vascular access and filter type. Blood Purif. 2:14, 1984.

14. Olbricht, C.J., Schurek, H.J., Tytul, S., Muller, C. and Stolte, H. Comparison between Scribner shunt and femoral catheters as vascular access for continuous arteriovenous hemofiltration. In: Arteriovenous Hemofiltration (Ed. P. Kramer), Springer-Verlag Berlin Heidelberg New York Tokyo, 1985, pp. 57.
15. Olbricht, C.J. Vascular access for CAVH. In: Proceedings of the Third International Symposium on Acute Continuous Renal Replacement Therapy (Eds. E. P. Paganini and R. Geronemus),Ft. Lauderdale Fla., 1987, pp. 23-26.
16. Sigler, M.H., Techan, B.P., Van Valkenburgh, D. Solute transport in continuous hemodialysis: A new treatment for acute renal failure. Kidney Intern. 32:562-571, 1987.
17. Band, J.D. and Maki, D.G. Infections caused by arterial catheters used for hemodynamic monitoring. Am. J. Med. 67:735-1979.
18. E. P. Paganini. Slow continuous hemofiltration and slow continuous ultrafiltration. Trans. Am. Soc. Artif. Intern. Organs 34:63-66, 1988.
19. Bosch, J., Geronemus, R., Glabman, S., Lysaght, M., Kah, T. and Von Albertini, B. High flux hemofiltration. Artif. Organs 2:339-342, 1978.
20. Cosentino, F., Swann, S., Kennedy, D., Magdinec, M. and Paganini, E. Comparison of "Hemaflow" blood flow device (HMF) and standard hematocrit methods (HCT) for determination of continuous therapy blood flow (Qb). (Abstract), Blood Purification (in press).
21. Ronco, C. Continuous arteriovenous hemofiltration in infants. In: Acute Continuous Renal Replacement Therapy (Ed. E. P. Paganini), Martinus Nijhoff, Boston, 1986, pp. 201-245.
22. Ronco, C., Brendolan, A., Bragatini, L., Chiaramonte, S., Feriani, M., Fabris, A., Dell'Aquila, R. and LaGreca, G. Treatment of acute renal failure in the newborn by continuous arteriovenous hemofiltratration. Kidney Intern. 29:908-915, 1986.
23. Favre, H., Lovy, M., Klohn, M. and Suter, P. Continuous veno-venous hemofiltration. In: Proceedings of the Third International Symposium on Acute Continuous Renal Replacement Therapy (Eds. E.P. Paganini and R. Geronemus), Ft. Lauderdale, Fla., 1987, pp. 87-93.
24. Pallone, T.L. and Petersen, J. Continuous arteriovenous hemofiltration: An in vitro simulation and mathematical model. Kidney Intern. 33:685-698, 1988.
25. Ronco, C., Brendolan, A., Gragantini, L., Chiaramonte, S., Feriani, M., Fabris, A. and LeGreca, G. Continuous arteriovenous hemofiltration. Contrib. Nephrol. 48:70-88, 1985.

26. Pallone, T.L. and Petersen, J. Continuous arteriovenous hemofiltration an in-vivo simulation. Trans. Am. Soc. Artif. Intern. Organs 33:304-308, 1987.
27. Bosch, J. Continuous arteriovenous hemofiltration (CAVH): Operational characteristics and clinical use. In: Proceedings of the Third International Symposium on Acute Continuous Renal Replacement Therapy (Eds. E. P. Paganini and R. Geronemus), Ft. Lauderdale, Fla., 1987, pp. 3-22.
28. Ronco, C., Brendolan, A., Bragantini, L., Fabris, A., Feriani, M., Chiaramonte, S., Fecondini, L. and LaGreca, G. Studies on blood flow dynamic and ultrafiltration kinetics during continuous arteriovenous hemofiltration. Blood Purif. 4:220, 1986.
29. Lindholm, T., Gullberg, C. and Akerlund, A. Laboratory and clinical experience with a new disposable parallel flow plate dialyzer. Scand. J. Urol. Nephrol. 13: 4-15, 1972.
30. Ronco, C., Bosch, J.P., Lew, S., Fecondini, L., Fabris, A., Feriani, M., Chiaramonte, S., Brendolan, A., Bragantini, L. and LaGreca, G. Technician and clinical evaluation of a new hemofilter for CAVH: Theoretical concepts and practical application of a different flow geometry. In: Proceedings of the International Symposium on Continuous Arteriovenous Hemofiltration (Eds. G. LaGreca and C. Ronco), Milan, Wichtig Editore, 1986, pp. 55-61.
31. Lysaght, M. and Boggs, D. Transport in continuous arteriovenous hemofiltration and slow continuous ultrafiltration. In: Acute Continuous Renal Replacement Therapy (Ed. E. P. Paganini), Martinus Nijhoff, Boston, 1986, pp. 43-50.
32. Gohl, H. and Konstantin, P. Membranes for hemofiltration. In: Hemofiltration (Eds. L.W. Henderson, E. A. Quellhorst, C.A. Baldamus and M.J. Lysaght), Springer-Verlag Berlin Heidelberg, 1986, pp. 42-82.
33. Ota, K., Suzuki, T., Ozaku, Y., Hoshino, T., Agishi, T. and Sugino, N. Short-time hemodiafiltration using polymethylmethacrylate hemodialfilter. Trans. Am. Soc. Artif. Intern. Organs 24:454-457, 1978.
34. Jacob, A.I., Gavellas, G., Zarco, R., Perry, G. and Bourgoignie, J.J. Leukopenia, hypoxia, and complement function with different hemodialysis membranes. Kidney Intern. 18:505-509, 1980.
35. Kaplan, A.A., Toueg, S. and Kennedy, T. Complement kinetics during continuous arteriovenous hemofiltration: Studies wit a new polysulfone hemofilter. Blood Purif. 6:27-36, 1988.
36. Golper, T.A. Continuous arteriovenous hemofiltration in acute renal failure. Am. J. Kid. Dis. 6:373-386, 1985.
37. Kaplan, A.A., Predilution versus postdilution for continuous arteriovenous hemofiltration. Trans. Am. Soc. Artif. Intern. Organs 31:28-31, 1985.

38. Kaplan, A.A., Longnecker, R.E. and Folkert, V.W. Continuous arteriovenous hemofiltration. A report of six months' experience. Annals Intern. Med. 100:358-367, 1984.
39. Kaplan, A.A., Longnecker, R.E., Folkert, V.W. Suction-assisted continuous arteriovenous hemofiltration. Trans. Am. Soc. Artif. Intern. Organs 29:408-413, 1983.
40. Paganini, E.P. Continuous replacement modalities in acute renal dysfunction. In: Acute Continuous Renal Replacement Therapy (Ed. E. P. Paganini), Martinus Nijhoff, Boston, 1986, pp. 7-41.
41. Smith, D., Paganini, E. P., Suhoza, K., Eisele, G., Swann, S. and Nakamoto, S. Non-heparin continuous renal replacement therapy is possible. In: Progress in Artif. ORgans (Eds. Y. Nose, C. Kjellstrand and P. Ivanovich), ISAO PRess, Cleveland 1986, pp. 226-228.
42. Cosentino, F., Paganini, E., Nakamoto, S. and Swann, S. Clinical experience with continuous renal replacement therapy in heart and liver transplant recipients. (Abstract) Am. J. Kid. Dis. 11:A4, 1988.
43. Geronemus, R.P. Slow continuous hemodialysis. Trans. Am. Soc. Artif. Intern. Organs 34:59-60, 1988.
44. Schrader, J., Valentin, R., Tonnis, H.J., Hilderbrand, U., Stibbe, W., Armstrong, V.W., Kandt, M., Kostering, H. and Quellhorst, E. Low molecular weight heparin in hemodialysis and hemofiltration patients. Kidney Intern. 28:823-829, 1985.
45. Bartlett, R.H., Bosch, J., Geronemus, R., Paganini, E., Ronco, C. and Swartz, R. Continuous arteriovenous hemofiltration for acute renal failure. Trans. Am. Soc. Artif. Intern. Organs. 34:67-77, 1988.
46. Pinnick, R.V., Wiegman, T.B. and Diederich, D.A. Regional citrate anticoagulation for hemodialysis in the patient at high risk for bleeding. New Eng. J. Med. 308:258-261, 1983.
47. Ota, K., Kawaguchi, H., Takahashi, K. and Ito, K. A new prostacycline analogue - an anticoagulant applicable to hemodialysis. Trans. Am. Soc. Artif. Intern. Organs 29:419-424, 1983.
48. Josefowicz, M. and Jozefonvicz, J. New approaches to anticoagulation with heparin-like biomaterials. Jour. ASAIO 8:218- , 1985.
49. Paganini, E.P., Flague, J., Whitman, G., Nakamoto, S. Amino acid balance in patients with oliguric renal failure undergoing slow continuous ultrafiltration (SCUF). Trans. Am. Soc. Artif. Intern. Organs 28: 615-620, 1982.
50. Colton, C.K., Henderson, L.W., Ford, C.A. and Lysaght, M.J. Kinetics of hemodiafiltration. In-vitro transport characteristics of a hollow fiber ultrafilter. J. Lab. Clin. Med. 355-371, 1985.

51. Lysaght, M. and Garber, J.W. CAPD and CAVH/CAVHD: Synthetic versus natural membranes for the continuous cleansing of uremic blood. In: Proceedings of the Third International Symposium on Acute Continuous Renal Replacement Therapy (Eds. E.P. Paganini and R. Geronemus), Ft. Lauderdale, Fla., 1987, pp. 175.186.
52. Ronco, C., Brendolan, A., Bargantini, L., Feriani, M., Fabris, A., Chiaramonte, S., Scarbardi, M. and LaGreca, G. Arteriovenous hemodiafiltration combines with continuous arteriovenous hemofiltration. (abstract) Blood Purif. 2, 4:227, 1985.
53. Olbricht, C. Continuous arteriovenous hemofiltration the control of azotemia in acute renal failure. In: Acute Continuous Renal Replacement Therapy (Ed. E.P. Paganini), Martinus Nijhoff, Boston, 1986, pp. 123-141.
54. Kaplan, A.A. The predilution mode for continuous arteriovenous hemofiltration: Operational characteristics and clinical application. In: Proceedings of the Third International Symposium on Acute Continuous Renal Replacement Therapy (Eds. E.P. Paganini and R. Geronemus), 1987, pp. 94-105.
55. Kaplan, A.A. Clinical trials with predilution and vacuum suction: Enhancing the efficiency of the CAVH treatment. Trans. Am. Soc. Artif. Intern. Organs 32: 49-51, 1986.
56. Geronemus, R. and Schneider, N. Continouos arteriovenous hemodialysis: A new modality for treatment of acute renal failure. Trans. Am. Soc. Artif. Intern. Organs 30:610-613, 1984.
57. Sigler, M.H. Solute transport in slow continuous arteriovenous hemodialysis: An improved method for treating acute renal failure. In: Proceedings of the Third International Symposium on Acute Continuous Renal Replacement Therapy (Eds. E.P. Paganini and R. Geronemus), Ft. Lauderdale, Fla., 1987, pp. 78-86.
58. Geronemus, R. and Schneider, N. Continuous arteriovenous hemodialysis. In: Proceedings of the Third International Symposium on Acute Continuous Renal Replacement Therapy (Eds. E.P. Paganini and R. Geronemus), Ft. Lauderdale, Fla., 1987, pp. 64-77.
59. Chanard, J., Milcent, T., Toupance, O., Melin, J., Roujouleh, H. and Lavaud, S. Ultrafiltration-pump assisted continuous arteriovenous hemofiltration (CAVH). Kidney Intern. 33: Suppl. 24, S-157 - S-158, 1988.
60. Canaud, B., Berand, J.J. and Mion, C. Pump assisted continuous veno-venous hemofiltration (PA-CVVH): A more flexible mode of acute uremia treatment in severely ill patients. In: Proceedings of the Third International Symposium on Continuous Arteriovenous Hemofiltration (Eds. G. LaGreca, A. fabris and Ronco, C.), Milan, Wichtig Editore, 1986, pp. 185-189.

61. Canaud, B., Garred, L.J., Christol, J., Aubas, S., Beraud, J.J. and Mion, C. Pump assisted venovenous hemofiltration for treating acute uremia. Kidney Intern. 33: Suppl. 24, S-154-S-156, 1988.
62. Kohen, J.A., Whitley, K.Y. and Kjellstrand, C.M. Continuous arteriovenous hemofiltration: a comparison with hemodialysis in acute renal failure. Trans Am Soc Artif Intern Organs 31:169-173, 1985.
63. Paganini, E.P., O'Hara, P. and Nakamoto, S. Continuous slow ultrafiltration in oliguric acute renal failure patients. Trans Am Soc Artif Intern Organs 30:173-178, 1984.
64. Rimondini, A., Cipolla, C.M., Della Bella, P. et. al. Hemofiltration as short-term treatment for refractory congestive heart failure. Am. J. Med. 83:43-48, 1987
65. Gotloib, L., Barzilay, E., Shustak, A. and Lev, A. The impact of using the artificial kidney as an artificial endocrine lung upon severe septic ARDS. Intensive and Critical Care Digest, 5:3-4, 1986.
66. Gotloib, L., Barzilay, E., Shustak, A., Wais, Z., Jaichenko, J. and Lev, A. Hemofiltration in septic ARDS. The artificial kidney as an artificial lung. Resuscitation, 13:123-132, 1986.

CHRONIC RENAL FAILURE

12

ERYTHROPOIETIN IN THE TREATMENT OF THE ANAEMIA OF CHRONIC RENAL FAILURE

C.G. WINEARLS
Renal Unit, Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 OHS.

INTRODUCTION

It has long been the aim of nephrologists to treat the anaemia of patients with chronic renal failure with erythropoietin. Although aware that many factors contribute to the development of this anaemia they were confident that replacement treatment would be effective (1). The problem was not of justifying this therapeutic approach but obtaining sufficient pure hormone for long-term administration to a large number of patients.

EVIDENCE THAT RENAL ANAEMIA IS PRIMARILY A CONSEQUENCE OF ERYTHROPOIETIN DEFICIENCY

Although it is clear that the anaemia of end-stage renal disease (ESRD) is a result of reduced red cell production, the critical question is whether the erythron itself is normal in uraemia. The excessive blood loss and shortened red cell lifespan of patients on dialysis are well recognised but would be well within the ability of a normal erythroid marrow to compensate. This compensation would, under normal circumstances, be triggered by increased secretion of erythropoietin. In fact the failed kidneys do seem to be able to respond to changes in haemoglobin concentration (in both directions) but the feedback loop, though intact, is damped (2). Measurement of erythropoietin concentrations has usually revealed that the levels are within or above the range found in normal non-anaemic subjects but the appropriate comparison is with concentrations found in subjects with similar degrees of anaemia but intact renal function. The difference is then striking in that patients with renal failure have much lower concentrations (reviewed 3). In uraemic subjects the marrow itself has

normal numbers of erythroid progenitors (CFU-e and BFU-e) but the ratio of CFU-e to BFU-e is much lower than would be expected for the degree of anaemia (4). Do uraemic inhibitors account for this sluggishness of the erythron and the improvement in haemoglobin levels after dialysis is instituted? Although such inhibitors can be detected in murine marrow culture systems the effect was not specific for the erythroid colonies (5). Experiments which involve culturing autologous or normal marrow with and without uraemic serum have not revealed depression of BFU-e or CFU-e derived colony growth (4, and Reid CDL unpublished). All these experiments require the addition of exogenous erythropoietin to the cultures and this implies that the response of the erythron to erythropoietin is unimpaired. Further support, albeit indirect, for this belief comes from the observed variation in the degree of anaemia seen in anephric and nephric patients and the tendency for some patients with adult polycystic kidney disease or acquired cystic disease to run higher haemoglobin concentrations than the average for dialysis patients (6,7). The experiments on uraemic sheep performed by Eschbach and colleagues were particularly persuasive for they found no differences in the response to exogenous erythropoietin, between normal and uraemic animals (8).

Taken together this evidence points to impaired production of erythropoietin by the damaged kidneys as the primary cause of the inadequate red cell production of uraemic subjects. The rationale for treatment was not in doubt, the problem was the source.

PRODUCTION OF RECOMBINANT HUMAN ERYTHROPOIETIN (r-HuEPO).

The cloning of the human erythropoietin gene was described independently by Jacobs et al (9) and Lin et al (10). This feat depended not only on the newer techniques of molecular biology but considerable additional ingenuity for there was no ready source of pure native erythropoietin or its mRNA and the amino-acid sequence had not been elucidated. Once cloned the gene was expressed in mammalian cells to allow glycosylation of the polypeptide, which is essential for it to be effective in vivo. Additional manipulation of the gene was required to increase the yield of the recombinant protein. The material obtained from the cultures was extensively purified and

characterised before clinical trials were undertaken. It is very pure and for practical purposes indistinguishable from the native hormone (11).

FIRST CLINICAL TRIALS

Two groups undertook the initial clinical trials in man. Both used the material produced by AMGen first described by Lin et al (10) and in more detail by Egrie et al (11).

Eschbach et al used fixed doses of 1.5, 5, 15, 50, 150, 500 and 1500 U/kg thrice weekly in small groups of patients. Although they observed changes in erythron transferrin uptake (ETU) and reticulocyte levels below 50 U/kg it was only at or above this dose that consistent rises in haemoglobin concentration occurred. There was apparently little difference in response between the 500U/kg and 1500U/kg groups implying that maximal stimulation of the erythroid marrow had been achieved. Their data demonstrated very elegantly that the rate of response was dose dependent (12).

The UK group of Cotes and colleagues (13) approached the problem of finding the effective dose differently. Ten patients received escalating doses of r-HuEPO from 12 to 192 U/kg until a response defined as a rise in haemoglobin of > 2g above basal was achieved. Thereafter doses were titrated to attempt to maintain the haemoglobin at $\pm$ 12 g/dl. All ten patients responded but the dose increments were instituted too soon to establish the dose level at which the patients first responded. Maintenance doses have proved lower than the maximum doses reached during the first weeks of the trial and have ranged between 24 and 96 U/kg thrice weekly (14).

Both these studies demonstrated the unequivocal efficacy of r-HuEPO in reversing the anaemia of chronic renal failure in patients maintained by haemodialysis and proved the proposition that erythropoietin deficiency is a sufficient if not exclusive cause. However, it was apparent even in these short-term studies that there were a number of important consequences of reversing anaemia in this group of patients. Further information on these is emerging from the larger clinical trials that have been set up subsequently (15, 16, 17, 18).

BENEFITS OF TREATMENT

The patients treated with r-HuEPO have reported remarkable improvements in their levels of energy and well-being (12,13,16,18). It is highly improbable that this was a placebo effect but some of the euphoria may have been enhanced by the novelty of the treatment. This sort of benefit is difficult to measure but health profiles performed by an independent observer before and after treatment of the Oxford patients supported the impressions of the clinician. Because of likely pressure from health economists more rigorous and placebo-controlled trials of the effect of treatment on the patients perceptions of their energy levels are in progress. Of the objective measures of benefit the most obvious is the relief from the need for regular or intermittent blood transfusions (12,13,17,19) which carry risks of infection, sensitisation to histocompatibility antigens and iron-overload. It will be possible to treat already iron-loaded patients by venesection though whether this will make any difference to the organs where the iron is deposited is open to question but it may reduce the susceptibility of these patients to bacterial infections such as Yersinia (reviewed 20). The abolition of the need for blood transfusion should not affect results of cadaveric renal transplantation for there is no reason why policies of deliberate transfusion, not indicated by the degree of anaemia, should not continue. Whether stopping transfusion will reduce the levels of cytotoxic antibodies in sensitised dialysis patients remains to be established.

Objective assessment of the effect of reversing anaemia has been performed by measuring changes in maximal oxygen consumption (VO_2 max), anaerobic threshold and maximal exercise capacity (21,22,23,24). Preliminary reports of these revealed improvements in most cases but the magnitude of the changes varied markedly.

The increase in haematocrit has been reported to result in a significant shortening of the bleeding time in dialysis patients (25). This is in general an advantage of treatment but it is possible that vascular access points may as a result be more vulnerable to thrombosis (see below).

RESULTS OF MULTICENTRE TRIALS

A number of multicentre trials are in progress but interim analyses are all that are available at present.

Bommer et al (15) and Casati et al (16) have reported their individual results from within the Cilag European Multicenter Study. This involves an escalating dose regimen and titration of the dose to achieve a Hb of 10g/dl. They confirmed the efficacy of r-HuEPO and noted some unexpected benefits such as improvemenet in symptoms of Raynauds phenomenon.

The AMGen Multicenter study has been described by Eschbach and Adamson for the Cooperative Multicenter Epo Clinical Trial Group (17). 247 patients were treated with 150-300 U/kg thrice weekly. All but six patients responded and the need for transfusion was abolished in 124/127 of those requiring it.

Boehringer have mounted a randomised trial of the r-HuEPO developed in collaboration with Genetics Institute, Cambridge Mass., in five German centres (26). Patients were randomised to one of three dose schedules - 40, 80 and 120 U/kg thrice weekly. The response was brisker in the groups receiving the higher doses and 21 of the 29 patients receiving 40U/kg were judged to have had a reduced or no response (27). Some patients were put on a twice weekly maintenance dose schedule which, though effective, may have resulted in a higher total dose requirement (26).

PHARMACOKINETICS

Detailed pharmacokinetic studies have not yet been published but some information is available from abstracts (28,29). Egrie et al reported an average half life (+SD) of first intravenous administration of 9.3 $\pm$ 3.2 hours and this fell to 6.2 $\pm$ 1.8 hours after seven doses. In five patients given the hormone subcutaneously peak concentrations which were reached 8 - 12 hours after administration were only 10% of those achieved by the intravenous route and were sustained for a further 12 - 16 hours. Cotes et al, cited in (29), reported a shorter half life than Egrie et al of 4.2 hours. The first dose of r-HuEPO had been administered intravenously at a dose of 12 U/Kg. There was no consistent change after chronic

treatment.

The very striking difference between the pharmacokinetic profiles of intravenous and subcutaneous administration raises the question of which route will be more effective, economical and acceptable to patients. The intravenous administration of r-HuEPO at doses of 96 U/kg results in peak serum levels of > 1000mU/ml. It seems unlikely that such high concentrations are necessary to stimulate the marrow for patients who undergo successful renal transplantation and correction of anaemia are found to have much lower concentrations - ~200mU/ml (30). The few patients on continuous ambulatory peritoneal dialysis who have received the drug subcutaneously thrice weekly have responded satisfactorily and have found self-administration by this route simple (Stevens et al unpublished). Results of formal comparisons of the effect of route on maintenance dose requirements are awaited.

EFFECT OF r-HuEPO ON BONE MARROW ERYTHROID PROGENITORS

Reid et al (31) studied nine haemodialysis patients before and after a therapeutic response to r-HuEPO. He reported a significant fall in mean (+ SEM) bone marrow BFU-e numbers from 384 $\pm$ 55 to 94 $\pm$ 14 per 10^6 cells but no significant change in the numbers of CFU-e, 382 $\pm$ 61 to 286 $\pm$ 24 per 10^6 cells. No consistent change in peripheral blood BFU-e was seen and he suggested that the fall in bone marrow BFU-e reflected an increase in maturation into later compartments that had not been compensated by the pluripotential stem cells. In contrast to the falls in actual numbers he found, using the tritiated thymidine suicide technique, a significant rise in the proportion of both progenitors that were in S-phase. Dessypris et al performed similar experiments but the studies were performed before and two weeks after starting i.v. r-HuEPO. They found a significant increase in both BFU-e and CFU-e but also found a rise in granulocyte progenitors (32). It is hard to reconcile these contradictory results but part of the explanation may be the differences in methods and timing of sampling.

FERROKINETICS

Pippard (33) performed extensive ferrokinetic measurements on the subjects participating in the trial reported by Winearls et al (13,29). These studies were performed before treatment and after the patients had achieved their target haemoglobin level. The results will be published in full elsewhere but a summary is given here. In the seven non-transfused patients the red cell mass increased from a mean (SD) of 14.1 (1.9) ml.kg to 26ml (3.9) ml/kg, a rise which was accompanied by a reciprocal fall in plasma volume from 60.5 (10.6) to 43.1 (5.3) ml/kg. Total blood volumes were little changed - 74.6 (10.9) mls/kg pretreatment and 69.2 (6.8) mls/kg after. The average mean cell lifespan before treatment was 72.6 days (range 59.6 - 90) which is shorter than than normal (mean 110 days range 70-150) and not significantly different after treatment - 79.1 days (range 66-105). $\%^{59}Fe$ utilisation which was normal before was unchanged by treatment showing that dyserythropoiesis was not a factor in the development of anaemia. The mean erythron transferrin uptake (ETU) increased after treatment to a level about 1.5 x normal which is further evidence of the responsiveness of the uraemic erythroid marrow to erythropoietin.

Eschbach et al (12) also found an increase in ETU after treatment and the effect was apparent after a short period of treatment and correlated with the reticulocyte response.

CAUSES OF A REDUCED RESPONSE TO r-HuEPO

The first and obvious cause of a diminished response is an inadequate dose (12,27). From the various studies cited above it appears that the maintenance dose of r-HuEPO administered intravenously is in the majority of patients between 150 and 300 U/kg per week. Now that erythropoietin is no longer limiting, attention has to be paid to the other factors which contribute to this anaemia. Iron deficiency may prevent an initial response (17) and cause a subsequent reduction in response (12). It has been suggested that the degree of aluminium loading may confer a degree of resistance (16,34) and in this context it is interesting to note that improvements in Hb following desferrioxamine treatment in patients who are not overtly

aluminium overloaded (35,36).

SIDE EFFECTS

There are problems in assessing the incidence of adverse events in the trials reported so far. None of them has included a control group and concomitant data on the incidence of such problems as vascular access failure, hypertensive episodes and fits is lacking. Moreover all these reports cover a relatively short time span only a proportion of which includes the period after the patients had achieved their target haemoglobin concentrations. Dialysis patients are subject to a variety of complications as a result of their chronic illness and so separating the unpredicted occurrence of these from direct effects of erythropoietin treatment or more important, changes in haemoglobin is very difficult. These caveats apart a number of points can be made.

The administration of r-HuEPO itself has been relatively free of side-effects but a few patients have experienced transient flu-like symptoms or abdominal pain after intravenous boluses (13,16,18).

The one consistent adverse effect has been an increase in blood pressure (12,13,15,16,17,37,40) which occurs more frequently in patients with pre-existing treated hypertension. The explanation for this (reviewed 38) is that peripheral resistance is increased not only by the increase in viscosity but also because the peripheral vasodilatation consequent upon anaemia is reversed. Nonnast-Daniel et al (39) have tested this hypothesis by measuring calf blood flow and transcutaneous oxygen pressure in patients treated with r-HuEPO. They found that as O_2 pressure rose mean arterial pressure (MAP) and peripheral resistance rose. As a corollary of this Mayer and colleagues have reported a useful rise in blood pressure in previously hypotensive patients after correction of anaemia. They recorded a rise in total peripheral resistance and a fall in cardiac output (40). The issue is not settled, however, for Paganini and colleagues found no change in blood pressure in their patients and recorded a rise in peripheral resistance (41).

Although these changes in blood pressure should be contained by

treatment there have been a number of episodes of quite sudden increases in blood pressure which have resulted in grand mal convulsions (12,13,42,43).

A small increase in platelet counts after treatment has been observed by a number of investigators (15,18) and it is possible that this results from an effect of erythropoietin on megakaryocyte precursors (44) or it may reflect iron deficiency. Although thise rise in platelet count is small and well within the normal range, bleeding times and heparin requirements during dialysis are increased. This has provoked the fear that the risk of vascular access thrombosis would be increased following correction of anaemia in haemodialysis patients. There have, not surprisingly been a number of episodes of fistula thrombosis in patients in the clinical trials but it is unwise to relate these directly to treatment (13,15,45). The controlled trials of r-HuEPO should settle this question.

The same uncertainty exists over the question of whether dialysis efficiency will be adversely affected by changes in haematocrit (46). Several centres have reported increases in pre-dialysis potassium levels (12,16) and attributed these to anabolism and increased protein intake. Although dialyser creatinine clearance would be expected to fall as haematocrit rose (47) available reports suggest that what changes do occur are not clinically significant (48).

So far no antibodies to recombinant erythropoietin have been identified in treated patients (12,14,16) and the stability of maintenance doses argues against there being any immune elimination of the injected hormone.

CONCLUSIONS

When recombinant erythropoietin is licensed and becomes generally available a new phase of management of renal failure will begin. The symptoms of uraemia will for the first time be separable from those of the previously accompanying anaemia. There are however a number of outstanding issues which will have to be resolved. These include: the optimum haemoglobin concentration to aim for; the safest rate at which to effect a reversal of anaemia; obtaining a clearer

understanding of the pathogenesis of the hypertension and strategies for avoiding and treating it.

REFERENCES

1. Eschbach, J.W. and Adamson J.W. Anemia of end-stage renal disease (ESRD). Kidney Int. 28: 1-5, 1985. .
2. Walle, A.J., Wong, G.Y., Clemons, G.K., Garcia, J.F. and Niedermeyer, W. Erythropoietin-haematocrit feedback circuit in the anemia of end-stage renal dsiease. Kidney Int. 31: 1205-1209, 1987.
3. Caro, J. and Erslev, A. Erythropoietin assays and their use in the study of anemias. Contr. Nephrol. 66: 54-62, 1988.
4. Segal, G.M., Eschbach, J.W., Egrie, J.C., Stueve, T. and Adamson, J.W. The anemia of end-stage renal disease: haematopoietic progenitor cell response. Kidney Int. 33: 983-988, 1988.
5. Delwiche, F., Segal, G.M., Eschbach, J.W. and Adamson, J.W. Haematopoietic inhibitors in chronic renal failure: lack of in vitro specificity. Kidney Int. 29: 641-648, 1986.
6. Chandra, M., Miller, M.E., Garcia, J.F., Mossey, R.T. and McVicar, M. Serum immunoreactive erythropoietin levels in patients with polycystic kidney disease as compared with other haemodialysis patients. Nephron 39, 26-29, 1985.
7. Shalhoub, R.J., Rajan, U., Kim, V.V., Goldwasser, E., Kark, J.A. and Antoniou L.D. Erythrocytosis in patients on longterm hemodialysis. Ann. Int. Med. 97: 686-690, 1982.
8. Eschbach, J.W., Mladenovic, J., Garcia J.F., Wahl, P.W. and Adamson J.W. The anemia of chronic renal failure in sheep. Response to erythropoietin-rich plasma in vivo. J. Clin. Invest. 74: 434-441, 1984.
9. Jacobs K., Shoemaker, C., Rudersdorf, R., Neill, E.F., Kaufman, R.J., Mufson, A., Seehra, J., Jones, S.S., Hewick, R., Fritzch, E.F., Kawakita, M., Shimaza T. and Miyake, T. Isolation and characterisation of genomic and cDNA clones of human erythropoietin. Nature 313: 806-810, 1985.

10. Lin, F-K., Suggs, S., Lin, C-H., Browne, J., Smalling, R., Egrie, J., Chen, K., Fox, G., Martin, F., Stainsky, S., Brdawi, S., Lai, P-H. and Goldwasser, E. Cloning and expression of the human erythropoietin gene. Proc. Natl. Acad. Sci' USA 82: 7580-7584, 1985.

11. Egrie, J.C., Strickland, T.W., Lane, J., Aoki, K., Cohen, A.M., Smalling, R., Trail, G., Lin, F-K., Browne, J.K. and Hines, D.K. Characterisation and biological effects of recombinant human erythropoietin. Immunobiol. 172: 213-224, 1986.

12. Eschbach, J.W., Egrie, J.C., Downing, M.R., Browne, J.K. and Adamson, J.W. Correction of the anaemia of end-stage renal disease with recombinant human erythropoietin: results of a combined phase I and II clinical trial. N. Eng. J. Med. 316: 73-78, 1987.

13. Winearls, C.G., Oliver, D.O., Pippard, M.J., Reid, C., Downing, M.R. and Cotes P.M. Effect of human erythropoietin derived from recombinant DNA on the anaemia of patients maintained by chronic haemodialysis. Lancet ii: 1175-1178, 1986.

14. Cotes, P.M., Pippard, M.J., Reid C.D.L., Oliver, D.O. and Winearls, C.G. Continuing correction of anaemia by treatment with recombinant erythropoietin in patients maintained by haemodialysis. (Abstr.) Exp. Haematol. 15: 437, 1987.

15. Bommer, J., Alexiou, C., Muller-Buhl, U., Eifert, J. and Ritz, E. Recombinant human erythropoietin therapy in haemodialysis patients, dose determination and clinical experience. Nephrol. Dial. Transpl. 2: 238-242, 1987.

16. Casati, S., Passerini, P., Campise, M.R., Graziani, G., Cesana, B., Perisic, M. and Ponticelli, C. Benefits and risks of protracted treatment with human recombinant erythropoietin in patients having haemodialysis. Br. Med. J. 295: 1017-1020, 1987.

17. Eschbach, J.W. and Adamson, J.W. Correction of anemia of hemodialysis (HD) patients with recombinant human erythropoietin (r-HuEPO). Results of a multicenter study. (Abstr.) Kidney Int. 33:189, 1988

18. Grutzmacher, P., Bergmann, M., Weirich, T., Nattermann, U., Reimers, E. and Pollok, M. Beneficial and adverse effects of correction of anemia by recombinant human erythropoietin in patients on maintenance haemodialysis. Contr. Nephrol. 66: 104-113, 1988.

19. Bommer, J., Huber W., Tewes, G., Ritz, E. Von Wedel, S., Kuppers, S., Weinreich, T. and Bommer, G. Treatment of polytransfused hemodialysis patients with recombinant human erythropoietin. Contr. Nephrol. 66; 131-138, 1988.

20. Seifert, A., von Herrath, D. and Schaefer, K. Iron overload, but not treatment with desferrioxamine favours the development of septicaemia in patients on maintenance hemodialysis. Quart. J. Med. 65: 1015-1024, 1987.

21. Graf, H., Mayer, G. and Thum, J. Low hemoglobin levels are the main cause of impaired working capacity and low exercise tolerance in patients on chronic hemodialysis. (Abstr) Nephrol. Dial Transpl. 2: 415, 1987.

22. Lundin, A.P., Delano, B.G., Stein, R., Quinn, R.M. and Friedman, E.A. Recombinant human erythropoietin (rHuEPO) treatment enhances exercise tolerance in hemodialysis patients (HD). (Abstr) Kidney Int. 33: 200, 1988.

23. Robertson, H.T., Haley, N.R., Adamson, J.W. and Eschbach, J.W. (Abstr) Increase in maximal exercise capacity in hemodialysis patients following correction of the anemia with recombinant human erythropoietin (rHuEPO). Kidney Int. 33: 206, 1988.

24. Bocker, A., Reimers, E., Nonnast-Daniel, B., Kuhn, K., Koch, K.M., Scigalla, P., Braumann, K-M., Brunkhorst, R. and Boning, D. Effect of erythropoietin treatment on O2 affinity and performance in patients with renal anemia. Contr. Nephrol. 66: 165-175, 1988.

25. Moia, M., Manruci, P.M., Vizzotti, L., Casati, S., Cattaneo, M and Ponticelli, C. Improvement in the hemostatic defect of uraemia after treatment with human erythropoietin. Lancet ii: 1227-1229, 1987.

26. Bommer, J., Kugel M., Schoeppe, W., Brunkhorst, R., Samtleben, W., Bramsiepl, P. and Scigalla, P. Multicenter trial of recombinant human erythropoietin: general results. Contr. Nephrol. 66: 85–93, 1987.

27. Kuhn, K., Nonnast-Daniel, B., Grutzmacher, P., Gruner, J., Pfaffl, W., Baldamus, C.A. and Scigalla, P. Analysis of initial resistance of erythropoiesis to treatment with recombinant human erythropoietin. Contr. Nephrol. 66: 94–103, 1988.

28. Egrie, J.C., Eschbach J.W., McGuire, T. and Adamson, J.W. Pharmacokientics of recombinant human erythropoietin (rHuEPO) administered to hemodialysis (HD) patients. (Abstr) Kidney Int. 33: 262, 1988.

29. Winearls C.G., Cotes, P.M., Pippard, M., Reid, C. and Oliver D.O. Correction of anaemia in haemodialysis patients with rHuEPO - follow-up and results of pharmacokinetics, ferrokinetic and bone marrow studies. (Abstr.) Proc. Xth Int. Congress Nephrol, London, 1987.

30. Sun, C-H., Paul, W., Ward, H.J., Koyle, M.A. and Lee D.B.N. Erythropoiesis and radio-immunoassayable erythropoietin in renal transplant (Tx) patients. (Abstr). Kidney Int. 33: 452, 1988.

31. Reid, C.D.L., Fidler, J., Winearls, C.G., Oliver, D.O. and Cotes P.M. The response of erythroid progenitors to administered recombinant erythropoietin in haemodialysed renal failure patients. (Abstr). Blood (suppl) 70: 142a, 1987.

32. Dessypris, E.N., Graber, S.E., Krantz, S.B. and Stone W.J. Effect of recombinant erythropoietin on human marrow haematopoietic progenitors in vitro. (Abstr). Blood (suppl) 70: 132a, 1987.

33. Cotes, P.M., Pippard, M.J., Reid C.D.L. et al. Characterisation of the anaemia of chronic renal failure and the mode of its correction by erythropoietin (in preparation).

34. van Wyck, D.B., Stivelman, J., Ruiz, J., Katz, M.A. and Ogden, D.A. Aluminium excess poses modest resistance to recombinant human erythropoietin (rHuEPO) for dialysis anemia (Abstr) Kidney Int. 33: 240, 1988.

35. de la Serna, F-J., Praga, M., Gilsanz, F., Rodicio, J-L., Ruilope, L-M. and Alcaza, J-M. Improvement in the erythropoiesis of chronic haemodialysis patients with desferrioxamine. Lancet i: 1009-1111, 1988.

36. Altmann, P., Plowman, D., Marsh, F. and Cunningham, J. Aluminium chelation therapy in dialysis patients: evidence for inhibition of haemoglobin synthesis by low levels of aluminium. Lancet i: 1012-1015, 1988.

37. Samtleben, W., Baldamus, C.A., Bommer, J., Fassbinder, W., Nonnast-Daniel, B. and Gurland, H.J. Blood pressure changes during treatment with recombinant human erythropoietin. Contr. Nephrol. 66: 114-122, 1988.

38. Raine, A.E.G. Hypertension, blood viscosity and cardiovascular morbidity in renal failure: implications of erythropoietin therapy. Lancet ii: 97-100, 1988.

39. Nonnast-Daniel, B., Creutzig, A., Kuhn, K., Bahlmann, J., Reimers, E., Brunkhorst, R., Caspary, L. and Koch, K.M. Effect of treatment with recombinant human erythropoietin on peripheral haemodynamics and oxygenation. Contr. Nephrol. 66: 185-194, 1988.

40. Mayer, G., Stefenelli, Th., Cada, E.M., Thum, J., Stumvoll, H.K. and Graf H. Blood pressure and erythropoietin (letter). Lancet i: 351-352, 1988.

41. Paganini, E., Thomas, T., Fouad, F., Garcia, J. and Bravo, E. The correction of anemia in hemodialysis patients using recombinant human erythropoietin (r-HuEPO) - hemodynamic effects. (Abstr) Kidney Int. 33: 204, 1988.

42. Tomson, C.R.V., Venning, M.C. and Ward, M.K. Blood pressure and erythropoietin. (letter) Lancet i: 351, 1988.

43. Edmunds, M.E. and Walls J. Blood pressure and erythropoietin. (letter) Lancet i: 352, 1988.

44. Dessypris, E.N., Gleaton, J.H. and Armstrong, O.L. Effect of human recombinant erythropoietin on human marrow megakaryocyte colony formation in vitro. Br. J. Haematol. 65: 265-269, 1987.

45. Eschbach, J.W. and Adamson, J.W. Correction of anemia of end-stage renal disease with recombinant human erythropoietin. (letter) N. Eng. J. Med. 317: 250-251, 1987.

46. Walczyk, M.H. and Golper, T.A. (letter) Correction of anemia of end-stage renal disease with recombinant human erythropoietin. (letter) N. Engl. J. Med. 317: 249, 1987.

47. Wolfinden, C., Hoenich, N.A. and Kerr D.N.S. Effect of haematocrit on the clearance of small molecules during haemodialysis. Int. J. Art. Organs 6: 127-130, 1983.

48. Stivelman, J., van Wyck, D., Kirkin, L. and Ogden, D. Use of recombinant erythropoietin (rHuEPO) with high flux dialysis (HFD) does not worsen azotemia or shorten access survival. (Abstr) Kidney Int. 33: 238, 1988.

DIALYSIS

13

NEW STRATEGIES FOR HIGH EFFICIENCY HEMODIALYSIS

PRAKASH R. KESHAVIAH, Ph.D.
ALLAN J. COLLINS, M.D.

Regional Kidney Disease Program, Hennepin County Medical Center, Minneapolis, Minnesota, USA

Introduction

Advances in dialysis technology have permitted reductions in treatment times from 36 hours per week to between 12 and 15 hours per week over a period of two decades. These technological advances include the development of single pass dialysate delivery systems, active perfusion of the extracorporeal circuit using blood pumps, more efficient dialyzer designs with thinner membranes and lower priming volumes, advances in blood access techniques and the ability to attain higher blood flow rates in the extracorporeal circuit. In reducing treatment time, the major concerns are adequacy of solute removal, adequacy of fluid removal and patient tolerance of the shorter, more efficient treatment. It has been documented that rapid removal of osmotically active solutes such as urea can provoke the disequilibrium syndrome with accompanying symptoms of headache, nauseau and vomiting, and in the extreme, seizures (1,2). It is also well documented that the combination of more efficient diffusive solute transport and more rapid removal of fluid can result in cardiovascular instability with symptoms such as nauseau, vomiting, cramps, light-headedness and hypotension (3,4,5,6). Most of these studies of cardiovascular instability were performed using acetate containing dialysate, it being well recognized that acetate is a potent vasodilator (7). Because of these findings, the process of reducing treatment time came to a standstill around the mid '70's and over the past decade, treatment times of 12 to 15 hours per week have remained unchanged and acquired the label of standard treatment time.

In the last four years, new technological advances have allowed further reductions in treatment time, to between 6 and 9 hours per week, without compromising the adequacy of solute and fluid removal and without

exacerbating patient symptoms during dialysis. We will consider in this chapter the new therapeutic strategies that have made such reductions in treatment time feasible and will also review briefly the clinical experience that has been accumulated with this new mode of high efficiency dialysis. In reviewing the clinical experience we will consider therapy prescription criteria, biochemical parameters, patient symptoms and complications, and patient morbidity. This clinical experience is still too limited to allow an assessment of patient survival on this mode of therapy.

Essential Ingredients of Rapid High Efficiency Therapies

As indicated earlier, in the third decade of hemodialysis, a new spurt of progress has been made in the reduction of treatment times. Treatment times of 6 to 9 hours per week are now possible with rapid high efficiency therapies. This new milestone in reducing treatment times has been reached because of further technological advances as well as an increased understanding of the etiology of dialysis disequilibrium and cardiovascular instability and a better assessment of therapy adequacy. The investigators who have pioneered this new phase of treatment time reduction include Von Albertini, et. al. with high efficiency hemodiafiltration (8,9), Keshaviah, Collins, et. al. (10,11,12,13) as well as Rotellar, et. al with high efficiency hemodialysis (14). Subsequently, Campbell, et. al. (15) and Keen, et. al (16) have achieved an equal measure of success with high flux dialysis which is equivalent to internal hemodiafiltration. These investigators have synthesized the available body of knowledge on the etiology of dialysis disequilibrium and hypotension into practical strategies for alleviating these complications despite significant reductions in treatment time. These new strategies include: 1) use of bicarbonate containing dialysate; 2) use of dialysate sodium concentrations between 140 and 145 mEq/l; 3) use of ultrafiltration control systems; and 4) individualization of treatment time with frequent assessment of "dry" weight.

We will now review our current state of understanding of the dialysis disequilibrium syndrome and cardiovascular instability and consider how the new strategies for shortening treatment time have steered clear of these complications.

Disequilibrium Syndrome

It is believed that the disequilibrium syndrome is associated with an osmotic imbalance across the blood-brain barrier with consequent movement of water into the cerebral space (1,2). This osmotic imbalance results from a rapid decrease of blood osmolality relative to that of the cerebro-spinal fluid. The imbalance may be accentuated by de novo production of idiogenic osmols within the cerebral space related to the rapidity of diffusive solute removal by the dialysis procedure (2).

Under standard conditions of dialysis, the dialysis disequilibrium syndrome is rarely observed in well dialyzed chronic dialysis patients. It is most often seen in the acute dialysis setting, because in this setting, the pre-dialysis levels of osmotically active solutes such as urea are high and are reduced to low levels in short durations of time by the dialysis procedure. However, early animal studies suggested that rapid dialysis could provoke the disequilibrium syndrome because of the rapid removal of osmotically active solutes (17). There is now a significant data base of clinical experience to indicate that this syndrome can be successfully avoided in the rapid high efficiency mode of therapy because of the use of the approaches outlined below.

There are two key factors that can help avoid the disequilibrium syndrome with high efficiency therapies, namely the prescribed dose of therapy and the composition of dialysate. With an adequate therapy prescription, pre-dialysis serum urea nitrogen levels as low as 70 to 80 mg % can be achieved even on the first dialysis of the week. The osmotic change due to urea removal during dialysis is therefore reduced. The second key factor is the composition of dialysate. With a serum sodium concentration of 140 mEq/l and a dialysate sodium concentration of the order of 143 mEq/l, there is diffusion equilibrium between serum and dialysate. There is, hence, no significant diffusive removal of sodium during the dialysis procedure. Therefore, the use of higher dialysate sodium concentrations ($\gtrsim$ 140 - 143 mEq/l) can prevent rapid changes in serum osmolality during high efficiency dialysis.

Cardiovascular Instability

Our understanding of cardiovascular instability during dialysis has increased greatly in the last ten years. While it is generally agreed that the etiology is multifactorial, it is also recognized that the principal determinants of dialysis induced hypotension are hypovolemia and the failure of peripheral resistance to compensate for this hypovolemia (4,5,6).

Hypovolemia is the consequence of an imbalance between the rate of ultrafiltration and the rate of vascular refilling from the interstitial space (18). This imbalance is accentuated by the higher rates of ultrafiltration required when treatment time is decreased in order to achieve adequate fluid removal. The rate of vascular refilling is dependent on the hydraulic permeability of the capillary endothelium and the oncotic pressure gradient that is set up between the interstitial and vascular space. There are data to suggest that the hydraulic permeability of the capillary endothelium may vary over a wide range in the dialysis population (18). Patients with a low hydraulic permeability may be more prone to hypovolemia.

Protein-free fluid is ultrafiltered from the vascular compartment across the dialyzer membrane. As a consequence, the plasma protein concentration increases, setting up an oncotic gradient that favors vascular refilling. As fluid refilling proceeds from the interstitial space, not only does the amount of freely mobilizable fluid in this space decrease, but the protein concentration of the interstitium also increases, unless fluid is recruited from the intracellular compartment. The successful use of high dialysate sodium concentrations in decreasing dialysis symptoms is related to such recruitment of intracellular fluid down an osmotic gradient (19). With low dialysate sodium concentrations on the other hand, fluid may shift in the opposite direction, into the intracellular compartment further depleting the interstitial fluid and compromising vascular refilling (19).

It has been observed by many investigators that compensatory increases of peripheral resistance in response to hypovolemia may be blunted or abolished during acetate dialysis (4,5,6). Uremic autonomic insufficiency may play a role in blunting this compensatory response in a few patients (20); in the vast majority of patients it is the general

consensus that compensatory vasoconstriction is blunted because of the vasodilatory effects of acetate exposure. In the isolated ultrafiltration setting, with no acetate exposure, compensatory vasoconstriction is elicited and blood pressure stability is maintained even with the same degree of hypovolemia as during acetate dialysis (21). The blunting of compensatory vasoconstriction during acetate dialysis is not observed to the same degree during bicarbonate dialysis (22). Also the incidence and severity of hypotension and accompanying symptoms is alleviated with bicarbonate dialysis (23). It is clear that the vasodilatory aspects of acetate metabolism play a key role in the blunting of compensatory vasoconstriction. Patients on dialysis have decreases in cardiac output related to hypovolemia, that are not compensated for by vasoconstriction, and can ultimately result in a fall in blood pressure with accompanying symptoms. The use of bicarbonate dialysis is, therefore, a key factor in maintaining cardiovascular stability with high efficiency therapies.

Bicarbonate Dialysis

With standard dialysis, it has generally been believed that the vast majority of dialysis patients are stable on acetate dialysis and only a small group of patients demonstrate a pronounced improvement in symptomatic hypotension and intradialytic symptoms with bicarbonate dialysis. The benefits of bicarbonate are however much more clear cut in the high efficiency dialysis setting. In our own initial studies at Minneapolis (10), we first attempted to reduce treatment time using acetate containing dialysate. We noted an increase in hypotension and associated symptoms with acetate dialysis and were also unable to achieve the desired weight removal. Upon switching the patients to bicarbonate dialysis, with no change in treatment time and other therapy parameters, we noted a dramatic improvement in hypotension and intradialytic symptoms. We were also able to achieve the desired weight removal and were, in fact, able to achieve dry weights that were even lower than those achievable with standard dialysis durations of 12 hours per week.

There are significant disincentives to performing bicarbonate dialysis. The cost of bicarbonate dialysis is higher, requiring as it does two

concentrates (bicarbonate concentrate and acid concentrate) as well as two proportioning and monitoring systems. The maintenance requirements of bicarbonate modules are higher than for standard acetate delivery systems. There are safety concerns related to a potential mixup of the two concentrates used for bicarbonate dialysis. There are also concerns of microbiological contamination of concentrate, dialysate and dialysate delivery systems with the use of bicarbonate dialysis. This concern is related to the fact that bicarbonate concentrate supports bacterial proliferation. Ebben, et. al. (24) and Bland, et. al. (25) have recently shown that, during storage, the bacterial levels in bicarbonate concentrate increase, in a matter of days, from less than 10 cfu/ml to as high as 10^5 to 10^6 cfu/ml; endotoxin concentrations increase from non detectable levels to between 25 and 75 ng/ml. The use of contaminated concentrate carries with it the risk of pyrogen reactions related to transfer of undissociated endotoxins and reactive endotoxin fragments across the dialysis membrane (26).

In order to achieve successful large scale delivery of bicarbonate dialysis in dialysis facilities in Minnesota, we have arrived at an innovative approach that we call the hybrid bicarbonate system (27). In this approach, water and bicarbonate concentrate are mixed at a central location with appropriate conductivity monitoring. The bicarbonated water is then supplied to the patient station and a standard acetate delivery system is used to mix this bicarbonated water with acid concentrate in the usual 34 to 1 ratio. This system is therefore a hybrid of central and patient station proportioning, and has been used by us successfully in approximately 500 patients with a cumulative experience in excess of 100,000 dialyses. This approach involves lower capital costs than individual bicarbonate modules at the patient station, and can also achieve more cost effective utilization of bicarbonate concentrate with less technician time for operating and maintaining the system.

Dialysate Sodium Concentration

As discussed above, low sodium concentrations in dialysate can

provoke intracellular fluid shifts, thereby compromising vascular refilling. High dialysate sodium concentrations are more effective in recruiting fluid from the intracellular space, thereby promoting vascular refilling and blunting hypovolemia. However, high dialysate sodium concentrations are associated with increased thirst and higher weight gains between treatments with the potential consequence of more intractable hypertension (28,10). A dialysate sodium concentration of the order of 143 mEq/l is in diffusion equilibrium with a normal serum sodium of 140 mEq/l. Sodium removal is achieved only as a consequence of fluid removal by ultrafiltration. In our studies of reduced treatment time with bicarbonate dialysis, we were unable to demonstrate any improvement in intradialytic symptoms when the dialysate sodium was increased from 140 mEq/l to 145 mEq/l (10). The higher dialysate sodium was associated with increased thirst and higher weight gains. The benefits of dialysate sodium concentrations higher than 140 to 143 mEq/l may be observed with acetate dialysis but appear to be less pronounced with bicarbonate dialysis (29).

Ultrafiltration Control Systems

It has been pointed out earlier that hypovolemia results from an imbalance between the rate of ultrafiltration and the rate of vascular refilling. In conventional dialysis, fluid removal is achieved by controlling transmembrane pressure based on a knowlege of the ultrafiltration coefficient of the dialyzer. The ultrafiltration coefficient of a new dialyzer may vary over a fairly wide range around the nominal value. With reuse of the dialyzer, the ultrafiltration coefficient becomes even less predictable (30). Also, the transmembrane pressure measured by most dialysate delivery systems is only an estimate of the true transmembrane pressure. Control of ultrafiltration through transmembrane pressure control, therefore, is often no better than a guessing game. If inadequate fluid removal is achieved in the initial phases of dialysis, attempts are made to compensate for this over the remainder of the dialysis duration, resulting in increased rates of ultrafiltration. On the other hand, if too high a transmembrane pressure is used initially, the rate of ultrafiltration achieved may be higher than desired, resulting in an exacerbation of hypovolemia.

This situation can deteriorate further with reduced treatment time, as the nursing staff have less time for corrective action during dialysis. Also because of an increased ultrafiltration coefficient for high efficiency dialyzers, and because of higher blood pressures in the extracorporeal circuit associated with higher blood flows, it becomes more difficult to control obligatory ultrafiltration in the rapid dialysis setting.

An effective solution to these problems is the use of an ultrafiltration control system that directly controls the rate of ultrafiltration rather than indirectly relying on control of transmembrane pressure. Three main categories of ultrafiltration control systems are currently available. The simplest and oldest type of ultrafiltration control uses a recirculating closed loop for the dialysate circuit. A pump is used to withdraw fluid from this closed loop at the desired rate of ultrafiltration and because of the non-compliant nature of this closed loop, fluid crosses over from blood to dialysate at the rate of withdrawal. The second type of ultrafiltration control system is known as a balancing system. In this type of ultrafiltration control, a quasi-closed loop is created in the dialysate circuit by accurately matching the dialysate inflow and outflow rates. As with the closed loop system, a separate pump withdraws fluid from this quasi-closed loop resulting in fluid crossing over from blood into the quasi-closed loop at the desired rate. The third type of ultrafiltration control system relies on actual measurement of the dialysate inflow and outflow rates, the difference being the rate of ultrafiltration. This difference is fed to a circuit which controls the transmembrane pressure until the measured difference is equal to the desired rate of ultrafiltration.

Individualization of Treatment Time and Frequent Assessment of 'Dry' Weight

In our initial studies of high efficiency dialysis (10), we reduced treatment time gradually over a period of several months until the goal of 150 minutes was achieved or until the reduction of treatment time was curtailed by poor cardiovascular tolerance to the reduced treatment time. This approach resulted in a spectrum of treatment times, representing the spectrum of patient tolerance. We therefore believe, that successful reductions in treatment time are best achieved with an

individualized approach, based on an appropriate assessment of the 'dry' weight of the patient.

The 'dry' weight of the dialysis patient is a nebulous concept and is based on imprecision. It is usually determined by a trial and error approach, more reliable estimates requiring more frequent assessment. The reported incidence of hypotension in dialysis varies over a wide range of 15 to 50 %. It is quite likely that this wide range of variation is not only related to inter-patient differences but may also reflect differences in the standards of care in dialysis. It has been our own experience that a more frequent assessment of 'dry' weight can result in a reduced frequency of symptomatic hypotension.

Therapy Prescription

Adequacy of therapy is an area of controversy and there are differences of opinion regarding the relative importance of small, middle and large molecule removal in dialysis. Some investigators maintain that the small solute urea is a good marker for all products of protein catabolism and that tailoring therapy based on urea removal allows adequate removal of other catabolites of dietary protein (31,32). There are others who maintain that there are unidentified middle molecular weight toxins that should be removed for adequate therapy (33,34). Vitamin B_{12} with a molecular weight of 1355 daltons is considered a surrogate marker for these middle molecules. Indices of adequacy have been formulated for urea removal and vitamin B_{12} removal. The KT/V urea index is the product of urea clearance K and treatment time T divided by V, the volume of urea distribution. An index of 1, represents a cleared volume equal to the distribution space of urea which is approximately equivalent to total body water. This index was arrived at by Gotch and Sargent when they analyzed the probability of therapy failure in the National Cooperative Dialysis Study (35). The Vitamin B_{12} index is based on the clinical observation that peripheral neuropathy is absent when residual renal clearance is equal to or greater than 3 ml/min (30 liters per week) (34). The weekly B_{12} clearance is normalized by this value of 30 liters per week in order to arrive at the Vitamin B_{12} index, a value of 1 representing adequate therapy.

Recently a large molecule Beta-2-microglobulin has assumed importance as a marker of adequate therapy. It has been suggested that the relatively poor diffusive removal of this large molecule by conventional cellulosic

membranes is responsible, in the long-term, for the development of carpal tunnel syndromes, arthropathies, and cystic bone lesions (36,37). It has also been shown that high flux membranes are capable of achieving clearances of the order of 30 to 60 ml/min for this large molecule (38). Beta-2-microglobulin has been shown to be the precursor of amyloid deposits that are found in carpal tunnels and in the joints of patients with arthropathies (36,39). The distribution space of this new marker of dialysis adequacy, its kinetics and the nature and extent of polymerization of Beta-2-microglobulin into the amyloid fibrils in joints is poorly understood. It is also not clear whether removal of this molecule from blood will influence amyloid deposition in joints to prevent carpal tunnel syndromes and arthropathies. Studies are currently under way to elucidate the importance of this large molecule as a marker of adequate dialysis.

In reducing treatment time, we have adopted a pragmatic approach to therapy prescription. We have maintained the product of urea clearance and treatment time constant while reducing treatment time. That is, we have increased the urea clearance proportionate to the reduction in treatment time so as to keep this KT product unchanged. We have thus matched the urea index of rapid therapy to that of standard therapy. In our own patient population, we have, for several years, achieved an urea index between 1.2 and 1.4 on standard therapy. Over this period, we have documented excellent patient survival, low morbidity manifested as a low frequency and duration of annual hospitilizations as well as good patient activity and rehabilitation monitored by the Karnofsky Index (40). Even thcugh the results of the National Cooperative Dialysis Study (NCDS) indicate that KT/V=1 connotes adequate therapy, we believe that because the NCDS is a short term study with short term outcome parameters, it cannot provide a satisfactory definition of the optimum therapy prescription relative to long term outcome. We have therefore maintained the KT/V index at or above 1.2, based on our own long term clinical results of patient activity and rehabilitation, morbidity and survival.

In order to achieve adequte urea clearances for reduced treatment times, it is necessary to use dialyzers that have a high value for the product of mass transfer coefficient (Ko) and surface area (A). Dialyzers used for standard therapy have KoA values of the order of 500 ml/min for urea. The dialyzers required for high efficiency therapies should have KoA values of the order of 700 to 1000 ml/min in order to provide the desired urea clearance for

reduced treatment times. In addition to using a more efficient dialyzer, it is necessary to operate this dialyzer at increased blood and dialysate flow rates in order to achieve the desired clearances. In our program, we have increased blood flow rates from standard values of 250 ml/min to values of the order of 400 ml/min. With these higher blood flow rates and with dialyzer KoA values of the order of 1000 ml/min, we are able to achieve urea clearances of the order of 300 ml/min. With these clearances, and with treatment times of the order of 150 minutes, we are able to achieve urea indices greater than 1.2 in our patient population.

The choice of a dialyzer with a higher mass transfer coefficient-area product for urea also yields increased Vitamin B_{12} clearances. We find that the weekly B_{12} clearances achieved with these dialyzers are higher than those achieved with standard dialyzers. We are, therefore, able to achieve equal or higher middle molecule indices despite the significant reduction in treatment time. We are thus able to achieve adequate small and middle molecule clearances with this approach to therapy prescription.

When higher blood flow rates are used to achieve the desired clearances, it is important to determine if access recirculation increases as a consequence. Increased access recirculation can negate the advantages achieved with the higher blood flow rates, patient solute clearances decreasing with recirculation despite the increased blood flow rate (41). It is therefore important to monitor access recirculation and ensure that it is below 15% in prescribing adequate therapy for high efficiency therapies.

Clinical Results

The studies of Von Albertini, et. al. with hemodiafiltration (8,9), Keshaviah, Collins, et.al. (10,11,12,13) and Rotellar, et.al. (14) with hemodialysis, and Campbell, et. al. (15) and Keen, et. al. (16) with high flux dialysis have all shown that the use of more efficient dialyzers operated at higher blood flow rates can achieve adequate solute removal based on the KT/V urea index. These investigators have shown that stable blood chemistries can be achieved despite the marked reduction in treatment time. They have also shown that the incidence of intradialytic symptoms is lower or comparable to that achieved with standard acetate dialysis with durations of 12 hours per week. This comparable or lower incidence of intradialytic symptoms has been achieved because of the use of bicarbonate dialysis and

ultrafiltration control. No compromise in the achievement of dry weights has been noted by these investigators. As the data base reported in the literature for many of these other studies is still small, we will confine our discussion of clinical results to the results of our own dialysis program at Minnesota, because of our large clinical data base. We have a cumulative patient experience of more than 450 patients with rapid high efficiency dialysis, and in some of these patients our experience exceeds two years (42).

Our research with rapid high efficiency dialysis began in 1983 and by the end of 1985 we had converted approximately 85 - 90% of our chronic hemodialysis population to this mode of therapy. We currently have approximately 325 patients on rapid high efficiency therapy. The therapy prescription for this patient population is summarized in Table 1. The mean age of our patients is of the order of 59 years and approximately 80% of our patients are older than 50 years. Also, approximately 30% of our patients are diabetic. In spite of the age and co-morbid conditions of our patient population, we have been able to convert 85-90% of our patients to rapid high efficiency dialysis. We find that the only exclusion criteria are the inability of the blood access to deliver blood flows of the order of 300-400 ml/min, excessive weight gains of the order of 5-6 kg. and a high incidence of hypotension (30 - 50%) on bicarbonate dialysis with standard treatment durations of 12 hours per week.

Table 1.
Therapy Prescription at RKDP, Minneapolis
(N=325 patients)

Treament Time	=	165 minutes
(KT/V) urea	=	1.3
Vitamin B12 index	=	1.3
Urea Clearance	=	300 ml/min
Dialyzers		Baxter CA 170 & CA 210 (cellulose acetate)
Dialysate Na^+	=	142 mEq/l
Dialysate HCO_3	=	35 mEq/l

Biochemical Parameters

We have monitored patients for a period of two years and have been able to demonstrate that urea nitrogen, creatinine, total CO_2, phosphorous, calcium and potassium can all be controlled at levels comparable to those achieved with standard dialysis. Table 2 lists values for these serum chemistries over a period of two years in 26 patients demonstrating the stability of biochemical parameters despite the significant reduction in treatment time.

Table 2
Long Term Follow Up of Serum Chemistries
On Rapid High Efficiency Dialysis
(N = 26 patients, Mean ± SEM)

Serum Concentration	Control	6 months	12 months	24 months
BUN (mg/dl)	71 ± 2.8	71 ± 3.8	73 ± 3.8	72 ± 4.3
Creatinine (mg/dl)	11.0 ± 0.4	12.0 ± 0.5	11.7 ± 0.5	11.5 ± 0.4
Total CO_2 (mEq/l)	20 ± 0.4	20 ± 0.5	20 ± 0.5	20 ± 0.5
Phosphorus(mg/dl)	5.8±.03	5.6±0.4	5.6 ± 0.3	5.6 ± 0.5
Ca^{++} (mg/dl)	9.6 ± 0.2	9.9 ± 0.2	9.8 ± 0.2	9.8 ± 0.1
K^{+} (mEq/l)	5.5 ± 0.1	5.4 ± 0.1	5.3 ± 0.1	5.3 ± 0.1

Intradialytic Symptoms

Patients on rapid high efficiency dialysis have an incidence of intradialytic symptoms that are comparable to those on standard acetate dialysis. The incidence of symptoms on standard and high efficiency dialysis are compared in Table 3. Table 4 compares the incidence of intradialytic symptoms in our patient population on rapid dialysis to those of the French Registry (43) for standard dialysis. The incidence of symptoms on high efficiency dialysis is comparable or lower than those of the French Registry for standard dialysis.

Table 3.
Incidence (%) of Intradialytic Complications

Symptom	Standard Dialysis (N=4411 treatments)	Rapid High Efficiency Dialysis (N=5772 treatments)
Hypotension	21.6	17.9*
Nausea	5.0	3.0*
Vomiting	1.9	0.5*
Headaches	4.1	1.7*
Cramps	7.4	7.1

+ Systolic pr. < 90 mm Hg
* $p < 0.001$

Table 4.
Incidence (%) of Intradialytic Complications

Symptom	Standard Dialysis French Registry (N=135,321 treatments)	Rapid High Efficiency Dialysis (RKDP) (N=22,128 treatments)
Hypotension +	21.7	22.3
Symptomatic hypotension	--	7.8
Cramps	10.2	8.5*
Headaches	3.1	1.2*
Vomiting	4.6	0.7*

+ Systolic pr. < 90 mm Hg (RKDP)
< 80 mm Hg (French registry)
* $p < 0.001$

Hospitalizations

We have compared the frequency and duration of hospitalizations in 120 patients on standard and high efficiency dialysis. These results are shown in Table 5 and indicate that the frequency and duration of hospitalizations are comparable to those on standard dialysis. The morbidity of high efficiency dialysis is, therefore, comparable to that of standard dialysis.

Table 5.

Hospitalizations on Standard and High Efficiency Dialysis
(N = 120 patients)

	Frequency of Hospitalization (No. per pt. trt. year)	Days Hospitalized (No. per pt. trt. year)
Standard Dialysis (194 pt. trt. years)	1.58	15.8
Rapid High Efficiency Dialysis (164 pt. trt. years)	1.66	13.4*

Therapy Outcome

Therapy outcome in 450 patients treated with rapid high efficiency dialysis over an observation period of 12 months is summarized in Table 6. We note that at the end of the 12 month observation period, 73% of the patients remained on high efficiency dialysis, 12% died, 10% were transplanted, 3% were transferred, and 2.4% failed therapy. When we examine the causes of death in the 12% who died, we note that they are similar to those observed in our population on standard dialysis and are also similar to the causes of death reported by our dialysis network (44). Twenty-three percent of the deaths were cardiac deaths, 19% were of unknown etiology, 17% were related to discontinuation of dialysis, and 12% were because of sepsis. The therapy failure percentage is small and consists of patients with excessive weight gains, blood access problems, and those with a high incidence of complications on both standard and high efficiency dialysis.

Table 6.
Therapy Outcome
(N = 450 patients, observation period = 12 months)

Alive on rapid hemodialysis	73.1%
Deaths	11.6%
Transplants	9.6%
Transfers	3.3%
Therapy failures	2.4%
TOTAL	100%

Future of Rapid High Efficiency Hemodialysis

We estimate that in the United States 10%, or less, of the dialysis population is being treated with high efficiency hemodialysis. However, we believe that the percentage of patients treated with high efficiency dialysis will increase significantly in the next 2 to 3 years in a manner analogous to the increased application of dialyzer reuse. The strong patient preference for shorter durations of treatment in conjunction with the economic advantage of lower personnel costs with high efficiency therapies will contribute to this rapid growth in the application of high efficiency dialysis.

We do believe, that in some programs, treatment times may be shortened without due attention being paid to individualization of treatment times and adequacy of therapy prescription, so that some patients may be inadequately treated on shortened durations of dialysis. If careful attention is paid to the literature cited above on the successful application of high efficiency therapies, it is clear that adequate solute and fluid removal with a low incidence of intradialytic symptoms can be achieved with shortened durations of treatment.

The anticipated introduction of human erythropoietin (EPO) in the dialysis setting (45) will create some technical problems related to the successful application of high efficiency therapies. The higher blood viscosity associated with higher hematocrits may make the achievement of high blood flow rates more difficult, with higher pressures being encountered in the extracorporeal blood circuit. Clotting of dialyzers may also pose problems and successful multiple use of dialyzers may be compromised. However, with improvements in dialyzer design specific to the increased hematocrits and viscosities associated with the use of EPO, these technical difficulties are not insurmountable. It will be necessary to document that with higher hematocrits, the resulting solute clearances are adequate for the shortened durations of treatment.

With appropriate equipment and with due attention paid to therapy prescription and individualization of treatment time, we believe that the increased sense of well-being related to the correction of anemia with EPO along with the decreased time associated with the dialysis procedure, will improve the quality of life of the dialysis patient significantly. We believe that the combination of EPO and rapid dialysis will change the future of dialysis in a most favorable direction.

REFERENCES:

1. Wakim, K.C. The pathophysiology of the dialysis disequilibrium syndrome. Mayo Clin Proc 44:406-429, 1969.
2. Arieff, A. Neurological complications in uremia. In: The Kidney (Eds. B. Brenner and F. Rector), W.B. Saunders, Philadelphia, p. 2324, 1981.
3. Kim, K.E., Neff, M., Cohen, B., et. al. Blood volume changes and hypotension during hemodialysis. Trans Amer Soc Artif Int Organs 16:508-522, 1970.
4. Henderson, L.W. Symptomatic hypotension during hemodialysis. Kidney Int 17:571-576, 1980.
5. Keshaviah, P., Shapiro, F. A critical examination of dialysis-induced hypotension. Am J Kidney Dis 2:290-301, 1982.
6. Kjellstrand, C. Can hypotension during dialysis be avoided? Controversies in Nephrology 2:12-28, 1980.
7. Liang, C.S., Lowenstein, J.M. Metabolic control of the circulation: Effects of acetate and pyruvate. J Clin Inves 62:1029-1038, 1978.
8. von Albertini, B., Miller, J.H., Gardner, P.W., Shinaberger, J.G. High-flux hemodiafiltration: Under six hours per week treatment. Trans Am Soc Artif Intern Organs 30:227, 1984.
9. Miller, J.H., von Albertini, B., Gardner, P.W., Shinaberger, J.H. Technical aspects of high-flux hemodiafiltration for adequate short (under 2 hours) treatment. Trans Am Soc Artif Intern Organs 30:377-381, 1984.
10. Keshaviah, P., Berkseth, R., Ilstrup, K., McMichael, C., Collins, A. Reduced treatment time: Hemodialysis (HD) versus hemofiltration (HF). Trans Am Soc Artif Intern Organs 31:176-182, 1985.
11. Collins, C., Keshaviah, P., Berkseth, R., Ilstrup, K., McMichael, C., Ebben, J. Short efficiency hemodialysis with reduced symptoms (Abstract). Kidney Int 27:158, 1985.
12. Keshaviah, P., Collins, A. Rapid high-efficiency bicarbonate hemodialysis. Trans Am Soc Artif Intern Organs 32:17-23, 1986.
13. Keshaviah, P.R., Davis-Pollack, R., Luhring, D., Lee, P. A practical guide to rapid high efficiency dialysis. (Regional Kidney Disease Program, Minneapolis Medical Research Foundation, Minneapolis, 1987).
14. Rotellar, E., Martinez, E., Samso, J.H., et. al. Why dialyze more than 6 hours a week? Trans Am Soc Artif Intern Organs 31:538, 1985.
15. Campbell, J., Dumler, F., Stall, K., Levin, N.W. High flux short time hemodialysis: Initial clinical experience (Abstract). 19th Annual Meeting of The American Society of Nephrology, December 1986.
16. Keen, M., Evans, M., Gotch, F., Davies, R.K. Comparison of morbidity in high flux dialysis (HFD) and conventional dialysis (CD) (Abstract). 19th Annual Meeting of The American Society of Nephrology, December 1986.

17. Arief, A.I., Massry, S.G., Barrientos, A., Kleeman, C.R. Brain water and electrolyte metabolism in uremia. Effects of slow and rapid hemodialysis. Kidney Int 4:177-187, 1973.
18. Keshaviah, P.R., Ilstrup, K.M., Shapiro, F.L. Dynamics of vascular refilling. Progress Artif Organs 2:506, 1983.
19. Van Stone, J.C., Bauer, J., Carey, J. The effects of dialysate sodium concentration on body fluid distribution during hemodialysis. Trans Am Soc Artif intern Organs 26:383-386, 1980.
20. Kersch, E.S., Kronfield, S.J., Unger, A., et. al. Autonomic insufficiency in uremia as a cause of hemodialysis-induced hypotension. N Engl J Med 290:650-653, 1974.
21. Keshaviah, P., Ilstrup, K., Berkseth, R., et. al. Transcompartmental fluid shifts induced by ultrafiltration (UF) and diffusion (D). Abstract, 11th Annual Meeting of The American Society of Nephrology, p. 43A, 1978.
22. Baldamus, C.A., Ernst, W., Fassbinder, W., Koch, K.M. Differing haemodynamic stability due to differing sympathetic response. Comparison of ultrafiltration,haemodialysis and haemofiltration. Proc Eur Dial Transplant Assoc 17:205-212, 1980.
23. Graefe, U., Milutenovic, J., Follette, W.C., et. al. Less dialysis induced morbidity and vascular instability with bicarbonate in dialysate. Ann Intern Med 88:332-336, 1978.
24. Ebben, J., Hirsch, D., Luehmann, D., Collins, A.J., Keshaviah, P.R. Microbiological contamination of liquid bicarbonate concentrate for hemodialysis. Trans Am Soc Artif Intern Organs 33:269-273, 1987.
25. Bland, L., Ridgeway, M., Aguero, S., Carson, L., Favero, M. Potential bacteriologic and endotoxin hazards associated with liquid bicarbonate concentrate. Trans Am Soc Artif Intern Organs 33:542-545, 1987.
26. Man, N.K., Ciancioni, C., Faivre, J.M., Diab, N., London, G., Maret, J., Wambergue, F.P. Dialysis-associated adverse reactions with high-flux membranes and microbial contamination of liquid bicarbonate concentrate. In: Contr Nephrol (Eds. M.E. Debroe, M. Foret, M.D. Kazatchkine, and G. Laurent), Karger, Basel, pp. 24-34, 1988.
27. Luehmann, D., Hirsch, D., Ebben, J., Collins, A., Keshaviah, P. Hybrid hardware scheme for bicarbonate dialysis. Progress in Artif Organs, pp. 188-191, 1985.
28. Steward, W.K., Fleming, L.W., Manuel, M.A. Benefits obtained by the use of high sodium dialysate during maintenance hemodialysis. Proc Eur Dial Transplant Assoc 9:111, 1972.
29. Wehle, B., Asaba, H., Castenfors, J., Furst, P., Grahn, A., Gunarsson, B., Shaldon, S., Bergstrom, J. The influence of dialysis fluid composition on the blood pressure response during dialysis. Clin Nephrol 10:62-66, 1978.

30. Berkseth, R., Luehmann, D., McMichael, C., Keshaviah, P., Kjellstrand, C. Peracetic acid for reuse of hemodialyzers clinical studies. Trans Am Soc Artif Intern Organs 30:270-275, 1984.
31. Gotch, F.A., Sargent, J.A., Peters, J.H. Studies on the molecular etiology of uremia. Kidney Int 7 (suppl 3):S276-S279, 1975.
32. Lowrie, E.G., Laird, N.M., Parker, T.F., Sargent, J.A. Effect of the hemodialysis prescription on patient morbidity. N Engl J Med 20:1176-1181, 1981.
33. Scribner, B.H., Baccay, P.C., Holar, E.M., et. al. The current status of research on middle molecules. Workshop on Dialysis and Transplantation. Amer Soc Artif Intern Organs 1:76-79, 1972.
34. Babb, A.L., Strand, M.J., Uvelli, D.A., et. al. Quantitative description of dialysis treatment: A dialysis index. Kidney Int 7 (suppl 3):S23-S29, 1975.
35. Gotch, F., Sargent, J.A. A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). Kidney Int 28:526-534, 1985.
36. Gejyo, F., Odani, S., Yamada, T., Honma, N., Saito, H., Suzuki, Y., Nakahawa, Y., Kobayashi, H., Maruyama, Y., Hirasawa, H., Suzuki, M., Arakawa, M. Beta-2-microglobulin: A new form of amyloid protein associated with chronic hemodialysis. Kidney Int 30:385-390, 1986.
37. Bardin, T., Zingraff, J., Kuntz, D., Drueke, T. Dialysis-related amyloidosis. Nephrol Dial Transplant 1:151-154, 1986.
38. Hauglustaine, D., Waer, M., Michielsen, P., Goebels, J., Vandeputte, M. Haemodialysis membranes, serum Beta-2-microglobulin, and dialysis amyloidosis. Lancet 1:1211, 1986.
39. Rowe, I.F. Synovial amyloid deposits and chronic hemodialysis. Ann Rheum Dis 45:438, 1986.
40. Karnofsky, D.A., Burchenal, J.H. The clinical evaluation of chemotherapeutic agents in cancer. In: Evaluation of Chemotherapeutic Agents (Ed. C.M. Macleod), Columbia University Press, New York, pp. 191-205, 1949.
41. Collins, A., Hanson, G., Berkseth, R., Keshaviah, P. Recirculation and effective clearances (Abstract). Am Soc of Nephrol, p. 72, 1987.
42. Keshaviah, P., Collins, A. High efficiency hemodialysis, contributions to nephrology. (Eds. G. D'Amico and G. Colasanti), presented at the 19th course on Advances in Nephrology and Dialysis, 1987, In Press.
43. Hakim, R.M., Lazarus, J.M. Complications during hemodialysis. In: Clinical Dialysis (Eds. A.R. Nissenson, R.N. Fine, and D.E. Gentile), Appleton-Century-Crofts, Norwalk, pp. 179-220, 1984.
44. Carlson, D.M., Duncan, D.A., Naessens, J.M., Johnson, W.J. Hospitalization in dialysis patients. Mayo Clin Proc 59:769-775, 1984.
45. Eschbach, J.W., Egrie, J.E., Downing, M.R., et. al. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin: Results of a combined phase I and II clinical trial. N Engl J Med 316:73-78, 1987.

14

HAS CPD* BEEN AS EFFECTIVE AS HEMODIALYSIS?

ALLEN R. NISSENSON, M.D.

Division of Nephrology, Department of Medicine, UCLA School of Medicine, Los Angeles, California, USA

INTRODUCTION

Since its inception in 1976(1), continuous ambulatory peritoneal dialysis (CAPD) and its variants CCPD and APD* have progressively developed into accepted ESRD treatment modalities. By the end of 1987 over 40,000 patients worldwide were maintained on this form of therapy, representing nearly 20% of all dialysis patients(2). Marked variations exist in the application of CPD with less than 10% of patients in Japan, Germany and Italy on this modality compared to over 40% of patients in the United Kingdom, New Zealand, Finland, Venezuela and Mexico. In the United States 17% of patients were on CPD at the end of 1987(2).

Much has been learned about CPD in the past 12 years. Many patients have been on CPD for over 5 years demonstrating the long term viability of the peritoneal membrane. Complication rates have steadily declined.

---

*For purposes of this presentation, CPD will be used to include continuous ambulatory peritoneal dialysis, continuous cycling peritoneal dialysis (CCPD) and automated peritoneal dialysis (APD).

For example, peritonitis rates have decreased 29% between 1982 and 1986, exit-site/tunnel infection rates 33%, and CAPD related hospital days 50%(3). Despite these encouraging trends, it has been difficult to determine if CPD is comparable to hemodialysis as an ESRD treatment.
Unfortunately, no controlled trials have been performed to help answer this question and it is unlikely that any will. What follows is an overview of the available literature in this area focusing on those studies where attempts are made to evaluate equivalent or matched patients on these modalities or where adjustment for modality selection bias is attempted. While not optimal from a scientific standpoint, such approaches do permit some conclusions to be drawn regarding the relative efficacy of CPD and HD as ESRD modalities.

PHYSIOLOGICAL DIFFERENCES BETWEEN CPD AND HD

There are major differences in the physiology of solute and water removal between CPD and HD. CPD relies on the "peritoneal membrane" as a dialyzing surface. This structure is poorly defined consisting of at least two cell layers (the capillary endothelium and the peritoneal mesothelium) separated by an interstitium.
Solutes traverse endothelial and mesothelial intercellular channels with the former the major barrier to large solute transport. Transport of small solutes is limited by stagnant layers of dialysate in the peritoneal cavity and can be enhanced by increasing dialysate flow rate(4). Ultrafiltration of fluid during CPD proceeds because of the high osmotic gradient created by the glucose containing dialysate (1.5%, 2.5% or 4.25%

dextrose)(5). Lymphatic reabsorption occurs at a rate of 10-40 ml/hr. and in part offsets the ultrafiltration that occurs(6).

Hemodialysis, when performed with conventional dialysis membranes, differs substantially from CPD in its efficiency for solute removal. For solutes up to 1000 daltons, HD far exceeds CPD in the rate of solute removal, whereas, for larger solutes, HD falls significantly behind, particularly as solute molecular weight exceeds 5000 daltons. Ultrafiltration with HD results from changes in transmembrane pressure induced by either positive pressure in the blood or negative pressure in the dialysate compartment(7).

To overcome the low small solute clearance when PD is used (urea clearance less than 30ml/min), CPD increases the time dialysis is taking place to 168 hours per week. This results in a weekly urea clearance of approximately 70 liters compared to 110-120 liters with HD. Concomitantly, larger solute weekly clearance (e.g. inulin, 5200 daltons) approaches 30 liters with CPD, but only 5-10 liters with HD.

Additional differences between CAPD and HD are the blood membrane interaction, need for heparinization, vascular access and use of acetate buffer in the latter, and the need for peritoneal access, use of lactate buffer and hypertonic, acidic dialysate in the former. Neither form of dialysis is able to replace the metabolic or endocrine functions of normal kidneys.

Using hemodialyis as the standard, therefore, has CPD equaled HD in terms of patient survival and morbidity? The remainder of this chapter will

attempt to critically address this question.

CONTROLLED CLINICAL COMPARISONS

There have not been, nor are there likely to be any controlled trials to compare patient outcome on HD vs. CPD. It is worth reviewing, however, such a study that compared HD and intermittent peritoneal dialysis(IPD)(8). Thirty-two patients with ESRD judged to be suitable for HD or IPD were prospectively, randomly assigned to either modality of therapy and followed for from 24 to 90 weeks. Hemodialysis patients received a dose of dialysis that could be considered "adequate" by current standards. IPD patients received 30 hours of treatment weekly divided into three 10 hour sessions, each consisting of 25-40 liters of dialysate flow. Four of 16 IPD and 2 of 16 HD patients died during the study. Hospitalizations and other aspects of morbidity were similar in the two groups. IPD patients had more normal levels of BUN, potassium, bicarbonate and hematocrit, while HD patients had more normal levels of albumin and calcium. Neurobehavioral abnormalities occurred in both groups. In summary, except for minor differences in biochemical parameters, minimal outcome differences were noted. This study suffers from a small number of patients and short follow-up time, but does show that IPD and HD are equally effective at least on the short term in patients who are suitable for either form of treatment.

UNCONTROLLED CLINICAL COMPARISONS

Only uncontrolled comparisons are available for morbidity and mortality of HD and CPD patients. In 1983, a Special Symposium on Morbidity and Mortality in dialysis treatment was held at the American

Society for Artificial Internal Organs meeting(9). Data was presented on a "standard population" of patients: 1) Age 20-60; 2) No systemic disease leading to renal failure; 3) No history of cerebrovascular or cardiovascular disease; 4) No history of cancer; 5) No serious pre-existing diseases. The results of this Symposium as well as other data in the literature comparing mortality of patients on CPD vs. other dialysis modalities are summarized in Table 1.

It is apparent that there is a wide variation in patient survival on a given modality from study to study. This illustrates the marked differences in patient selection criteria, and therefore, patient characteristics represented by these publications. Overall, however, there appears to be little difference in patient outcome between CPD and other dialysis modalities. Burton et al (21) evaluated the effect of modality on survival by adjusting the data in their patient population for selection bias and performing a Cox analysis. They identified nine independent variables as having a significant influence on survival: age, presence of amyloidosis, ischemic heart disease, seizures and an acute presentation adversely affected survival while male sex, parenthood, pyelonephritis and place of residence improved survival. When the influence of these variables was corrected for, the relative risk of death for patients on CAPD was 1 and HD 1.30. These risks were not different statistically, further illustrating the comparability of CPD to HD in terms of patient survival. These survival data are all short-term for CPD, however. Whether long-term survival will remain comparable to HD remains to be seen.

TABLE 1: Survival of CPD vs. HD Patients*

Ref.	Type of Dial.	Time (yrs.)	Age** (yrs.)	Diabetics** (%)	Survival** (%)	Comments
10	HHD	2	44	5	85	Computer matching of CAPD to HHD patients
	Center self care HD	2	44	5	66	
	CAPD	2	44	5	59	
11	CHD and HHD	2	20 to 60	0	90	Asaio Symposium
12	CHD and HHD	2	20 to 60	0	94	Asaio Symposium
13	CAPD	2	20 to 60	0	100	Asaio Symposium
14	CHD	2	20 to 60	0	92	Asaio Symposium
	HHD	2	20 to 60	0	98	
	CAPD	2	20 to 60	0	90	
15	CHD and HHD	1	20 to 60	0	90	Asaio Symposium
	CAPD	1	20 to 60	0	98	
16	CAPD	1	20 to 60	0	94	Asaio Symposium
17	CAPD	2	Matched	Matched	92	Retrospective matching. Includes elderly patients
	CHD	2	Matched	Matched	94	
18	HF	2	50	32	91	Asaio Symposium
	CAPD	2	42	34	79	
19	HHD	2	48	0	96	No matching performed. Patients chose the dial. modality.
	CAPD	2	50	0	91	

Ref.	Type of Dial.	Time (yrs.)	Age** (yrs.)	Diabetics** (%)	Survival** (%)	Comments
20	CHD and HHD	2	15 to 44	0	90	Patient selection criteria varied from center to center. Patient matching was not done.
	CAPD	2	15 to 44	0	91	
	CHD and HHD	2	45 to 64	0	78	
	CAPD	2	45 to 64	0	80	
	CHD and HHD	2	65+	0	44	
	CAPD	2	65+	0	58	
21	CHD and HHD	2	42	4	87	These raw survival figures when adjusted for risk factors show no difference between HD and CAPD (see text).
	CAPD	2	51	12	80	
22	CHD and HHD	2	43	5	85	No patient matching was done - widely different patient characteristics.
	CAPD	2	47	16	85	
23	CHDH	2	52	49	70	Patients at different centers were compared. Vastly different patient character-istics.
	CHDW	2	45	14	55	
	CPD	2	48	19	82	

*HHD=Home Hemodialysis; CHD=Center hemodialysis; CAPD=Continuous ambulatory peritoneal dialysis; CPD=Continuous peritoneal dialysis (CAPD, CCPD and/or APD);HF=Hemofiltration; CHDH=Center hemodialysis, Honolulu, Hawaii; CHDW=Center hemodialysis, Washington, D.C., Modified with permission from reference 24a.

** Figures rounded-off

TABLE 2: Hospitalizations in CPD vs. HD Patients*

Reference	Type of Dialysis	Age** (yrs)	Diabetics** (%)	Total days/yr**	Days for dialysis complications**
11	CHD	-	-	19	
	HHD	-	-	9	-
	CAPD	-	-	20	-
13	CAPD	20 to 60	0	3 to 17	1 to 10
14	CAPD	20 to 60	0	22	-
	CHD	20 to 60	0	11	-
	HHD	20 to 60	0	15	-
16	CAPD	20 to 60	0	14 to 25	8 to 10
18	HF	50	32	23	8
	CAPD	42	34	29	11
19	HHD	48	0	5	2
	CAPD	50	0	10	6
22	CHD and HHD	43	5	16	6
	CAPD	47	16	18	8
24	CAPD	-	24	19	8

*See Table 1 for explanation of abbreviations. Modified with permission from reference 24a.

**Figures rounded-off

There are several areas of morbidity that have been compared in CPD and HD patients. Essentially all such studies suffer from a lack of ramdomized patient assignment or no attempt at patient matching. Nevertheless, many of the data are interesting and worthy of review.

Hospitalizations: Hospitalization is a major source of morbidity for the ESRD patient. Table 2 summarizes data on hospitalization rates reported from several of the studies cited in Table 1.

The differences between CPD and other modalities are not striking, though there is clearly a tendency for more hospital days for the CPD patients. Some of this clearly represents programmatic considerations rather than actual medical necessity, particularly related to hospitalization for peritonitis(25). In addition, differences in patient mix on CPD vs. other modalities may further confound the results.

Modality Success: CPD has been characterized as successful on the short term, but associated with a high drop-out rate. Table 3 summarizes comparative drop-out rates for CPD and other dialysis modalities.

When viewed uncritically, home HD seems to be a longer-lived modality than center HD or CPD. Whether this reflects patient selection bias, the ease with which patients can transfer from CPD to HD or true modality differences cannot be resolved from the available data. Similarly, CPD seems to be longer-lived than CHD, but the trend is less marked.

MISCELLANEOUS ABNORMALITIES ON ESRD PATIENTS

A number of abnormalities in ESRD patients have been compared in those on CPD vs. HD. Most studies make little or no attempt to match patients and results are primarily descriptive. Some of these results are summarized in Table 4.

TABLE 3: Modality Success in CPD vs. HD Patients*

Ref.	Type of Dial.	Time (yrs)	Age** (yrs)	Diabetics** (%)	Patients still on dialysis*(%)	Comments
13	CAPD	2	22 to 60	0	88	Includes death or transfer to another dialysis modality.
14	HHD	2	20 to 60	0	90	Same as above
	CHD	2	20 to 60	0	80	
	CAPD	2	20 to 60	0	50	
15	CAPD	2	50 to 60	0	55	Same as above
	CAPD[a]	2	20 to 60	0	67	
16	CAPD	1.5	20 to 60	0	58	Same as above
20	CHD and HHD	2	15 to 44	0	85	Deaths and trans-plantation considered "lost-to-follow-up".
	CAPD	2	15 to 44	0	57	
	CHD and HHD	2	45 to 64	0	72	
	CAPD	2	45 to 64	0	65	
	CHD and HHD	2	65+	0	72	
	CAPD	2	65+	0	72	

Ref.	Type of Dial.	Time (yrs)	Age** (yrs)	Diabetics** (%)	Patients still on dialysis*(%)	Comments
22	CHD and HHD	2	43	16	90	Same as above
	CAPD	2	47	18	78	
24	CAPD	2	20 to 59	22	46	Includes death or transfer to another dialysis modality.
26	HHD	2	36	0	78	Same as above
	CAPD	2	36	0	36	

*See Table 1 for explanation of abbreviations. Modified with permission from reference 24a.

**Figures rounded-off a=started CAPD in 1981

TABLE 4: EFFECTS OF CPD OR HD ON ESRD PATIENTS

CPD	HD	Reference
RESUMPTION OF MENSES		27
↓↓ T3 ↓ T4 ↓ rT3	↓↓ T3 ↓↓ T4 ↓ rT3	28
↑RENIN ↑ALDOSTERONE ↑↑18-HYDROXYCORTICOSTERONE		29
EOSINOPHILIA (CCPD>CAPD)	EOSINOPHILIA (HD>CPD)	30
IMPROVED RENAL OSTEODYSTROPHY		31
ACQUIRED CYSTIC DISEASE	ACQUIRED CYSTIC DISEASE	32

As is apparent, the differences seen are either minor in nature (thyroid function tests), predictable based on the differing physiology of HD and CPD (renin-angiotensin system) or need further clarification and confirmation (renal osteodystrophy). From a purely medical perspective, these studies do not provide a clear difference between CPD and HD.

NEUROLOGICAL FUNCTION

A single study has attemped to compare objective brain function in CPD vs. HD patients(33). Subjects were matched for a variety of characteristics and then a battery of evoked and event-related potential measures were used to measure brain function. With tasks involving simple stimuli, HD patients had significantly less efficient brain functioning than did CPD patients. As task complexity increased, modality differences disappeared. These results are quite intriguing and, if confirmed in larger groups of patients, would provide a clear objective advantage of CPD over HD.

QUALITY OF LIFE/REHABILITATION

More data are available on comparative psychosocial adaptation and rehabilitation of CPD vs. HD patients. These studies are for the most part well designed and many involved matched patients. Their findings are summarized in Table 5.

Home dialysis is associated with higher levels of patient adaptation and quality of life than in-center dialysis. Of the home modalities, neither CPD nor HHD seems superior in this regard.

CPD vs. HD IN SPECIAL CIRCUMSTANCES

Elderly patients: the widespread use of CPD has had a major impact on the elderly patient with ESRD. In some countries, patients previously excluded from

TABLE 5: PSYCHOSOCIAL ADAPTATION in CPD vs. HD Patients

Reference	NUMBER OF PATIENTS CHD	HHD	CPD	Results	Comments
34	-	37	40	CPD patients better adapted than those on HHD	Matched for time on dialysis, demographics.
35	-	150	89	Higher stress in HHD patients; lower employment in CPD patients	Unmatched, retrospective study.
36	70	-	251	More favorable adjustment for CPD vs. HD patients	Questionnaire data.
37	42	-	17	Similar "worth" for CHD and CPD (see comments)	Modified version of the time trade-off technique whereby the worth of a given health state is evaluated by the patient.
38	347	287	81	Both home modalities had higher subjective quality of life than CHD. HHD had much greater patient ability to work than CAPD	Adjustment for case-mix was made.

	NUMBER OF PATIENTS				
Reference	CHD	HHD	CPD	Results	Comments
39	208	-	46	CAPD patients had slightly better adaptation than CHD patients, but not statistically significant.	Similar demographics, but not matched.
40	77 at start, 65 at end	11 at start, 7 at end	1 at start, 5 at end	HHD patients had the highest quality of life over an 18 month interval	Small sample size for HHD and CPD make results difficult to interpret.
41	63	29	34	Little difference between CHD, HHD and CPD patients in adjustment to dialysis, vocational or social rehabilitation	Home patients (CPD or HHD) were matched to CHD patients. All patients in study were married and spouses were interviewed.
42	33	-	33	CPD patients had higher quality of life and lower illness and modality related stress. CPD patients were more likely to be vocationally active	Patients matched for demographic and medical variables.

ESRD care now receive it with excellent survival results(43). Few direct comparisons of elderly patient morbidity and mortality exist for CPD vs. HD. On the short term, IPD was found comparable to HD, but inferior after one year(44). In this study, however, patient selection was a crucial factor, with significantly sicker patients being placed on IPD. On the other hand, the Canadian Registry Data showed equivalent technique survival and better patient survival for the elderly on CPD compared to HD(20). The reported advantages of CPD in the elderly include: excellent blood pressure control, slow continuous fluid removal, higher hematocrit and no need for anticoagulation. The disadvantages in this age group include: possible vascular ischemia, hernias, fluid leaks and poor tolerance of peritonitis(45). In addition, hemodialysis in-center offers the elderly the opportunity for social contact and interaction with other patients that often is important. At the present time, neither HD nor CPD is clearly superior for the elderly patient. In spite of this, and the fact that many nephrologists feel that CPD is the treatment of choice for the elderly(46), it remains far less utilized than center HD in this population.

Diabetics: On a theoretical basis, CPD would seem superior to HD for patients with diabetes(47). CPD provides excellent blood pressure control, tight glucose control with intra-peritoneal insulin, slow continuous fluid removal and avoidance of heparin and potential vascular access problems. Unfortunately, however, no study has compared the outcome of matched diabetic patients on CPD vs. HD. The best comparative study was published recently and reviewed the experience with 71 diabetic patients placed on

CPD (N=34) or HD (N=37) at a single medical center over a 5 year period(48). Only patients who received CPD or HD as an initial dialysis modalilty were included in the analysis, and demographic features of the two groups were similar. Survival was significantly better in the CPD compared to the HD group (81% vs. 76% one-year; 81% vs. 40% three-year). Excluding initial hospitalization in the CPD group for catheter placement and training, the CPD patients spent fewer days in the hospital than the HD patients. In addition, access repairs (vascular vs. peritoneal) were more common in the HD group. Finally, technique success in the CPD group was 71% for one, two and three years, while in the HD group it was 76%, 54% and 18% respectively for the same time periods. These results are quite intriguing, but involve small numbers of patients and need further verification in larger, multi-center studies.

SUMMARY AND CONCLUSIONS

Has CAPD been as effective as hemodialysis? The data reviewed above clearly demonstrate why this question cannot be answered with scientific certainty - no prospective, randomized, controlled trials in equivalent patients have been or are likely to be carried out. Based on the imperfect data available, however, some tentative conclusions can be drawn:

1. Despite differences in small and large solute mass transport with CPD vs. HD, no striking differences in the amilioration of the manifestations of uremia are apparent between these two modalities, with the possible exception of improved brain function with CPD.
2. Mortality of patients with similar risk factors is the same whether CPD or HD is used.
3. Morbidity as measured by hospitalization rate and technique success is slightly less with HD vs.

CPD, although this is most true for HHD rather than CHD, suggesting patient selection bias, rather than modality per se as causal.

4. Patient adaptation to chronic renal failure is poorest when CHD is used and better with CPD. Significant abnormalities of psychosocial function and inadequate rehabilitation remain with all dialysis modalities.
5. Special groups including the elderly and diabetics receive unique benefits from CPD, though more careful study of these populations are needed to see whether these benefits result in objective improvement in morbidity over that seen with CHD.

It should be apparent, then, that both CPD and HD offer adequate treatment of renal failure. The challenge to the nephrologist and health care team is to select patients prospectively who are most likely to succeed on one modality or the other. This will require a better understanding of the risk factors that lead to morbidity and modality failure and application of this knowledge to the patient selection process. Either treatment performed properly and carefully in appropriately selected patients will be successful and maximize the patient's health and quality of life.

REFERENCES:

1. Popovich, R.P., Moncrief, J.W., Decherd, J.F., Bomar, J.B. and Pyle, W.K. The definition of a novel portable/wearable equilibrium dialysis technique. Abst. Trans. Amer. Soc. Artif. Int. Organs 5:64, 1976.
2. Baxter-Travenol, Deerfield, Illinois, data on file.
3. Nolph, K.D., Cutler, S.J., Steinberg, S.M. and Novak, J.W. Special studies from the NIH USA CAPD registry. Perit. Dial. Bull. 6:28-34, 1986.
4. Nolph, K.D., Popovich, R.P., Ghods, A.J. and Twardowski, Z. Determinants of low clearances of small solutes during peritoneal dialysis. Kidney Int. 13:117-124, 1978.

5. Nolph, K.D., Miller, F.N., Pyle, W.K. and Sorkin, M.I. An hypothesis to explain the ultrafiltration characteristics of peritoneal dialysis. Kidney Int. 20:543-546, 1981.
6. Mactier, R.A., Khanna, R., Twardowski, Z.J. and Nolph, K.D. Role of peritoneal cavity lymphatic absorption in peritoneal dialysis. Kidney Int. 32:165-169, 1987.
7. Easterling, R.E. Mechanical aspects of dialysis including dialysate delivery systems and water for dialysis. In: Clinical Dialysis (Eds. A.R. Nissenson, R.N. Fine and D.E. Gentile), Appleton-Century-Crofts Publishers, Norwalk,1984, pp. 82-83.
8. Roxe, D.M., DelGreco, F., Hughes, J., Krumlovsky, F., Ghantous, W., Ivanovich, P., Quintanilla, A., Salkin, M., Stone, N.J. and Reins, M. Hemodialysis vs. peritoneal dialysis: Results of a 3-year prospective controlled study. Kidney Int. 19:341-348, 1981.
9. Kjellstrand, C.M. Introduction to a workshop on morbidity and mortality in hemodialysis, hemofiltration and continuous ambulatory peritoneal dialysis. asaio J. 6:167-169, 1983.
10. Capelli, J.P., Camiscioli, T.C. and Vallorani, R.D. Comparative analysis of survival on home hemodialysis, in-center hemodialysis and chronic peritoneal dialysis (CAPD-IPD) therapies. Proc. Eur. Dial. Transplant. Assoc. 14:38-52, 1985.
11. Blagg, C.R., Wahl, P.W. and Lamers, J.Y. Treatment of chronic renal failure at the Northwest Kidney Center, Seattle, from 1960-1982. asaio J. 6:170-175, 1983.
12. Shapiro, F.L. and Umen, A. Risk factors in hemodialysis patient survival. asaio J. 6:176-184, 1983.
13. Khanna, R., Wu, G., Vas, S. and Oreopoulos, D.G. Mortality and morbidity on continuous ambulatory peritoneal dialysis. asaio J. 6:197-204, 1983.
14. Mion, C.M., Mourad, G. and Canaud, B. Maintenance dialyis: a survey of 17 years experience in Languedoc-Roussillon with a comparison of methods in a standard population. asaio J. 6:205-213, 1983.
15. Wing, A.J., Broyer, M. and Brunner, F.P. The contribution of continuous ambulatory peritoneal dialysis in Europe. asaio J. 6:214-219, 1983.
16. Nolph, K.D., Pyle, W.K. and Hiatt, M. Mortality and morbidity in continuous ambulatory peritoneal dialysis: Full and selected Registry populations. asaio J. 6:220-226, 1983.
17. Kramer, P, Broyer, M., Brunner, F.P., Brynger, H., Oules, R., Rizzoni G., Selwood, N.H., Wing,

A.J. and Balas,E.A. Combined report on regular dialysis and transplantation in Europe, XIV, 1983. Proc. Eur. Dial. Transplant. Assoc. 21:2-68, 1983.
18. Quellhorst, E.A., Schuenemann, B. and Hildebrand, V. Morbidity and mortality in long-term hemofiltration. asaio J. 6:185-191, 1983.
19. Kurtz, S.B. and Johnson, W.J. A four-year comparison of continuous ambulatory peritoneal dialysis and home hemodialysis: A preliminary report. Mayo Clinic Proc. 59:659-662,1984.
20. Schriel, J., Sillins, J., Colburn, H.N., Posen,G.A. and Cole, A.E. Canadian Renal Failure Register, 1985 Report, Kidney Foundation of Canada Publication, 1986.
21. Burton, P.R. and Walls, J. Selection-adjusted comparison of life-expectancy of patients on continuous ambulatory peritoneal dialysis, hemodialysis, and renal transplantation. Lancet 1:1115-1119, 1987.
22. Gokol, R., Lloyd, C., Baillod, R., Marsh, F., Ogg, C., Oliver, D., Ward, M. and Wilkinson, R. Multi-center study on the outcome of patients on CAPD and hemodialysis. In: Frontiers in Peritoneal Dialysis (Eds. J.F. Maher and J.F. Winchester), Field, Rich and Associates, Inc., New York, 1986, pp. 293-296.
23. Mackow, R.C., Argy, W.P., Rakowski, T.A., Winchester, J.F., Chester, A.C., Siemsen, A.S., Jenkins, S. and Schreiner, G.E. Prognostic correlates in ambulatory peritoneal dialysis versus hemodialysis. In: Frontiers Peritoneal Dialysis (Eds. J.F. Maher and J.F. Winchester), Field, Rich and Associates, Inc., New York, 1986, pp. 341-346.
24a. Nolph, K.D. Comparison of continuous ambulatory peritoneal dialysis and hemodialysis. Kidney Int. 33 (Suppl.24):S123-S131, 1988.
24b. Nolph, K.D., Prowant, B., Novak, J.W., Lindblod, A.S., Cutler, S.J., Stablein, D.M., Denekas, M.L. and Deffenbaugh, R. Report of the National CAPD Registry of the NIH, 1987, p.4-4.
25. Nissenson, A.R., Gentile, D.E., Soderblom, R. and Brax, C. Long-term morbidity and mortality of CAPD patients. Amer. J. Kid. Dis. 3:229-235, 1986.
26. Rubin, J., Barnes, T. and Bower, J. Morbidity and mortality in CAPD and home hemodialysis. asaio J. 8:22-27, 1985.
27. Galler, M., Spinowitz, B., Charytan, C., Kabadi, M. and Freeman, R. Reproductive function in dialysis patients: CAPD vs. hemodialysis. Perit. Dial. Bull. 3 (Suppl.):S30-S32, 1983.

28. Charytan, C., Thysen, B., Gatz, M., Freeman, R. and Alpert, B.E. Thyroid function tests in uremic patients on maintenance dialysis: A comparison of CAPD and hemodialysis. Perit. Dial. Bull. 3 (Suppl.): S27-S29, 1983.
29. Zager, P.G., Frey, J. and Gerdes, G. Plasma concentrations of 18-hydroxycorticosterone and aldosterone in continuous ambulatory peritoneal dialysis and hemodialysis patients. Amer. J. Kid. Dis. 3:213-218, 1983.
30. Backenroth, R., Spinowitz, B.S., Galler, M., Golden, R.A., Rascoff, J.H. and Charytan, C. Comparison of eosinophilia in patients undergoing peritoneal dialysis and hemodialysis. Amer. J. Kid. Dis. 8:186-191, 1986.
31. Shusterman, N.H., Wasserstein, A.G., Morrison, G., Audet, P., Fallon, M.D. and Kaplan, F. Controlled study of renal osteodystrophy in patients undergoing dialysis: Improved response to continuous ambulatory peritoneal dialysis compared with hemodialysis. Amer. J. Med. 82:1148-1156, 1987.
32. Truong, L.D., Ansari, Q., Ansari, J., Wheeler, T.M., Mattioli, C.M. and Gillum, D. Acquired cystic kidney disease: Occurence in patients on chronic peritoneal dialysis. Amer. J. Kid. Dis. 11:192-195, 1988.
33. Marsh, J.T., Brown, W.S., Wolcott, D., Landsverk, J. and Nissenson, A.R. Electrophysiological indices of CNS function in hemodialysis and CAPD. Kidney Int. 30:957-963, 1986.
34. Burton, H.J., Kaplan De-Nour, A., Conley, J.A., Wells, G.A. and Wai, L. Comparison of psychological adjustment to continuous ambulatory peritoneal dialysis and home hemodialysis. Perit. Dial. Bull. 2:76-78, 1982.
35. Lindsey, R.M., Oreopoulos, D.G., Burton, H., Conley, J., Wells, G. and Fenton, S.S.A. Adaptation to home dialysis: A comparison of continuous ambulatory peritoneal dialysis and hemodialysis. Proc. 1st. Int. Sympos. on CAPD, 1980, pp. 120-130.
36. Simmons, R.G., Anderson, C. and Kamsten, L. Comparison of quality of life of patients on continuous ambulatory peritoneal dialysis, hemodialysis and after transplantation. Amer. J. Kid. Dis. 4:253-255, 1984.
37. Churchill, D.N., Morgan, J. and Torrance, G.W. Quality of life in end-stage renal disease. Perit. Dial. Bull. 4:20-23, 1984.
38. Evans, R.W., Manninen, D.L., Garrison, L.P., Hart, G., Blagg, C.R., Gutman, R.A., Hull, A.R. and Lowrie, E.G. The quality of life of patients

with end-stage renal disease. New Engl. J. Med. 312:553-559, 1985.
39. Rozenbaum, E.A., Pliskin, J.S., Barnoon, S. and Chaimovitz, C. Comparative study of costs and quality of life of chronic ambulatory peritoneal dialysis and hemodialysis patients in Israel. Israel J. Med. Sci. 21:335-339, 1985.
40. Kutner, N.G., Brogan, D. and Kutner, M.H. End-stage renal disease treatment modality and patients' quality of life: Longitudinal assessment. Am. J. Nephrol. 6:396-402, 1986.
41. Soskolne, V. and Kaplan De-Nour, A. Psychosocial adjustment of home dialysis, continuous ambulatory peritoneal dialysis and hospital dialysis patients and their spouses. Nephron 47:266-273, 1987.
42. Wolcott, D.L. and Nissenson, A.R. Quality of life in chronic dialysis patients: A critical comparison of CAPD and hemodialysis. Amer. J. Kid. Dis. (In press, 1988).
43. Nicholls, A.J., Waldek, S., Platts, M.M., Moorhead, P.J. and Brown, C.B. Impact of continuous ambulatory peritoneal dialysis on treatment of renal failure in patients aged over 60. Brit. Med. J. 288:18-19, 1984.
44. Marai, A., Rathaus, M., Gibor, Y. and Bernheim, J. Chronic dialysis in the elderly: Intermittant peritoneal dialysis or hemodialysis? Perit. Dial. Bull. 3:183-186, 1983.
45. Nissenon, A.R., Gentile, D.E., Soderblom, R.E. and Brax, C. Peritoneal dialysis in the elderly. In: Geriatric Nephrology (Ed: D.G. Oreopoulos), Martinus Nijhoff, Publisher, Boston, 1986, pp. 147-156.
46. Mattern, W.D., McGaghie, W.C., Rigby, R. Nissenson, A.R., Dunham, C.B. and Khayrallah, M.A. Selection of ESRD options by nephrologists: An international study. Submitted for publication.
47. Nissenson, A.R. Chronic peritoneal dialysis in diabetics. In press (Internal. J. Artif. Organs, 1988).
48. Mejia, G. and Zimmerman, S.W. Comparison of continuous ambulatory peritoneal dialysis and hemodialysis for diabetics. Perit. Dial. Bull. 5:7-11, 1985.

RENAL TRANSPLANTATION

15

MONOCLONAL ANTIBODIES IN THE TREATMENT OF TRANSPLANT REJECTION

DAVID J. COHEN

Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York 10032 USA

INTRODUCTION

Despite advances in tissue typing, pretransplant conditioning of recipients, and immunosuppressive therapy, immunologic graft loss has remained the leading cause of renal allograft failure in the first year following transplantation. One year allograft survival rates at most major transplantation centers are in the 75-85% range, with the majority of graft failures due to irreversible acute rejection episodes. While conventional therapies have been moderately effective in reversing acute rejection episodes, many infectious and metabolic complications are attributable to anti-rejection treatment. These undesirable side effects often limit the intensity, and hence the efficacy of therapy, and are the motivation for the development of new therapeutic modalities and innovative therapeutic strategies. This chapter will review the results achieved with the use of monoclonal antibodies in the prevention and treatment of acute renal transplant rejection.

T cell role in rejection

Although the rejection process remains imperfectly understood, there is little doubt as to the central role of the T lymphocyte in all phases of the host response to the allografted organ (1-3). HLA class II-directed

CD4+ T lymphocytes participate in the initial recognition of the allograft. Exposure to alloantigen induces CD4+ production of lymphokines and differentiation factors central to the development of the rejection process. CD4+ cells may also subserve a direct cytolytic function and form the basis of the delayed-type-hypersensitivity (DTH) and other non-specific inflammatory responses. Antigen activated B lymphocytes and HLA class I-directed CD8+ T lymphocytes respond to CD4+ derived growth and activation signals, and elaborate antibody and cytotoxic cell responses, respectively. T cell derived factors also serve to augment the expression of HLA antigens on graft endothelial and tubular cells, thus enhancing graft immunogenicity. If unchecked, these processes lead rapidly to irreversible graft destruction. Both CD4+ and CD8+ lymphocytes are found in rejecting allografts (4,5). The T lymphocyte is, thus, the logical target of anti-rejection therapy. However, only a few percent of host T cells recognize and are activated by the histoincompatible graft antigens. Expansion of these graft-reactive clones leads to the generation of an effective alloimmune response. Ideally, immuno-suppression would inhibit only these activated T cell clones, such that donor-specific hypo-responsiveness might be achieved without compromising immune reactivity against infectious organisms or malignant cells. The advent of monoclonal antibody technology places this heretofore elusive goal within reach.

"Conventional" anti-rejection therapy

High dose corticosteroids have remained the cornerstone of anti-rejection therapy for some 25 years. Extensive experience has demonstrated a reversal rate of approximately 70%-75% (6). However, the actions of corticosteroids are quite non-specific. Not only do they inhibit lymphocyte activity, but granulocyte and

monocyte/macrophage function are also impaired (7). Steroids act upon multiple other tissues as well. Side effects are frequent, and include infections, poor wound healing, hyperglycemia, altered appearance and mood, myopathy, avascular necrosis of bone, and others.

Polyclonal anti-lymphocyte antibody preparations were first tested in the late 1970's. These reagents, representing the serum IgG fraction of horses or rabbits immunized with human lymphoid cells, proved to be more effective than high dose steroids, both in the treatment of acute rejection, and in promoting long term renal allograft survival. Randomized trials, first reported in 1979, demonstrated rejection reversal rates of approximately 90% with anti-thymocyte globulin (ATG) or anti-lymphoblast globulin (ALG), compared with approximately 75% with high dose steroid treatment (6). One year graft survival was similarly improved with 78% success compared with 60% for steroid-treated patients. Long-term (8 - 9 year) follow up demonstrated improved allograft survival rates in ATG treated patients (8).

Side effects from polyclonal anti-lymphocyte preparations, although varying somewhat with the specific preparation, have been quite frequent. Fever, chills, and dyspnea are common with the initial infusion and may continue for several doses. Thrombocytopenia, pruritic skin eruptions and Cytomegalovirus and Herpes virus infections may occur somewhat later in the course. Severe arthralgias, and other signs and symptoms suggestive of serum sickness, have been observed by several centers.

Although effective when tolerated, there are unavoidable drawbacks to the use of polyclonal antilymphocyte preparations. They are a heterogeneous group of antibodies, containing multiple anti-T cell specificities, often anti-B cell reactivity, as well as large amounts of extraneous immunoglobulin, either targeting non-lymphoid tissue or completely non-

reactive with human tissue. A related problem is the frequently encountered batch-to-batch variability in potency. These problems have rendered standardization of preparations quite difficult.

Monoclonal antibodies offer several advantages compared with the polyclonal preparations described above. One of the most important is the specificity of their action. Reagents can be tailored to target T cells, B cells or any lymphocyte subpopulation believed to be playing a role in initiating or maintaining the rejection process. Undesirable reactivity with other tissues can be avoided by selection of the proper hybridoma product. In the few short years in which these reagents have been available, several pan-T cell monoclonals have been tested, as well as two that are specific for activated T cell subpopulations.

The second important characteristic of monoclonal antibodies is their uniformity. Whereas different lots of polyclonal preparations will necessarily vary somewhat in potency and specificity, each lot of a given monoclonal antibody is produced by identical clones of a single cell, each producing identical antibody molecules. Thus, each lot is identical to every other lot, and standardization, uniformity and purity of product are guaranteed. The high concentration of active antibody enables a much lower total dose of foreign protein to be administered, thus avoiding the problem of serum sickness, seen with polyclonal preparations, which commonly require doses of 1 g/day.

In the discussion which follows, monoclonal antibodies used in the treatment of renal transplant rejection are divided into two groups, according to their specificity.

PAN T CELL MONOCLONAL ANTIBODIES

OKT3

OKT3 was the first monoclonal antibody tested and

approved for the treatment of renal allograft rejection. It is the most widely used, and therefore, a great deal more experience and information have accumulated with its clinical effects than with any other monoclonal.

OKT3 is a murine IgG_{2a} monoclonal antibody, directed against the CD3 molecular complex, present on the surface of all mature, post-thymic T lymphocytes (9). The CD3 complex consists of 3 glycoprotein molecules, which are non-covalently bound to the T cell antigen receptor. The function of the CD3 molecular complex is not well defined at present, but it appears to be involved in the transduction of signals from the cell surface antigen receptor to intracellular activation processes (10). OKT3 binds exclusively to the CD3 complex, and has no cross-reactivity with any other human tissue. Following antibody binding to the CD3 complex with the initial dose of OKT3, there is a rapid disappearance of detectable T cells from the peripheral blood (11). This appears to be due to opsonization of antibody coated T cells by the reticuloendothelial cell system, rather than cell lysis. Following several days of therapy, T cells begin to reappear in the peripheral blood. These cells, however, are either CD4+ or CD8+, but do not express the CD3 antigen, which they have modulated off their surface (11). The T cell antigen receptor co-modulates along with the OKT3-CD3 complex. These CD3- T lymphocytes are thus unable to recognize antigen, and are immunologically incompetent. Interestingly, under certain experimental conditions, OKT3 has been shown to have a potent mitogenic effect on T cells in vitro (12). Whether this is relevant to its in vivo effects remains unknown. Thus, OKT3 appears to function as a T cell-blocking drug, rather than as a cytocidal antibody.

OKT3 was first shown to be effective in the treatment of acute renal allograft rejection in an open pilot study. All ten patients who received OKT3 had reversal

of their rejection episodes. (13,14) This was followed by a prospective randomized muticenter trial which compared OKT3 with high-dose corticosteroids for initial anti-rejection therapy in patients whose baseline immunosuppression was azathioprine and prednisone (15). Patients who received OKT3 had their azathioprine and prednisone doses markedly reduced during the 14 days of monoclonal antibody therapy. OKT3 reversed 94% of rejections, significantly higher than the 75% reversal rate achieved with high dose corticosteroid therapy. This superior rejection reversal rate was reflected in an 17% improvement in the one year graft survival rate (62% vs 45%). Several open supportive studies confirmed the > 90% success rate when OKT3 was used as the initial treatment for acute rejection. These included patients on maintenance cyclosporine/prednisone. The rejection reversal rate was 92% for patients whose cyclosporine was discontinued during the initial 7 - 10 days of OKT3 administration. Unexpectedly, the rejection reversal rate was significantly lower - 71% - for patients who were continued on cyclosporine throughout the course of OKT3 (16). Although unproven, it is likely that cyclosporine-induced nephrotoxicity, rather than acute rejection, was responsible for several of the episodes of allograft dysfunction. It is also possible that, in the presence of cyclosporine, some patients experience irreversible nephrotoxicity from the OKT3-induced release of T cell lymphokines.

OKT3 has also been effective in the treatment of rejections unresponsive to steroids and/or ATG. Monaco, et al (17) reported on 173 patients from 33 centers who received OKT3 following unsuccessful anti-rejection therapy with conventional treatments. Of 66 patients who had failed to respond to a full course of steroids and ATG, 49 (74%) had their rejections reversed with OKT3. A comparable success rate was achieved in patients who had previously failed high dose steroid therapy alone (67 of

100 rejections reversed). Long-term follow-up demonstrated a 61% graft survival rate one year following the course of OKT3, with a patient survival rate of 96%.

A third use of OKT3 in renal transplantation has been in the prophylaxis of acute rejection in the immediate post-operative period. Kreis et al (18) administered low dose prednisone and azathioprine along with OKT3 daily for up to 30 days following transplantation to 18 patients. OKT3 was discontinued if anti-OKT3 antibodies were detected. Five of the 18 experienced acute rejction episodes during this 30 day period, all in association with the development of anti-OKT3 IgG antibodies. An earlier study by the same group demonstrated that OKT3 alone, in the absence of other immunosuppressive therapy, was able to prevent acute rejection in the immmediate post-transplant period until anti-OKT3 antibodies appeared, generally between 9 and 21 days following the inital dose (19). Norman and co-workers (20) reported a randomized prospective study comparing OKT3 prophylaxis for 14 days (34 patients) with conventional immunotherapy (38 patients). The incidence of delayed graft function was comparable in both groups. The OKT3 patients had only a 6% incidence of acute rejection in the first post-operative month, compared to a 50% incidence in the control group. None of the OKT3 patients underwent rejection episodes during the 14 days of OKT3 administration. During the period of follow-up (a mean of aproximately 6 months), there was a trend toward a higher rate of allograft failure in the control group (24% vs 9% for the OKT3 patients), but this did not achieve statistical significance. Similar results were obtained by Ackerman, et al (21). Thus, the long term benefits of OKT3 prophylaxis remain unproven.

Use of OKT3 has been associated with two important clinical problems: first dose reactions, including asceptic meningitis; and the development of anti-OKT3

antibodies. The first injection of OKT3 causes a typical symptom complex in the vast majority of patients (15,22). This includes fever (70 - 90%), rigors (30-60%), respiratory symptoms - dyspnea, wheezing, chest pain and tightness - (10-20%), and gastrointestinal symptoms - nausea, vomiting, diarrhea - (10-20%). These symptoms generally occur within 45-60 minutes of the first dose of OKT3, to a much lesser extent following the second dose, and rarely thereafter. They are thought to be due to release of pyrogenic and vasoactive mediators from T lymphocytes following opsonization of OKT3 coated cells. Administration of 1 mg/kg intravenous methylprednisolone, accompanied by an antipyretic and and an anti-histamine, immediately prior to the first dose has been recommmended to minimize the severity of these symptoms. The presence of pulmonary vascular congestion when the first dose of OKT3 was given led to severe pulmonary edema in several patients. Careful assessment of the fluid status of each patient is thus mandatory prior to initiation of OKT3 therapy.

Several cases of asceptic meningitis, occurring within the first few days of OKT3 treatment, have recently been reported (22-24). Symptoms and lumbar pucture findings were typical of infectious meningitis, but viral, fungal, and bacterial cultures were negative. Symptoms resolved without sequellae despite continuation of OKT3. The etiology may be similar to other first dose reactions.

OKT3 is not only a potent immunosuppressive reagent, but, as a polypeptide of murine origin, is immunogenic. The development of anti-OKT3 antibodies is frequent and has important clinical implications. This anti-OKT3 response is characterized by two categories of antibodies: anti-isotypic (IgG_{2a}) and anti-idiotypic, the first reactive with all murine class IgG_{2a} antibodies, the second specific for the antigen combining site of the OKT3 antibody (22,25). A broad

anti-murine response, which migh preclude the future administration of any murine monoclonal antibody has not been reported. Because the nature and degree of concomitantly administered immunosuppression influence the frequency of anti-OKT3 antibody development (26), detectable anti-isotype responses may occur in from 46% to 70% of treated patients, with anti-idiotype responses detectable in 45% to 60%. Theoretically, an anti-isotype response might not prevent OKT3 from binding to the CD3 antigen, while an anti-idiotypic antibody would be expected to block OKT3. However, it appears that almost all patients who develop an anti-OKT3 response will produce both types of antibodies (22,25). When attempts have been made to re-treat patients with documented anti-OKT3 titers of $\geq$ 1:100, rejection reversal rarely occurred. In contrast, patients who have not made detectable antibodies at any time following OKT3 administration have rejection reversal rates comparable to those patients never previously treated (27). Thus, it is essential to monitor patients for the presence of anti-OKT3 antibodies. Antibodies most frequently develop 2 to 4 weeks following OKT3 use, but may develop as late as 6 to 8 weeks, with many patients subsequently becoming negative. Thus, patients should be checked for evidence of OKT3 sensitization at least once within the 4 to 8 weeks following completion of a course of OKT3. Patients who have made a detectable response at any time, even if it is no longer present, should not be retreated with OKT3. Patients who do receive a second course of OKT3 should be watched carefully, with either serum anti-OKT3 antibody levels or peripheral blood CD3+ cell numbers, for evidence of a developing anti-OKT3 response (22,28).

The incidence of infectious complications following OKT3 therapy appears to be comparable to that seen with other anti-rejection regimens (15,21).

WT32

A second anti-CD3 monoclonal - WT32 - has been tested in a small number of patients (29). WT32 is a murine IgG2a directed against the CD3 molecular complex. No information is available as to whether OKT3 and WT32 target identical CD3 epitopes. Following injection of WT32, changes similar to those induced by OKT3 are seen in the peripheral blood. This includes reduction of CD3+ cells to very low levels for the duration of treatment, with a gradual rise in CD3-CD4+ and CD3-CD8+ cell levels. WT32 was given as a once daily intravenous injection, 2 - 8 mg/day for 14 days, with the dosage adjusted based on the peripheral CD3+ cell level.

Nine patients were treated, 8 for acute rejection, 1 as prophylaxis. No data is available regarding the success of the prophylactic therapy, but 7 of the 8 rejection episodes were reversed. The patient who failed to respond to WT32 was noted to have a severe vascular rejection. Four of the patients experienced "rebound" rejections within approximately 2 weeks after completion of therapy. "First dose" reactions - fever and chills - were common, as was the development of anti-WT32 antibodies. No serious complications were reported. Details regarding long term follow-up were not provided.

Anti-T12

A third pan-T cell monoclonal antibody that has been used in the treatment of acute renal allograft rejection is anti-T12. This is a cytotoxic murine monoclonal IgM antibody directed against a 120K glycoprotein present on post-thymic T lymphocytes (30). It has no other known reactivity with human tissue. The function of the T12 (or CD6) antigen is unknown. In a manner similar to that of OKT3, administration of anti-T12 leads to the rapid disappearance of all T cells from the peripheral blood. Within a few days, however, T cells begin to reappear (31,32). These cells are T12- (CD6-) but are

CD3+CD4+ or CD3+CD8+, and persist throughout the therapy. This is likely due to modulation of the T12 antigen from the T cell surface induced by antibody binding. When administration of anti-T12 ceases, T12+ cells rapidly reappear in the peripheral blood. In contrast to OKT3, anti-T12 has no mitogenic effect on T cells. Anti-T12 was given intravenously in doses ranging from 200-600 ugm/kg/d for 7-10 days.

To date, 46 patients treated with anti-T12 have been reported. All patients had biopsy confirmation of acute rejection. Twenty of the patients (46%) responded to anti-T12. Eighteen of the 26 who failed to respond were sucessfully treated with high dose corticosteroids. The long term graft survival rate was 78% at a mean follow-up of approximately 22 months. No "first dose" reactions were seen with anti-T12. Infectious complications were limited to localized Herpes simplex type I infections, and urinary tract infections (4 patients each). Sixty percent of the patients developed anti-murine antibodies within 3 weeks of treatment. The specificity of these antibodies has not been detailed.

Anti-CD2

Thurlow, et al, reported the unsuccessful use of another pan-T cell monoclonal reagent - anti-HuLy-m1- in three renal allograft recipients (33). The antibody, a murine IgG2b, reacts with a 50 Kd glycoprotein structure, T11 (or CD2), which is part of, or closely associated with, the E-rosette forming cell (ERFC) receptor. Despite documentation of T cell coating by anti-HuLy-m1, there were no detectable changes in peripheral blood cell lymphocyte counts. There was no improvement in allograft function despite 10 days of therapy. Antibody-coated T cells were detected in the allografts, where the acute rejection process continued unabated.

Campath-1

Campath-1 is a rat monoclonal IgM that recognizes human peripheral T and B cells and is cytolytic in the presence of human complement (34). There is no information reported on the lymphoctye antigen(s) recognized by Campath-1. It does not bind to red cells, platelets, or bone marrow colony-forming cells. In a randomized trial in the prophylaxis of acute rejection, Campath-1 was administered for the first 10 post-operative days to 26 recipients of cadaver kidneys, whose maintenance immunosuppression consisted of daily cyclosporine only (35,36). Campath-1 patients received 25 mg twice daily of monoclonal antibody, while the 26 control patients received only cyclosporine. During the first 10 days, there was an 8% incidence of acute rejection in the Campath-1 treated patients, compared to a 46% incidence in the control patients. In the following 6 months, however, there was little difference in the overall incidence of rejection (Campath-1 46%, control 58%) and in graft survival (Campath-1 73%, control 69%). Of the Campath-1 treated patients, 42% experienced a major infectious complication, compared to only 12% of the control patients. Minor adverse reactions to monoclonal antibody occurred in 69% of patients. These reactions, treated with anti-histamines, included pruritis, fever, chills, tachycardia and wheezing. Thus, the short-term benefit of Campath-1 therapy appeared to be outweighed by the increased incidence of life-threatening infections. Prophylactic use of this powerful immunosuppressive agent did not appear to improve long-term results.

MONOCLONAL ANTIBODIES WHICH TARGET ACTIVATED T CELLS

CBL1

CBL1 is a complement-fixing, murine IgM monoclonal antibody raised against a lymphoblastoid T ALL cell line (37). The blast cell antigen it recognizes has not been

identified. It reacts with lymphoblasts and normal bone marrow stem cells (CFU-C), but not with mature peripheral blood cells except monocytes. There are no detectable changes in peripheral blood counts following administration of CBL1. Its immunosuppressive effect is presumed to be due to deletion or inhibition of activated lymphoblasts located in rejecting allografts or lymphoid tissue. There is also some reactivity with kidney tubules and colon tissue, although this does not appear to be of clinical significance. The dosage of CBL1 ranged from 5 - 10 mg/day, administered as a daily intravenous infusion for 9 days.

In limited Phase I trials, CBL1 has been used successfully in the treatment of acute rejection (38,39). A total of 42 patients treated with CBL1 are reported in the literature. CBL1 was used as a first line therapy for acute rejection, as rescue therapy and as prophylaxis against acute rejection in the immediate post-transplant period. Fourteen recipients of 1-haplotype mismatched kidneys from living related donors received CBL1 for the treatment of steroid-resistant rejections or severe rejections requiring hemodialysis. All patients had been conditioned with pre-transplant donor-specific blood transfusions (DST). Thirteen of the 14 patients responded to CBL1, with 8 experiencing no further rejection episodes and 1 graft lost to a second rejection. An additional 10 DST patients received low dose (5 mg/d) CBL1 for 9 days as prophylaxis against acute rejection. All 10 patients experienced acute rejection episodes during the period of CBL1 prophylaxis, two of which were irreversible. In the 18 cadaver kidney recipients, rejection was successfully reversed in 15, 5 of whom had subsequent acute rejection episodes. Most of these subsequent rejection episodes were mild, with only 1 graft lost. One patient was reported as having received a second course of CBL1 without any complications.

CBL1 appeared to be relatively free of side effects. As noted above, there were no detectable changes in peripheral blood lymphocyte or platelet counts. No fever or chills were noted following administration of the first or second doses. No infectious complications were reported. The development of anti-mouse anibodies was detected within 2 weeks of the initiation of CBL1 therapy in 14 of the original 19 patients. In some patients this occurred within 3 days of the start of treatment, but did not have an adverse effect on the outcome.

Anti-interleukin 2 receptor antibody

Interleukin 2 (IL2) is a growth factor needed by antigen activated T lymphocytes to enter the proliferative phase of the cell cycle. In the resting state, T cells neither produce IL2, nor express IL2 receptors. In the alloimmune response, IL2 production by CD4+ cells and IL2 receptor expression (on both CD4+ and CD8+ cells) appear following exposure of the T cell to antigen and monokine. The production of IL2, and its interaction with the IL2 receptor are pivotal events in the development of an effective immune response, as they support the viability and expansion of alloactivated T cell clones (40). Several different anti-IL2 receptor monoclonal antibodies have been developed (41). One of these, 33B3.1, a rat IgG2a, has been used successfully in the prophylaxis of acute rejection in the immediate post-transplant period (42,43). This antibody selectively targets the 55Kd alpha chain of the human IL2-R and non-competitively inhibits binding of IL2 to its high affinity receptor. In vitro studies demonstrated its ability to block IL2 driven proliferation of activated T cells (41). Injections of 10 mg/day resulted in serum concentrations of 33B3.1 30 times the Kd of the antibody for the IL2 receptor.

Cantarovich, et al reported on the prophylactic use

of 33B3.1 in 30 patients following cadaveric renal transplantation (43). Patients received a 14 day course of 10 mg/day by intravenous injection. These patients were compared to the 55 immediately preceding cadaver kidney recipients who received ATG prophylaxis. Only a single patient (3.3%) experienced a rejection episode during the first post-transplant month including the 2 week period of 33B3.1 administration. In the first 90 post-transplant days, there was a cumulative rejection incidence of 26.6%. The results with ATG were comparable. There appeared to be a lower rate of infectious complications with 33B3.1 than with ATG. With a reported follow-up of 1 - 7 months, the graft survival rate in 33B3.1 treated patients was 97%.

CONCLUSION

The anti-rejection monoclonal antibodies discussed above represent the "first generation" application of this technology to transplantation therapy. The successes and failures serve to illustrate certain principles and to indicate future directions. Immunosuppressive effect does not depend upon lysis of target cells. There is no evidence that OKT3 is lytic in vivo, yet it is the most effective anti-rejection monoclonal tested. WT32, non-complement fixing, whose specificity is similar to that of OKT3, enjoyed a comparable short-term success rate. Anti-T12 and Campath-1, despite fixing complement, were much less effective in reversing rejection than was OKT3, while anti-CD2 monoclonal (anti HuLy-m1) had no demonstrable immunosuppressive effect. Thus monoclonals may be viewed as potential T cell function blocking "drugs", as well as cytolytic reagents.

One determinant of immunosuppressive potency is the target of the monoclonal. The ability to inactivate the T cell by binding to a functionally important site appears to be of equal or greater importance than the

ability to lyse the cell. The efficacy of OKT3 is a function of its ability to denude the T cell of its antigen receptor. Interleukin 2 receptor-directed monoclonals, not surprisingly, appear to be effective anti-rejection therapy, as they, too, block a structure whose function is central to the rejection process. The goal of clonal deletion and graft tolerance is unfortunately not achieved despite successful prophylaxis and/or reversal of rejection by any of the available activated-lymphocyte-specific monoclonals. Re-rejections, manifestations of donor-antigen-directed immune reactivity, are not prevented. As other functionally vital sites on the T cell surface are identified, they will undoubtedly serve as targets of monoclonal antibody anti-rejection therapy.

Efficient complement fixation and target cell lysis can be expected to potentiate the immunosuppressive properties of monoclonal reagents. Waldmann (44) has explored means of augmenting the lytic ability of monoclonals. He has demonstrated the enhanced lytic ability of univalent monoclonals, ie antibody molecules with mixed light chains, and only one of the two sets of heavy and light chains able to bind the target cell. In addition, two monoclonals to different epitopes on the same cell surface structure are more efficient at initiating complement-mediated cell ablation than a single monoclonal. Similarly, monoclonals designed to optimize reticuloendothelial cell Fc receptor-mediated opsonization of antibody coated cells may potentiate immunosuppressive activity. The immunogenicity of rat or murine monoclonals might be reduced, and complement fixation improved, by the development of mouse/rat-human chimeric antibodies, with human constant regions and murine/rat antigen-binding domains.

The ultimate refinement in anti-rejection therapy will be the development of reagents which inactivate only those T cells expressing receptors for donor

antigen, sparing all other arms of the immune system. Monoclonal antibodies may be the vehicle for achieving this goal of selective, yet non-toxic immunosuppression.

REFERENCES

1. Strom TB. Immunosuppressive agents in renal Transplantation. Kidney Int 26:353-365, 1984

2. Engleman EG, Benike CJ, Grumet FC, Evans RL. Activation of human T lymphocyte subsets: helper and suppressor cytotoxic T cells recognize and respond to distinct histocompatibility antigens. J Immunol 127:2124, 1981

3. Meuer SC, Schlossman SF, Reinherz EL. Clonal analysis of human cytotoxic T lymphocytes:T4+ and T8+ effector T cells recognize products of different major histocompatibility complex regions. Proc Natl Acad Sci 79:4395-4399, 1982

4. Platt JL, LeBien TW, Michael AF. Interstitial mononuclear cell population in renal graft rejection: identification by monoclonal antibodies in tissue section. J Exp Med 155: 17-30, 1983.

5. McWhinnie DL, Thompson JF, Taylor HM, et al. Morphometric analysis of cellular infiltration assessed by monoclonal antibody labelling in sequential human renal allograft biopsies. Transplantation 42: 352-358, 1986.

6. Cosimi AB. Antilymphocyte globulin and monoclonal antibodies: present status as therapy. in Nephrology Proceedings of the IXth Int Congress of Nephrology (Los Angeles) Springer-Verlag, New York 1984, pp 1681-1694.

7. Cupps TR, Fauci AS. Corticosteroid mediated immunoregulation in man. Immunol Rev 65: 133-155, 1982.

8. Beekman K, Cohen DJ, Appel GB, Hardy MA. Randomized trial of anti-thymocyte globulin vs high-dose steroids in acute rejection of renal transplants: long term follow-up. Kidney Int 31: 454, 1987

9. Kung PC, Goldstein G, Reinherz EL, Schossman SF. Monoclonal antibodies defining distinctive human T cell surface antigens. Science 206: 347-349, 1979

10. Imboden J, Stobo JD. Transmembrane signalling by the

T cell antigen receptor. J Exp Med 161:446-456, 1985

11. Chatenoud L, Baudrihaye MF, Kreis H, et al. Human in vivo antigenic modulation induced by the anti-T cell OKT3 monoclonal antibody. Eur J Immunol 12: 979-982, 1982

12. VanWauwe JP, DeMay JR, Goossens JG. OKT3: a monoclonal anti-human T lymphocyte antibody with potent mitogenic properties. J Immunol 124: 2708-2713, 1980.

13. Cosimi AB, Burton RC, Colbin RB, et al. Treatment of acute renal allograft rejection with OKT3 monoclonal antibody. Transplantation 32: 535-539, 1981

14. Thistlethwaite JR, Cosimi AB, Delmonico FL, et al. Evolving use of OKT3 monoclonal antibody for treatment of renal allograft rejection. Transplantation 38: 695-701, 1984

15. Ortho Multicenter Transplant Study Group. A randomized clinical trial of OKT3 monoclonal antibody for acute rejection of cadaveric renal transplants. N Eng J Med 313: 337-342, 1985

16. Hirsch RL, Layton PC, Barnes LA, Kremer AB, Goldstein G. Orthoclone OKT3 treatment of acute renal allograft rejection in patients receiving maintenance cyclosporine therapy. Transplant Proc 19: 32-36, 1987 (Supp 1).

17. Monaco A, Goldstein G, Barnes L. Use of Orthoclone OKT3 monoclonal antibody to reverse acute renal allograft rejection unresponsive to treatment with conventional immunosuppressive regimens. Transplant Proc 19: 28-38, 1987

18. Debure A, Chkoff N, Chatenoud L, et al. One-month prophylactic use of OKT3 in cadaver renal transplant recipients. Transplantation 45: 546-553, 1988.

19. Vigeral P, Chkoff N, Chatenoud, et al. Prophylactic use of OKT3 monoclonal antibody in cadaver kidney recipients. Transplantation 41: 730-733, 1986.

20. Norman DJ, Shield CF, Barry J, et al. Early use of

OKT3 monoclonal antibody in renal transplantation to prevent rejection. Am J Kid Dis 11: 107-110, 1988.

21. Ackerman JR, LeFor WM, Kahana L, Weinstein S, Shires DL. Prophylactic use of OKT3 in renal transplantation: Part of a prospective randomized multicenter trial. Transplant Proc 20:242-244, 1988

22. Thistlethwaite JR, Stuart JK, Mayes JT, et al. Complications and monitoring of OKT3 therapy. Am J Kid Dis 11: 112-119, 1988.

23. Emmons C, Smith J, Flanigan M. Cerebrospinal fluid inflammation during OKT3 therapy. Lancet 2: 510-511, 1986

24. Roden J, Klintmalm GBG, Husberg BS, Nery J, Olsen LM. Cerebral spinal fluid inflammation during OKT3 therapy. Lancet 2: 272, 1987

25. Jaffers GJ, Fuller TC, Cosimi AB, et al. Monoclonal antibody therapy. Anti-idiotypic and non-anti-idiotypic antibodies to OKT3 arising despite intense immunosuppression. Transplantation 41: 572-578, 1986

26. Goldstein G, Fuccello AJ, Norman DJ, et al. OKT3 monoclonal antibody plasma levels during therapy and the subsequent development of host antibodies to OKT3. Transplantation 42: 507-511, 1986

27. Thistlethwaite JR, Stuart JK, Mayes JT, Galser AO, Stuart FP. Use of a brief steroid trial before initiating OKT3 therapy for renal allograft recipients. Am J Kid Dis 11: 94-98, 1988

28. Shield CF, Norman DJ. Immunologic monitoring during and after OKT3 therapy. Am J Kid Dis 11: 120-124, 1988.

29. Tax WJM, Van de Heijden HMW, Willems HW, et al. Immunosuppression with monoclonal anti-T3 antibody (WT32) in renal transplantation. Transplant Proc 19: 1905-1907, 1987

30. Reinherz EL, Meuer S, Fitzgerald KA, et al. Antigen recognition by human T lymphocytes is linked to surface expression of the T3 molecular complex. Cell 30: 735-743, 1982.

31. Kirkman RL, Araujo JL, Busch GJ, et al. Treatment of acute renal allograft rejection with monoclonal anti-T12 antibody. Transplantation 36: 620-626, 1983

32. Milford EL, Carpenter CB, Kirkman RL, et al. Anti-T12 monoclonal antibody therapy of acute renal allograft rejection. Transplant Proc 19: 1910, 1987

33. Thurlow PJ, Lovering E, D'Apice AJF, McKenzie IFC. A monoclonal anti-pan-T-cell antibody. In vitro and in vivo studies. Transplantation 36: 293-298, 1983.

34. Hale G, Bright S, Chumbley G, et al. Removal of T cells from bone marrow for transplantation: a monoclonal anti-lymphocytic antibody that fixes complement. Blood 62:873-882, 1983.

35. Hale G, Waldmann H, Friend P, Calne, R. Pilot study of Campath-1, a rat monoclonal antibody that fixes human complement, as an immunusuppressant in organ transplantation. Transplantation 42: 308-311, 1982

36. Friend, PJ, Calne, R Y, Hale G, at al. Prophylactic use of an anti-lymphocyte monoclonal antibody following renal transplantation: a randomized controlled trial. Transplant Proc 19: 1898-1900, 1987

37. Billing R, Wells J, Zettel D, Teresakki PI. Monoclonal and heteroantibody reacting with different antigens common to human blast cells and monocytes. Hybridoma 1:303-311, 1982

38. Takahashi H, Okazaki H, Teresaki PI, et al. Reversal of transplant rejection by monoclonal antiblast antibody. Lancet 2:1155-1158, 1983

39. Takahashi H, Okazaki H, Teresaki PI, et al. Follow-up on initial trials of kidney transplant rejection reversal by a monoclonal antiblast antibody. Transplant Proc 17:69-71, 1985

40. Smith KA. Interleukin 2. Ann Rev Immunol 2:319-333, 1984

41. Diamantstein T, Osawa H, Kirkman RL, et al. Interleukin 2 receptor - a target for immunosuppressive therapy. in Transplantation Review, Morris PJ and Tilney NL, eds. Grune and Stratton, Orlando FL, USA; Vol 1:177-196, 1987

42. Soulillou JP, Peyronnet P, LeMauff, B. Prevention of rejection of kidney transplants by monoclonal antibody directed against interleukin. Lancet 1: 1339-1342, 1987

43. Cantarovich D, Le Mauff D, Hourmant M, et al. Prophylactic use of a monoclonal antibody (33B3.1) directed against interleukin 2 receptor following renal transplantation. Am J Kid Dis 11:101-106, 1988

44. Waldmann H. Monoclonal antibodies for organ transplantation: prospects for the future. Am J Kid Dis 11:154-158, 1988

DIAGNOSTIC METHODS IN NEPHROLOGY

16

MAGNETIC RESONANCE IMAGING OF THE KIDNEYS

Zoran L. Barbaric, MD

Department of Radiological Sciences, U.C.L.A. School of Medicine, Los Angeles, Ca, USA.

MR signal.

When hydrogen and certain other atomic nuclei are placed in a high strength magnetic field and exposed to a short radio-frequency pulse, they emit a rapidly decaying radio signal. Frequency of the emitted radio signal is specific for different atoms and is called Larmor frequency. Signal strength is directly proportional to the specific concentration of nuclei examined. Since hydrogen is the most abundant nucleus in living tissue, magnetic resonance imaging visually displays differences in hydrogen concentration in the body.

Besides specific frequency and signal strength, the emitted MR signal has two additional measurable characteristic features. The rate by which the signal diminishes is dependent on two different physical decay processes characterized by the decay times T1 and T2. By applying two or three stimulating RF pulses, manipulating their duration, amplitude, and interval, either T1 or T2 characteristics of the sample can be emphasized. These manipulations of the stimulating RF pulses are known as pulse sequences.

Most of the hydrogen nuclei in living tissues are present in water and lipids. The rate of signal decay is markedly influenced by the bonds the water molecules have within different tissues. The reconstructed MR image in reality represents water bonding characteristics in different tissues.

For example, on pulse sequences emphasizing T1 characteristics (T1-weighted image), subcutaneous and retroperitoneal fat is presented as white on an MR image and is a strong signal producer. Muscle, urine, and calcium are depicted dark on the image as they emit a signal of low intensity. Liver, spleen, pancreas, adrenal glands, and lymph nodes emit signals of medium intensity and are shown as gray. An interesting phenomenon in the kidney is that cortex and medulla have somewhat different signal returns and therefore cortex and medulla can be seen as different entities (Fig. 1).

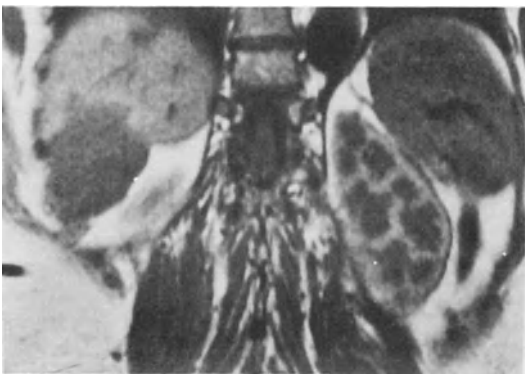


Fig. 1. T1-weighted image in coronal plane of the upper abdomen. The left kidney is visualized and there is excellent cortico-medullary differentiation. Liver is seen under the dome of the right hemidiaphragm and has higher signal intensity then the spleen which is under the left hemidiaphragm. At the bottom of the liver, there is a tumor mass of lower signal intensity than that of liver parenchyma. Retroperitoneal fat appears white and is said to be hyperintense.

On T2-weighted images signals from the same tissues appear totally different. Liver and muscle become much darker (hypointense), while the spleen and kidneys emit more signal and become bright (hyperintense).

Needless to say, different tumors have T1 and T2 characteristics of their own and are commonly hyperintense on T2-weighted images (Fig. 2 and 3). If a neoplasm is in the liver, the contrast difference is remarkable and much more pronounced than on CT.

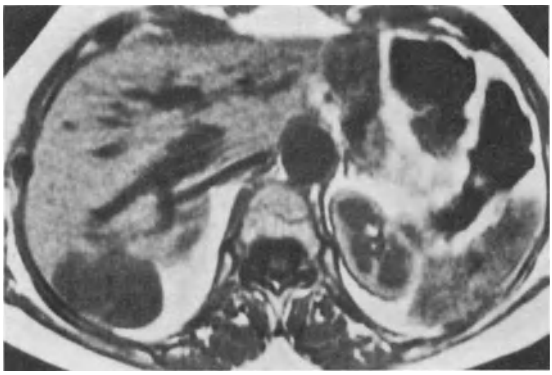


Fig. 2. Axial T1-weighted image of the patient presented in Fig. 1. The top of the left kidney is seen and corticomedullary differentiation is present. The liver tumor is clearly posterior and away from major vessels. Spinal fluid appears black (hypointense) and surrounds the spinal cord.

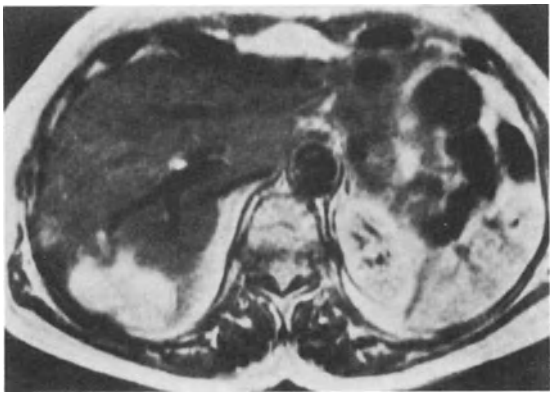


Fig. 3. Axial T2-weighted image through the same area as in Fig. 2. Liver is now hypointense (darker) as compared to T1-weighted image. The tumor has drastically changed, becoming bright and well contrasted to the dark liver. Both spleen and kidney have also become hyperintense and corticomedullary differentiation is no longer visible. Spinal fluid has also become hyperintense.

Degenerative lumbar disc, for instance, has a markedly different water content as compared to normal and thus it looks distinctively

different on MR image. In the brain white matter and gray matter are seen as different anatomical structures (1-6).

Hemorrhage and blood clots change their signal characteristics with time. Flowing blood may be recognized as a low or high signal intensity area depending on whether the signal is emitted while still in the part of the body being imaged or elsewhere.

Adverse effects of motion.

The abdomen, however, is difficult to examine using magnetic resonance. Since images are acquired over a period of time, usually spanning 10 to 20 minutes, any motion may adversely affect image quality. Sources of motion are respiration, bowel peristalsis, vascular and cardiac pulsation, voluntary and involuntary muscular movements. Patient cooperation therefore becomes one of the important means for obtaining good images. Respiratory gating, a technique which limits data acquisition to end-respiration, improves resolution but significantly prolongs the examination. Many different techniques are being investigated to reduce motion problems with this imaging modality (7-10).

Body habitus.

Excellent contrast discrimination is essential for obtaining good images. A generous amount of body fat generally produces better images, just as it tends to do in CT. Intense signal from body fat on T1-weighted images contrasts parenchymal organs, vessels, and fluid-filled structures nicely.

Choice of sequences and plains.

An abdominal examination will usually require both T1 and T2-weighted imaging sequences. Coronal T1-weighted sequence will cover retroperitoneum, great vessels, kidneys, adrenal glands, much of the liver, spleen and spine. Depending on clinical circumstances, T1-weighted axial sequence is done over the area of interest, followed by T2-weighted imaging sequences also displaying axial anatomy similar to CT (11).

Single sequence may well be diagnostic and will demonstrate all of the pathology present and in many instances is sufficient for follow up examinations. However a single plane (or sequence) may be insufficient for ruling out the presence of a pathological process.

High, mid or low field magnets.

The strength of the magnetic field is measured in Tesla (T). Commercially available magnets range between 0.3 T to 2 T. The stronger the magnet, the more expensive the installation. It appears that mid-strength field magnets are adequate and perhaps better in depicting abdominal organs than high field. Using a permanent magnet one can examine difficult patients with the intravenous pole and oxygen tanks located right next to the magnet, without fear of them becoming projectiles flying through the room. The recent discovery of superconductivity at temperatures well above absolute 0 degrees (Kelvin) may dramatically change magnet technology within the next five years.

Paramagnetic contrast materials.

Paramagnetic contrasts do not produce MR signal, but rather alter local magnetic field and thereby affect both T1 and T2 relaxation times of adjacent hydrogen nuclei in the tissues where they may concentrate. In general, in their presence, signal intensity on T1-weighted images is increased and on T2-weighted images decreased.

Free metal ions are potentially the best paramagnetic agents. However they are either too toxic or are cleared from the body too rapidly for medical imaging. Chelated metal ions have the advantage of marked toxicity reduction and relative tissue specificity.

The best known paramagnetic compound is gadolinium-DTPA, a very stable chelate which is administered intravenously, does not cross the blood-brain barrier and is excreted unchanged by the kidney. The recommended dose is 0.1 mmol per kg body weight. Following injection, normal kidneys will exhibit a rapid decrease in T1 relaxation time while in renal ischemia there is only minimal decrease. While the the true value of these substances in evaluation of renal disease still remains somewhat elusive, it appears that there is a definite benefit in the imaging of brain and heart (12-18).

Paramagnetic macrocyclic chelates are comparable in stability to those of DTPA chelates but because of their effectiveness, a relative dose as compared to gadolinium-DTPA may be reduced ten-fold if shown to be safe (19).

Since bowel may in some instances simulate abdominal tumors, oral paramagnetic contrast materials are being developed. Ferric (Geritol) or ferrous iron seem to be agents of choice.

Normal MR anatomy of the kidneys.

On T1-weighted sequence the kidneys are well depicted. In the great majority of patients, cortex and medulla are seen as separate anatomical structures. Intense signal emanating from the surrounding perinephric fat contrasts the renal parenchyma from the outside, while a similar signal from renal sinus fat contrasts parenchyma and pelvocalyceal system from the "inside." Renal arteries and veins are seen at least partially in the majority of patients, and so are the great vessels. The resolution is insufficient to clearly identify smaller, non-dilated calyces, but renal pelvis, ureteropelvic junction and ureters are frequently seen. Psoas muscles are well outlined by retroperitoneal fat. Renal fascia (Gerota's) is exquisitely seen on occasion. Adrenal glands can be clearly seen in almost all patients. Relation to liver, spleen, portal vein, and other anatomical structures can be facilitated by choosing either coronal, axial, sagital or any oblique imaging plane in between (20).

Physiologic evaluation of the kidneys.

Gadolinium-DTPA is eliminated mainly by glomerular filtration with 95% clearance in 6 hours. Sequential 3-second images in an identical coronal plane may be obtained over the kidneys after an intravenous bolus of this paramagnetic contrast material. Curves indicating signal intensities over period of time have striking similarity to those of nuclear medicine angiography with Tc99mDTPA (21).

Congenital anomalies.

Pelvic kidneys, horseshoe kidneys, and crossed-fused renal ectopia sometimes present diagnostic difficulties. Pelvic kidneys, for example, may be mistakenly diagnosed as pelvic tumor and inadvertently operated upon. Since they do not appear reniform they may be misdiagnosed on ultrasound or non-enhanced CT scan. They are involved more frequently with pathological processes such as obstruction, infection, and other congenital anomalies than are normal kidneys. The relative position of large vessels may be identified in patients in whom radiographic contrast is contraindicated.

Occasionally abnormal position of the renal hilum (junctional parenchymal defect) (22) may simulate a solid renal mass. This anomaly is obvious on sagital projection. Duplication of the collecting system, hypertrophied septum of Bertin, and renal dysmorphism are easily detected.

Renal masses.

Radiologist's role regarding renal masses is:

1) Detection

2) Classification into three subgroups: a. simple cyst, b. lipomatous tumor c. all others.

3) Staging of all others. Since the chance of these tumors being malignant is over 85%, one must assume they are renal carcinoma and act accordingly.

Renal carcinoma. Renal carcinoma is usually iso-intense as compared with surrounding renal parenchyma and on occasion relatively hypo-intense on T1-weighted images (Fig. 4 and 5). On T2-weighted images both the kidney and the tumor are hyperintense and and the tumor is difficult to perceive (Fig. 6). In addition to differences in signal intensity, diagnosis is made by detecting change in shape, contour, size, and displacement of the adjacent organs, pelvocalyceal system or sinus fat by a mass.

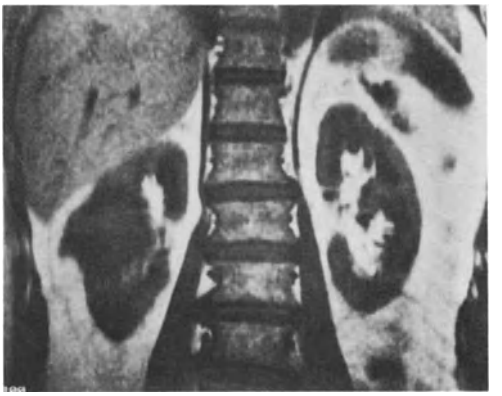


Fig. 4. T1-weighted image in the coronal plane through both kidneys. Right renal mass is present, isointense to the renal cortex. Mass displaces renal sinus fat and does not extend through renal fascia.

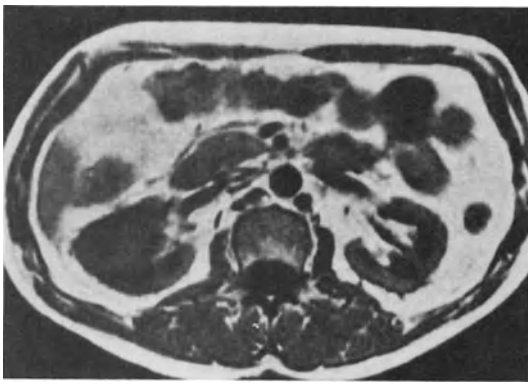


Fig. 5. Axial T1-weighted image of the patient in Fig. 4. The tumor does not extend into the renal vein. There are no regional lymph node enlargements.

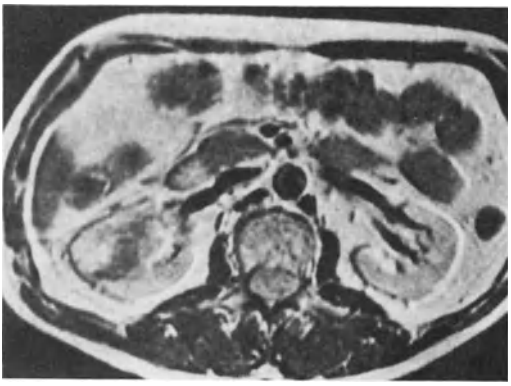


Fig. 6. Axial T2-weighted image of the patient in Fig. 5. Like the liver tumor, renal tumor becomes hyperintense. Unfortunately the kidney does the same; therefore the two entities are not well contrasted. However, the major vessels remain black and it is certain the tumor did not extend via this route.

Detection of renal carcinoma and other mass lesions is clearly dependent on their size. Lesions larger than 3 cm are detected without difficulty in 100% of cases (data is for 0.35 T field strength magnet). Lesions smaller than 3 cm in diameter are detected in 62% of cases. For comparison purposes the sensitivity for detection of smaller than 3 cm lesions of other imaging modalities is presented in Table 1 (23).

Table 1.

CT	94%
US	79%
ANGIO	74%
IVP	67%
MRI	62%

It follows that CT currently is clearly the superior method for detection of small renal neoplasms. Small lesions are undetected on MR imaging if they are of same signal intensity as that of renal cortex and if no distortion of the renal contour is visible.

Staging is 82% correct overall (24-34). Although the number is on the low side, understaging does not have serious treatment implications. For instance, renal capsule is invisible on MR images and capsular penetration is impossible to detect. However, treatment for both stage I and stage II disease is identical. Extension into the very proximal renal vein branches is also underestimated on MR, but likewise it does not change basic surgical approach. Differentiation of enlarged lymph nodes from other retroperitoneal vessels such as retrocaval left renal vein is much easier than on CT since larger vessels are very low in signal. The problem arises if a concomitant malignant disease is present, such as lymphoma, where lymph node enlargement may be due to either of the two diseases.

Other solid (non-fatty) renal masses.

Renal metastases. Metastases are indistinguishable from renal carcinomas. Change in shape, size and general contour suggest the presence of the mass within the kidney. In a patient with a known primary elsewhere, a diagnosis of metastasis is entertained. There are no characteristic features on MR imaging to differentiate such a

mass from renal carcinoma or other solid renal masses. T2-weighted images are of no help, as tumor mass usually becomes iso-intense to the kidney.

Renal sarcomas. Several histological types of renal sarcomas are known to arise from the kidney. These are lyomyosarcoma, hemangiopericytoma, liposarcoma, rabdomyosarcoma, osteosarcoma and fibrosarcoma. These tumors may arise from the renal capsule or other connective tissue elements within or around the kidney and usually attain large size before they are detected. A solid renal mass, quite homogeneous on T1-weighted image is seen, usually displacing the kidney and adjacent organs. There are no distinguishing features on MR examination with the exception of fibrosarcoma which like all fibrous tissues may be of low signal intensity on T2-weighted images.

Renal lymphoma. Lymphoma usually presents as multiple renal masses and less commonly as a solitary nodule. Even less common is diffuse parenchymal infiltration. Signal intensity of the neoplasm is equal to that of the kidney on T1-weighted sequence and and has equal or higher signal intensity than the kidney on T2-weighted images. The tumor masses have a tendency to penetrate renal capsule and invade perinephric space and renal sinus. Concomitant lymph node enlargement is common.

Transitional cell carcinoma of the kidney. This tumor does not exhibit features distinguishable from other renal neoplasms either on T1 or T2 sequences. The origin of this cancer may be suggested only if it appears it is arising from within the collecting system, rather than displacing it. Presence of infundibular stenosis and localized hydronephrosis should suggest this neoplasm, and it should be included in the differential diagnosis. It is difficult however to examine transitional cell epithelium bearing area closely, looking for minute irregularities representing early radiographic signs of transitional cell carcinoma. This is still best left to excretory urography and retrograde pyelography, as well as urinanalysis for malignant cells.

Wilm's tumor (nephroblastoma). This tumor is the most common renal malignancy in children. Tumor is bilateral in 5% and congenital anomalies are found in 15% (genitourinary, hemihypertrophy, aniridia, neurofibromatosis,etc). Mass with a pseudocapsule and

occasional cystic component is seen. Renal vein and caval extension are possible. Metastases are to lymph nodes, lungs, liver, skeleton, and central nervous system.

Common presentation is a large symptomatic abdominal mass.

Sonography is the screening examination of choice to determine whether the mass is cystic or solid and to confirm that it is renal in origin. Vascular extension may be detected as well as liver metastases.

MR imaging is the method of choice in further evaluation and staging of the disease (35-37). Variable signal intensities are seen on T1 and T2-weighted sequences depending on the presence of cystic components and hemorrhage. Vessels are usually well depicted and abnormal lymph nodes detected.

CT is almost as good as MR imaging except for the necessity of intravenous contrast. Since lung metastases are present in 10% of all patients at the time of diagnosis CT of the thorax is usually part of imaging work-up.

Oncocytoma. This benign tumor originating from tubular cells has so far been indistinguishable from renal carcinoma or metastasis. When the tumor attains a certain size, a central renal scar may be identified (38-39).

Fatty renal tumors

Angiomyolipoma. This tumor is composed largely of fatty tissue and therefore exhibits a strong signal on T1 imaging sequence (40-41). Considerable vasculature may be observed within the tumor. Fatty tissue is often seen surrounding the renal vein which may be somewhat enlarged. This tumor is commonly seen in patients with tuberous sclerosis. Occasionally multiple cysts are found concomitantly in the kidneys so that they may resemble polycystic renal disease. Additional benign tumors in the liver, pancreas, and heart may be found, as well as bony changes which have rather low signal intensity on T1-weighted image. Small angiomyolipomas present a difficult diagnostic problem. A tumor one or two cm in diameter may have to be biopsied or explored if the diagnosis is made on CT or US alone. If characteristic signal intensities are demonstrated on both T1 and T2-weighted spin echo imaging sequences, presence of fat should be easily established.

Hybernoma. Brown fat is found in hibernating animals. It has somewhat more pronounced metabolic activity, more mytochondria than ordinary fat, and can occasionally produce benign renal sinus tumors in humans. These should have a strong signal intensity on T1.

Lipoma is a rare benign tumor of the kidney and most probably originates from the renal sinus fat. Diagnostic feature is radiolucent appearance on CT or isointense aberrance to the retroperitoneal fat on T1 and T2-weighted sequences on MR imaging. Differential diagnosis includes other fatty renal tumors and localized peripelvic lipomatosis (lipomatosis circumscripta).

Renal cysts

Simple renal cysts are a common finding. Incidence increases with age. The primary method of radiological examination still remains ultrasound. However, since the cysts are frequently encountered on abdominal MRI, done for whatever other purposes, it is important to familiarize oneself with their appearance. By their location, renal cysts are divided into cortical and peripelvic. A simple renal cyst will present as a rounded structure with low signal intensity. It should be perfectly rounded, with smooth, thin walls. There should be no filling defects or irregularity at the base. If the cyst is not clearly seen because of motion artifacts, an ultrasonographic examination should be done. T1-weighted coronal and axial sequences are probably insufficient. On T2-weighted sequence the cyst fluid becomes isointense to the kidney. In the presence of high protein content within the cyst fluid it may become intensely hyperintense compared to the kidney on T2-weighted image. One should always remember the poor performance of magnetic resonance in imaging of small deposits of calcium. Even moderate amounts of calcifications within the cyst wall may go unrecognized. Since anything more than a crescent of calcification within the wall should be regarded as a potential malignant cyst, CT imaging technique is superior to MR imaging in this respect.

Hemorrhagic renal cyst will usually have an intense signal on T1-weighted image, as well as an intense signal on T2-weighted image. But variations are possible and are frequent. The signal intensity largely depends on the length of time the blood was present within the cyst and therefore may be hypo, iso or hypointense on both imaging

sequences. Up to 30% of hemorrhagic renal cysts larger than 3 cm may contain renal carcinoma and should be further investigated by thin needle aspiration technique (42-43). Hemorrhagic cysts smaller than 3 cm should be re-examined after six months to determine any change in size. In general, hemorrhagic cysts should be treated much the same as "hyperdense" cysts seen on CT.

Polycystic kidneys are seen to contain a variety of small and large cysts. These, if simple, have low signal intensity on T1-weighted imaging sequence. In addition, multiple hyperintense hemorrhagic cysts are frequently seen scattered throughout the kidney. Often, there are also cysts which exhibit an intermediate signal intensity. Detecting hydronephrosis in this group of patients may be an impossible task for ultrasound or non-enhanced CT scan. MR imaging in coronal or sagital planes circumvents this problem. 20% of patients with polycystic renal disease will develop and pass renal calculi in due course. Also hematuria and blood clots may cause ureteral obstruction. Pain and discomfort from enlarging kidney, hemorrhage into the cyst, infected cysts, compression on adjacent organs etc., may mimic renal colic due to obstruction and passage of a ureteral calculus. MR imaging of the base of the brain for screening of vascular aneurysms in all known polycystic disease patients, is not recommended at the present time.

Acquired cystic renal disease is an entity seen in over 50% of patients who have undergone renal dialysis treatment over a period of several years (44). Small, contracted kidneys develop multiple small cysts, but there may also be a small adenoma and occasionally a renal carcinoma. Recommended follow-up for these patients has been CT imaging at yearly intervals. From our preliminary experience, MRI appears to be less sensitive.

Inflammatory diseases.

Chronic pyelonephritis is seen as an irregular small kidney with scars and blunted calyces. Changes are best seen on coronal projection. Dilated ureter may suggest vesico-ureteral reflux.

Xantogranulomatous pyelonephritis may present as a mass lesion. renal fascia is usually thickened and perinephric space may be involved with inflammatory process. This disease is usually associated

with renal calculi. Calculi may be difficult to recognize. On T1-weighted sequence and T2-weighted sequence, calculus will exhibit low signal intensity.

The inability of MR imaging to discriminate renal calculus disease anywhere near that of CT, projection radiography or even ultrasound is one of the major drawbacks of this imaging modality in evaluation of the urinary tract system.

Acute renal failure

General enlargement of the kidney is present and there is associated loss of corticomedullary differentiation on T1-weighted sequences. This finding is non-specific and is seen in practically every parenchymal disease.

Obstruction

Dilatation of the collecting system is readily apparent. The most common cause of the obstruction is calculus disease which, of course, is the major drawback for MR imaging. Other causes of the obstruction may be very obvious on the MR examination, particularly in patients with malignant diseases. Retroperitoneal lymph node enlargement, primary retroperitoneal neoplasm, retroperitoneal fibrosis, and aortic aneurysm may be apparent on this examination. This is not to suggest that magnetic resonance should be the primary method of examination for this group of patients, rather to point out that in the course of MR imaging one is bound to encounter hydronephrosis and should recognize it for what it is.

Perirenal spaces.

Retroperitoneal hemorrhage. Chronic, (present for a week or longer), blood accumulation will have an intense signal on T1 and T2. Acute hemorrhage will present more or less as a mass lesion permeating along the retroperitoneal septations and fatty tissues. Occasionally on axial scans sedimented blood is seen where distinct layers are clearly visible.

Urinoma. Collections of extravasated urine are seen as distinct low signal areas, usually loculated. On T2 images urine becomes grayish and indistinguishable from retroperitoneal fat. Lymphoceles, on the other hand, are hypointense on T1 and intensely white on T2.

Renal transplants.

Cortico-medullary junction is clearly seen in normal renal allografts, and so is renal sinusoidal fat, perinephric (extraperitoneal) space, bladder, and psoas. Uretero-neocystotomy site is seen on occasion. Pelvocalyceal system may be seen even in the absence of obstruction. In the presence of obstruction the collecting system and the ureter are clearly visible and sometimes even the point of the obstruction can be identified.

Post-transplantation renal demise can be due to a variety of causes, but the most important are ureteral obstruction, renal artery occlusion or stenosis, acute rejection, cyclosporine nephrotoxicity, acute tubular necrosis (ATN) and acute infection. Differentiation between acute rejection and cyclosporine nephrotoxicity is particularly difficult and of the utmost importance. If the renal allograft is being rejected, cyclosporine dose may have to be increased. However if the renal failure is due to this drug, it should be discontinued.

Magnetic resonance imaging criteria for acute rejection of the transplanted kidney are shown on Table 2.

Table 2. MR imaging of renal allografts

	CMJ	SINUS FAT	SIZE
Normal	distinct	clearly seen	normal
Rejection (mild)	indistinct but present	identified	normal
Rejection (moderate)	obliterated	identified	mildly enlarged
Rejection (severe)	obliterated	obliterated	markedly enlarged

Several studies report that cortico-medullary differentiation (CMD) is preserved in nephrotoxicity and ATN, whereas it is indistinct or obliterated during an episode of acute rejection. Also during such an episode, and depending on the severity of rejection, renal sinus fat may be obliterated, and the kidney may be mildly, moderately or markedly

enlarged. Extremely high sensitivity and specificity in diagnosing acute rejection are reported using MR imaging (97%-100%) as compared to either ultrasonography (70%-77%) or nuclear medicine scintigraphy (80%-70%). Other investigators are reporting less optimistic results. Obliteration of cortico-medullary junction may be seen in ureteral obstruction, renal artery stenosis, acute allograft pyelonephritis, and allograft renal vein thrombosis. In all of these there may be significant renal enlargement, tenderness, and loss of renal function, enough to make the diagnosis of rejection extremely difficult on MR imaging. Despite optimistic reports on MR performance in this area, Doppler US should be the imaging method of choice in the initial evaluation of a renal allograft (45-52).

Perinephric fluid collections are seen somewhat better on MR images than on ultrasound and the same is true for hydronephrosis (Fig. 7, 8, 9 and 10). To a certain degree the nature of perinephric fluid can be determined by virtue of different signal characteristics on T2-weighted images. Lymphoceles tend to become bright; urinomas behave as urine within the bladder does. Because the entire anatomical area is presented either on axial or coronal projection, MR images are more understandable for the urologist and nephrologist.

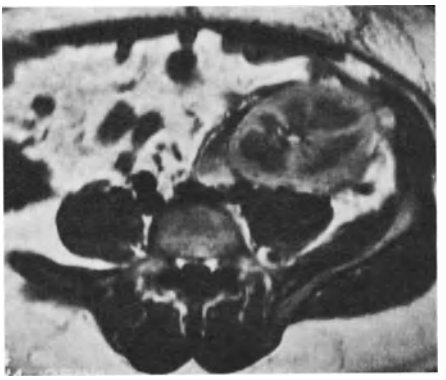
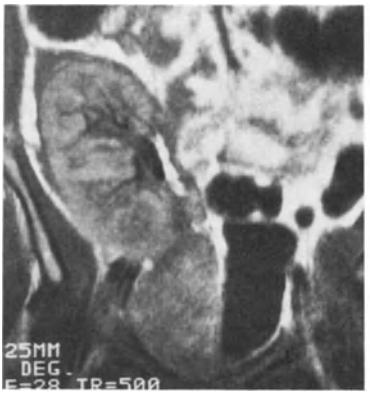


Fig. 7. Axial T1-weighted image of a patient with renal allograft. There is excellent corticomedullary differentiation. Medial to the kidney is a fluid collection, which has several distinct fluid layers of different signal intensity. These represent layers of sedimented blood in the area around the kidney.



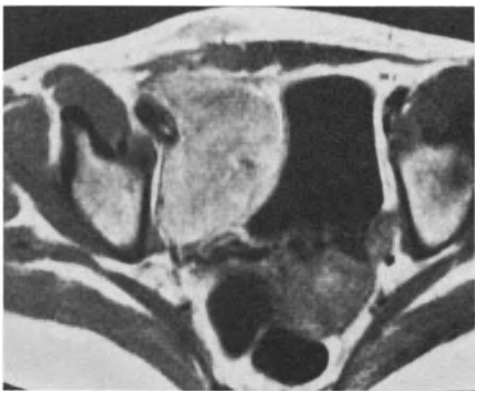


Fig. 8 (top left). Coronal T1-weighted image of the right renal allograft. Corticomedullary junction is not as clearly identified as compared with the one in previous patient. Around and below the kidney there is a gray collection of fluid. This is definitely not urine, since urine appears hypointense (black) on this pulse sequence as can be seen in the displaced bladder.

Fig. 9 (top right). Axial T1-weighted image below the kidney, through bladder and fluid collection. Medium signal intensity (grayish) of the fluid on this sequence speaks not only against it being urine but also against it being lymph, since the latter should also be hypointense (black).

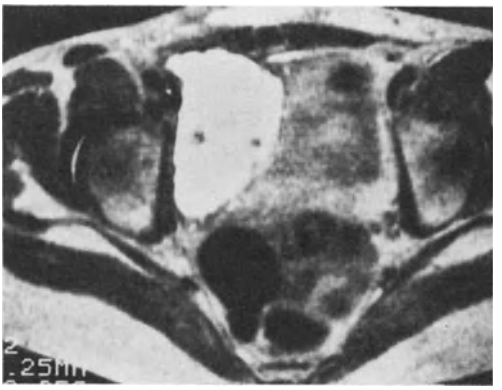


Fig. 10. Axial T2-weighted image on the same patient as in Fig. 9. Fluid collection is now hyperintense and different than grayish urine in the bladder. The appearance on T1 and T2-weighted sequences is very suggestive of hematoma.

One area which has been disappointing so far is the inability of MR imaging to clearly demonstrate renal artery - hypogastric artery (or iliac artery) anastomotic site and to diagnose or exclude renal artery stenosis. Renal arteriography (analog or digital) and recently Doppler ultrasound, are far superior in the evaluation of patency of this vessel. Because of the low cost, immediate availability, and simplicity, ultrasound will remain the method of choice for initial examination of the renal transplant, not only for definition of rejection, but also for obstruction, evaluation of perinephric fluid, and renal artery stenosis.

REFERENCES.

1. Damadian R. Tumor detection by nuclear magnetic resonance. Science 171:1151-1153, 1971.
2. Lauterbur PC. Image formation by induced local interactions: Examples of employing nuclear magnetic resonance. Nature 242:190-191. 1973.
3. Mansfield P, Pykett IL, Morris PG, Coupland RE. Human whole body line-scan imaging by NMR. Br J Radiol 51:921-922, 1978.
4. Henshaw WS, Bottomley PA, Holland GN. Radiographic thin-section image of the human wrist by nuclear magnetic resonance. Nature 270:722-723, 1977.
5. Council on Scientific Affairs, AMA. Fundamentals of magnetic resonance imaging. JAMA 258:3417-3423, 1987.
6. Balter S. An introduction to the physics of magnetic resonance imaging. Radiographics 7:371-381, 1987.
7. Haacke EM, Lenz GW. Improving MR image quality in the presence of motion by using rephasing gradients. AJR 148:1251-1258, 1987.
8. Stark DD, Hendrick RE, Hahn PF, Ferrucci JT Jr. Motion artifact reduction with fast spin-echo imaging. Radiology 164:183-191, 1987.
9. Pattany PM, Phillips JJ, Chiu LC, et al. Motion artifact suppression technique (MAST) for MR imaging. JCAT 11:369-377, 1987.
10. Ehman RL, McNamara MT, Brach RC, et al. Influence of physiologic motion on the appearance of tissue in MR images. Radiology 159:777-782, 1986.
11. Newhouse JH. Image contrast and pulse sequences in urinary tract magnetic resonance imaging. Urol Radiol 8:120-127, 1986.
12. Brash RC, Weinmann HJ, Wesbey GE. Contrast-enhanced NMR imaging: animal studies using gadolinium-DTPA complex. AJR 142:625-630, 1984.
13. Slutsky RA, Peterson T, Strich G, Brown JJ. Hemodynamic effects of rapid and slow infusions of manganese chloride and gadolinium-DPTA in dogs. Radiology 154:733-735, 1985.
14. Lamarque JL, Almes C, Rouanet JP, et al. Ideal imaging in MR: contrast-enhancing pharmaceuticals. Evaluation of tempo carboxilic acid as nitroxide diagnostic agent. Eur J Radiol 6:48-52, 1986.
15. Saini S, Stark DD, Hahn PF, Bousquet JC, et al. Ferrite particles: superparamagnetic MR contrast agent for enhanced detection of liver carcinoma. Radiology 162:217-222, 1987.

16. Pettersson H, Ackerman N, Kaude J, et al. Gadolium-DTPA enhancement of experimental soft tissue carcinoma and hemorrhage in magnetic resonance imaging. Acta Radiol 28:75-78, 1987.
17. Koenig SH, Spiller M, Brown RD III, et al. Magnetic field dependence (NMRD profile) of 1/T1 of rabbit kidney medulla and urine after intravenous injection of Gd (DTPA). Invest Radiol 21:697-704, 1986.
18. Schmiedl U, Organ M, Paajanen H, et al. Albumin labeled with Gd-DTPA as an intravascular, blood-pool-enhancing agent for MR imaging: biodistribution and imaging studies. Radiology 162:205-210, 1987.
19. Jackels SC, Kroos BR, Hinson WH, et al. Paramagnetic Macrocyclic complexes as contrast agents for MR imaging: proton nuclear relaxation rate enhancement in aqueous solutions and in rat tissues. Radiology 159:525-530, 1986.
20. Holliday J, Saxon R, Lufkin RB, Rauschning W, et al. Anatomic correlations of magnetic resonance images with cadaver cryosections. Radiographics 5:887-921, 1985.
21. Pettigrew RI, Avruch L, Dannels W, Coumans J, Bernardino ME. Fast-field-echo MR imaging with Gd-DTPA: physiologic evaluation of the kidney and liver. Radiology 160:561-563, 1986.
22. Carter AR, Horogan JG, Jennings TA, Rosenfield AT: The junctional parenchymal defect: A sonographic variant of renal anatomy. Radiology 154:499-502, 1985.
23. Amendola MA, Bree RL, Pollack HM, et al. Small renal carcinomas: resolving a diagnostic dilemma. Radiology 166:637-641, 1988.
24. Robson CJ, Churchill BM, Anderson W: The results of radical nephrectomy for renal cell carcinoma. J Urology 101:297-301, 1969.
25. Hricak H, Crooks L, Sheldon P, Kaufman L: Nuclear magnetic resonance in the imaging of the kidneys. Radiology 146:425-432, 1983.
26. Hricak H, Williams RD, Moon KL et al: Nuclear magnetic resonance imaging of the kidney: Renal masses. Radiology 147:765-772, 1983.
27. Lang EK: Angio-computed tomography and dynamic computed tomography in staging of renal cell carcinoma. Radiology 151:149-155, 1984.
28. Hricak H, Williams RA, Hedgcock MW: The value of NMR in depicting and staging renal malignancies. Magn Reson Med 94:172-173, 1984.
29. Hricak H, Demas BE, Williams RD, et al : Magnetic resonance imaging in the diagnosis and staging of renal and perirenal neoplasms. Radiology 154:709-715, 1985.
30. Choyke PL, Kressel HY, Pollack HM, et al: Focal renal Masses: Magnetic resonance imaging. Radiology 152:471-477, 1984.
31. Selli C, Bartolozzi C, Lizzadro G, et al: Arteriovenous fistula associated with renal cell carcinoma: demonstration by magnetic resonance imaging. Urol Radiol 8:190-191, 1986.
32. Fein AB, Lee JKT, Balfe DM, et al: Diagnosis and staging of renal cell carcinoma: A comparison of MR imaging and CT. AJR 148:749-753, 1987.
33. Patel SK, Stack CM, Taner DA. Magnetic resonance imaging in staging of renal cell carcinoma. Radiographics 7:703-728, 1987.
34. Hricak H, Theoni RF, Carroll PR, et al: Detection and staging of renal neoplasms: a reassessment of MR imaging. Radiology 166:643-649, 1988.
35. Kangarloo H, Dietrich RB, Erlich RM, et al. Magnetic resonance imaging of Wilm's tumor. Radiology 163:291-291, 1987.
36. Belt TG, Cohen MD, Smith JA, et al. MRI of Wilm's tumor: promise as the primary imaging method. AJR 146:955-961, 1986.
37. Dietrich RB, Kangarloo H. Kidneys in infants and children: evaluation with MR. Radiology 159:215-221, 1986.
38. Remark RR, Berquist TH, Lieber MM, et al. Magnetic resonance imaging of renal oncocytoma. Urol 31:176-179, 1988.

39. Ball DS, Friedman AC, Hartman DS, et al. Scar sign of renal oncocytoma: Magnetic resonance imaging appearance and lack of specificity. Urol Radiol 8:46-48, 1986.
40. Bret PM, Bretagnolle M, Gaillard D, et al: Small, asymptomatic angiomyolipomas of the kidney. Radiology 154:7-10, 1985.
41. Vas W, Wolverson MK, Johnson F, et al. MRI of an angiomyolipoma. Magn Res Imag 4:485-486, 1986.
42. Marotti M, Hricak H, Fritzsche P, et al: Complex and simple renal cysts: Comparative evaluation with MR imaging. Radiology 162:679-684, 1987.
43. Brown JJ, vanSonnenberg E, Gerber KH, Strich G, Wittich GR, Slutsky RA: Magnetic resonance relaxation times of percutaneously obtained normal and abnormal body fluids. Radiology 154:727-731, 1985.
44. Scanlon MH, Karasick SR: Acquired renal cystic disease and neoplasia: Complications of hemodialysis. Radiology 147:837-838, 1983.
45. Rholl KS, Lee JKT, Ling D et al: Acute renal rejection versus acute tubular necrosis in a canine model: MR evaluation. Radiology 160:113-117, 1986.
46. Hricak H, Terrier F, Demas B: Renal allografts: Evaluation by MR imaging. Radiology 159:435-441, 1986.
47. Geisinger MA, Risius B, Jordan ML, et al: Magnetic resonance imaging of renal transplants. AJR 143:1229-1231, 1986.
48. Hricak H, Terrier F, Marotti M, et al: Posttransplant renal rejection: Comparison of Quantitative scintigraphy, US, and MR imaging. Radiology 162:685-688, 1987.
49. Mitchell DG, Roza AM, Spritzer CE, et al: Acute renal allograft rejection: difficulty in diagnosis of histologically mild cases by MR imaging. JCAT 11:655-663, 1986.
50. Halasz NA: Differential diagnosis of renal transplant rejection: is MR imaging the answer? AJR 147:954-955, 1986.
51. Mitchell DG, Rao VM, Dalinka MK, Spritzer CE, et al. Femoral head avascular necrosis: Correlation of MR imaging, radiographic staging, radionuclide imaging, and clinical findings. Radiology 162:709-715, 1987.
52. Steinberg HV, Nelsson RC, Murphy FB, Chezmar JL, Baumgartner BR, Delaney VB, Whelchel JD, Bernardino ME. Renal allograft rejection: evaluation by Doppler US and MR imaging. Radiology 162:337-342, 1987.

INDEX

Page numbers followed by the letter "T" refer to tables; page numbers followed by the letter "F" refer to figures.

Abortions, 213, 214, 214T, 215F
Abruptio placentae, 144
ACB (Antibody-coating bacteria), 58
ACE inhibitors, 115-128, 115F
Acetate dialysis, 284, 285, 287
Acetate, 239, 240T, 281, 284, 285, 286, 287
Acetohydroxamic acid, 75
Acetylsalicylic acid, 211
Acidosis, lactic, 72, 239
Acidosis, metabolic, 72, 187, 239
Acidosis, renal tubular, 72, 75, 79, 81
ACTH, 4T
Acute Cortical Necrosis, 209, 212, 213, 214
Acute Renal Failure, 207-226, 208T, 209F, 210T, 214T, 215F, 218T, 219F, 219T
Acute Tubular Necrosis (ATN), 172, 209, 211, 212, 213, 215T, 217, 218, 218T, 219, 219T, 219F, 220, 221, 361
AII (Angiotensin II), 175, 176, 177, 185
Aldosterone, 115F, 122, 125, 178, 187, 312T
ALG (Anti-Lymphoblast Globulin), 327
Alkaline phosphatase, 69
Alkalosis, metabolic, 239, 247
Allopurinol, 77T, 79, 80
Aluminium, 269, 270
Amikacin, 54
Amino acid infusion, 5, 12
Aminoglycoside, 105, 173, 181T, 212
Ammonium chloride, 4T, 6, 8
Amoxycillin, 51, 52, 53, 54, 55, 56, 57, 58, 59
Amphotericin B, 181T
Ampicillin, 49, 50, 53, 55, 58
Amyloid, 290
Amyloidosis, 305
Analgesics, 211
Analgin, 211
Androgenic steroids, 181T
Anemia, 185, 263-277
Angiomyolipoma (in Magnetic Resonance), 357
Angioplasty, percutaneous transluminal, 116, 120
Angiotensin sensitivity test, 131-132, 139
Angiotensin, 115, 115F, 116, 125, 131, 132, 139, 175
Angiotensin converting enzyme inhibitors, 103, 115-128, 115F
Anti-CD2, 335
Anti-interleukin 2 receptor antibody, 338-339
Anti-lymphoblast globulin (ALG), 327
Anti-T12, 334-335, 339

Anti-thymocyte globulin (ATG), 327
Antibiotics, 49, 50, 53, 59, 181T, 220, 221
Anticoagulation, 138-140, 241, 243
Antifungal agents, 181T
Antimalarial drugs, 211
Antimitotic agents, 181T
Antiplatelet (treatment, in pregnancy) 138, 140
APD (Automated Peritoneal Dialysis), 301-322, 306T, 308T, 310T, 312T, 314T
ARF (See Acute Renal Failure)
Arteriography, renal, 364
Arteriolopathy, acute, by cyclosporine, 184-185
Ascorbic acid, 72
Aspirin, 139, 140, 145
Atenolol, 117, 118F, 123, 124, 124F, 142
ATG (Anti-thymocyte globulin), 327, 330
ATN (See Acute Tubular Necrosis)
ATP-MgCl2, 189
Autoimmune diseases, 194
Azathioprine, 187, 188, 191, 192, 194, 195, 330, 331
B cells (lymphocytes), 30, 157, 327, 328, 336
Bacteria, antibody-coating, 58
Bacterial resistance, 58
Bacteriuria, 136, 138
Barbiturates, 212
Behcet's Syndrome, 195
Berger's disease, 23-46
Beta blockers, 96, 97, 103, 119, 123, 142
Beta-2-microglobulin, 289, 290
Beta-lactam antibiotics, 57, 58
Bicarbonate dialysis, 285-286, 287, 291, 292
Bicarbonate, 187, 239, 240, 240T, 241, 246, 282, 285, 286, 287, 291, 292, 304
Biocompatibility, 237
Bleeding, 242, 251, 266, 271
Blood flow (in hemofiltration), 242, 244
Blood transfusion, 337
Bone marrow, 171, 178, 185
Bradykinin, 116
Brush border enzymes, 173
C3 (complement), 23, 27, 31, 35, 155
C4 (Complement), 27, 31
Calcium channel blocking drugs, 89-113, 142, 172, 180, 181T, 188-189
Calcium oxalate, 67, 68T, 72, 75, 76T, 80
Calcium, 67-85, 68T, 73, 76-77T, 79, 172, 180, 185, 188-189, 240, 241, 243, 293, 293T, 304
Calmodulin, 90
Campath-1, 336, 339
Cannulation (of the femoral vein), 229, 230, 234
Cannulation (of the femoral artery), 229, 230, 234
CAPD (Continuous Ambulatory Peritoneal Dialysis) 301-322, 306T, 208T, 310T, 312T, 314T
Captopril, 116, 117, 119, 120, 121, 121F, 122, 123, 125, 143, 175, 176

Cardiac output, 91, 99
Cardiovascular instability (in dialysis), 284-285
Carpal tunnel syndrome, 290
Catecholamines, 122, 176, 177, 178
Catheters, 234, 235-236, 317
CAVH (Continuous Arteriovenous Hemofiltration), 227, 228, 229, 230, 232F, 234, 236, 237, 239, 240, 245, 247, 248, 249, 250, 251, 252
CAVHD (Continuous Arteriovenous Hemodialysis), 228, 230, 233F, 234, 236, 237, 242, 247, 248, 249, 250
CBL1, 336-338
CCPD (Continuous Cycling Peritoneal Dialysis), 301-322, 306T, 308T, 310T, 312T, 314T
CD3, 329, 333
CD4+ cells, 326, 329
CD8+, 329
Cefaclor, 52, 55
Cefadroxil, 52, 55
Cephalexin, 52, 53
Cephaloridine, 50, 52, 53
Cephalosporins, 51, 58, 59, 212
CHD (Center Hemodialysis) 306T, 308T, 310T, 314T
Children, 53, 59, 155-168, 188, 209, 210, 213, 235
Chlorambucil, 156
Chloroquin, 211
Chlorthalidone, 75
Cholesterol, 94, 123
Choroiditis, 192
Cimetidine, 180, 181T
Citrate, 72, 73, 75, 77T, 78, 79, 80, 81, 243
CLi (Lithium clearance), 174, 178, 188
Co-trimoxazole, 51, 52, 54, 55, 58, 59
Coagulation, intravascular, 136, 138, 143, 144
Complement, 27, 31, 155, 237, 336, 339, 340
Conn's syndrome, 122
Continuous Arteriovenous Hemodialysis (See CAVHD)
Continuous Venovenous Hemofiltration (CVVH), 228, 250
Continuous Arteriovenous Hemofiltration (See CAVH)
Continuous Renal Replacement Therapy, 227-259
Contrast agents (radiological), 212, 218, 221, 351
Contrast materials, paramagnetic, 351-352
Converting enzyme inhibitors, 142
Copper sulphate, 210T, 212
CPD (Continuous Peritoneal Dialysis), 268, 301-322, 306T, 308T, 310T, 312T, 314T
Creatinine, serum, 35, 120, 121, 135, 182, 187, 189, 190, 293, 293T
Cuprophane, 237
Cushing's syndrome, 122
CVVH (Continuous Venovenous Hemofiltration), 228, 250
Cyclacillin, 52
Cyclophosphamide, 156
Cyclosporine nephrotoxicity, chronic, 189-195
Cyclosporine nephrotoxicity, acute, 171-189, 181T, 183F, 330, 361
Cyclosporine A nephrotoxicity, 171-203, 181T, 330, 361

Cyclosporine, 36, 155-168, 171-203
Cystic (renal) disease, acquired, 312T, 359
Cytomegalovirus, 327
Danazol, 35, 181T
Demyelinating polyradiculoneuropathy, 192
Di-hydropyridine drugs, 89, 90, 91, 98-99
Diabetes mellitus, 4T, 5, 11, 13, 123, 137, 138, 180, 253, 316-317
Diabetic glomerulosclerosis, 12
Diafiltration, 228
Dialysate (in Peritoneal Dialysis), 302, 303, 304
Dialysate (in Hemodialysis), 248, 249, 250, 283, 284, 285, 286, 287, 291, 292T
Dialysis, 217, 219T, 251, 263, 264, 266, 268, 270, 271, 281, 282, 283, 284, 285, 287, 289, 290, 291, 292, 294, 294T, 295, 295T, 296
Dialysis, Peritoneal (See Peritoneal Dialysis)
Diarrhoeal diseases, 209, 210, 210T, 216
DIC (Disseminated Intravascular Coagulation), 211, 212
Digoxin, 96
Dihydropyridine, 95
Dilazep, 34
Diltiazem, 89, 91, 95, 97-98, 104, 172, 181T
Dipyridamole, 34, 139
Disequilibrium syndrome, 281, 282, 283
Disseminated intravascular coagulation, 211, 212
Diuretics, 75, 94, 104, 117, 119, 123, 125, 141, 181T, 188, 229, 251
Dopamine, 35, 175, 178, 193
Doxyciclin, 181T
Drug interactions, 96
Dry weight (in Hemodialysis), 282, 285, 288-289, 292
Dysuria, 50
Eclampsia, 136, 139, 213
Edema, 103, 104, 125, 131, 135, 141, 143
Elderly, 93, 95, 123
Enalapril, 116, 117, 118F, 119, 123, 124, 124F
Encephalopathy, hypertensive, 100
Endotoxins, 286
Enzymes, tubular, 173
Epidemiology of Acute Renal Failure, 207-226
Erythromycin, 180, 181T
Erythropoietin, 263-277, 296
Extracellular fluid volume, 121
Felodipine, 90, 98, 100, 101, 102, 103, 104, 105
Fibronectin, 134
Fluid overload, 227, 228
Fosfomicin trometamol, 52, 59
Functional ARF (Acute Renal Failure), 186, 193
Functional reserve, 10
Furosemide, 181T
Gallapomil, 89, 104
Gamma GT enzyme, 173, 174
Gentamicin, 173, 181T

GFR, 173, 174, 176, 177, 178, 181, 188, 190, 191, 193, 194
Gingival enlargement, 104, 165
Glomerulonephritis, 6, 23, 34, 35, 105, 210T, 212
Glomerulosclerosis, 10, 12, 155, 162, 163T, 164, 165, 191
Glucocorticoid hormones, 122
Gluten, 28
Glycolic acid, 72
Gout, 72
Gouty diathesis, 67, 68T, 72, , 77T, 80
Graft-vs-host disease, 178, 185
Graves ophtalmopathy, 178
Growth factor (hormone), 3, 4, 4T, 5, 6, 11, 12
Gum hypertrophy, 104, 165
HDL (High Density Lipoprotein), 94
Heart failure, 100, 115, 141, 252, 252T
Heart, 171, 185, 187
HELLP syndrome, 143, 144
Helper T cells (lymphocytes), 30, 157, 184
Hematocrit, 266, 271, 296, 304, 316
Hematoma (in Magnetic Resonance), 363T
Hematuria, 33
Hemodiafiltration, 240, 282, 291
Hemodialysis, high efficiency, 281-299, 292T, 293T, 294T, 295T
Hemodialysis (See also Dialysis), 227, 228, 229, 230, 233F, 237, 248, 251, 268, 271, 281-299, 292T, 293T, 294T, 295T, 301-322
Hemodynamics, renal, 173, 174, 177
Hemofilter, 229, 230, 236-239, 238T
Hemofiltration, 228, 237, 240, 247, 307T, 308T
Hemoglobin, 263, 274, 265, 269, 270, 271
Hemolysis, 210, 210T, 211, 212
Hemolytic Uremic Syndrome, 184, 209
Hemorrhage, 213
Heparin, 236, 241, 242, 243
Hepatic failure, 239
Hepatotoxicity, 96
Herpes (simplex virus), 327, 335
HHD (Home Hemodialysis), 306T, 308T, 310T, 313, 314T
HLA antigens, 31
Hybernoma (in Magnetic Resonance), 358
Hydralazine, 102, 104, 142
Hydrochlorothiazide, 75, 102, 123
Hydronephrosis, 10, 11, 362
Hydroxyproline, 69
Hypercalcemia, 70, 78, 81
Hypercalciuria, 67, 68, 68T, 69, 70, 71, 74, 75, 76T, 78, 80, 81
Hyperglycemia, 327
Hyperkalemia, 121, 125, 165, 187, 188, 239
Hyperoxaluria, 67, 68T, 72, 77T, 79
Hyperparathyroidism, 70, 73, 78, 81
Hypertension, pregnancy-induced, 133, 139
Hypertension, chronic, in pregnancy, 132, 135-136, 141, 142, 145
Hypertension in the elderly, 123
Hypertension of pregnancy, 122-123, 131-151

Hypertension, secondary, 120-122, 121F
Hypertension, renal parenchymatous, 120-121, 121F
Hypertension, renovascular, 116-117, 120, 121F
Hypertension, 9, 33, 87-128, 131-151, 184, 185-186, 191, 193, 194, 270, 282, 287
Hypertrichosis, 165
Hypertriglyceridemia, 72
Hypertrophy, renal, 3-19, 4T, 180
Hyperuricemia, 72, 79, 80, 123, 133, 188
Hyperuricosuria, 67, 68T, 71, 77T, 79, 80
Hypocitraturia, 67, 68T, 72, 75, 77T, 78, 79, 81
Hypokalemia, 68T, 72, 75, 78, 79
Hypomagnesemia, 188
Hyponatremia, 241
Hypophosphatemia, 70, 241
Hypovolemia, 135, 284, 285, 287
IgA nephropathy, 23-46
IgA, 23-46, 155
IgM nephropathy, 155, 162, 163T
IL2 (Interleukin 2), 338, 340
Imipenem, 181T
Immuno complexes, 23, 24, 27, 28, 29
Immunosuppressive therapy, 324-344
Indomethacin, 177
Insects (ARF by), 210T, 211
Insulin, 4T, 5, 316
Interferon, 158
Interleukine, 157, 158, 338, 340
Inulin clearance, 174
IPD (Peritoneal Dialysis Intermittent), 304, 316
Iridocyclitis, 178
Iron, 266, 269, 271
Ischemia, renal, 179, 193, 211, 351
Josamycin, 181
Juxtaglomerular apparatus, 179, 186, 191
Kanamycin, 51, 52, 57
Ketaconazole, 180, 181T
Kf (glomerular ultrafiltration coefficient), 174, 175
Kinins, 125
KT/V urea, 289, 290, 292T
Labetalol, 93
Lactate, 239, 240T, 303
Leptospirosis, 212
Leukocytes, 27
Leukopenia, 125, 237
Levonorgestrel, 181T
Linoleic acid, 135
Lipoma (in Magnetic Resonance), 358
Lisinopril, 116
Lithium clearance, 174, 178, 188
Lithotripsy, extracorporeal, 67
Liver, 115, 171, 180, 185, 190, 349

Lymphoceles (in Magnetic Resonance), 360, 362
Lymphocytes, 29, 157, 158, 172, 184, 325, 326, 328, 329, 334, 336, 338
Lymphokine, 31, 158, 326, 330
Lysosomal enzymes, 173
Lysosomes, 173, 183
Macrodantin, 53
Magnesium, 77T, 78, 240, 241
Magnetic resonance imaging, 347-366
Malaria, 212
Mannitol, 181T
Melphalan, 181T
Membranes (for hemofilters), 236, 237, 238T, 239, 243F
Meningitis, 331, 332
Metabolic acidosis, 4T
Metazolone, 181T
Methyldopa, 103, 123, 142
Methylprednisolone, 159, 166, 182, 332
Methyltestosterone, 181T
Metoprolol, 97, 142
Minimal change glomerular disease, 155-168, 163T
Minoxidil, 102, 104, 119
Mitochondria, 179, 183
Monoclonal antibodies, 325-344
MR (Magnetic Resonance), 347-366
MR image, 347, 348, 348F, 349F, 350, 353F, 354F, 361T, 362F, 363F
Myeloma, 217
Myoglobinuria, 212
N-acetyl-p glucosaminidase (NAG), 173, 174
Na/H exchange, 7-8,
Nephrectomy, 8, 9, 10, 11, 120, 175, 179
Nephroblastoma (in Magnetic Resonance), 356-357
Nephrolithotomy, 67
Nephrolithiasis, 67-85, 68T, 76-77T
Nephrosclerosis, 190, 192
Nephrotic syndrome, 34, 155-168, 181
Nephrotoxicity, 163, 164, 166, 171-203, 181T, 183F, 212
Nicardipine, 90, 98, 100, 104, 180, 181T
Nifedipine, 89, 90, 97, 98, 99, 100, 101, 103, 104, 185, 188, 189
Nimodipine, 98
Nisoldipine, 90, 98, 99, 100, 101, 102
Nitrendipine, 98, 100, 101, 102, 104, 105
Nitrofurantoin, 52, 55
Nonsteroidal antiinflammatory drugs, 35, 177
Norepinephrine (Noradrenaline), 99, 122
Norfloxacin, 181T
Obstetric renal failure, 213-215, 214T, 215F, 217, 220, 221
Obstruction (ureteral, in Magnetic Resonance), 360, 361, 362
OKT3, 328-333, 334, 339, 340
OKT4/OKT8, 30
Oncocytoma (in Magnetic Resonance), 357
Orthophosphate, 76T, 78-79, 80
Osmotic agents, 181T
Osteitis, 70

Osteocalcin, 69
Osteodystrophy, renal, 312T, 313
Oxalate calcium, renal stones, 67-85, 68T, 76-77T
PAH clearance, 174, 177
Papaverine, 91, 96
Para-aminohippurate clearance, 9
Parathyroid function, 78
Parathyroidectomy, 73
Parenteral nutrition, total, 4T, 8, 12
Pemphigoid, 192
Peritoneal Dialysis, Intermittent (IPD), 304, 316
Peritoneal Dialysis, Continuous Ambulatory (CAPD), 301-322, 306T, 308T, 310T, 312T, 314T
Peritoneal Dialysis, Automated (APD), 301-322, 306T, 308T, 310T, 312T, 314T
Peritoneal Dialysis, Continuous Cycling (CCPD), 301-322, 306T, 308T, 310T, 312T, 314T
Peritoneal Dialysis, Continuous (CPD), 268, 301-322, 306T, 308T, 310T, 312T, 314T
Peritonitis, 302, 309, 316
PGs (Prostaglandins), 68T, 71, 122, 176, 177
pH, urinary, 73, 77T, 80
Phaeochromocytoma, 100
Phenacetin,, 211
Phenoxibenzamine, 176
Phenytoin sodium, 36
Phosphate, 9, 68T, 70, 76T, 78, 81, 190
Phospholipids, 135
Phosphorus, 241, 293, 293T
Pindolol, 93, 142
Plasma exchange, 36
Plasma renin activity (PRA), 95, 120, 121, 122, 178, 185, 186, 187
Plasma volume, 132, 140, 141, 143, 145
Platelet, 134, 138, 143, 177, 242, 271, 336, 338
Polyacrylonitrile (PAN), 237, 238T
Polyamide, 237, 238T
Polychondritis, 195
Polycystic (kidneys, in Magnetic Resonance), 357, 359
Polymethylmethacrylate, 237
Polysulfone, 228, 237, 238T
Postdilution (hemofiltration), 230, 240, 247, 249
Postrenal failure, 220
Potassium citrate, 75, 77T, 78, 79, 80, 81
Potassium depletion, 4T, 6
Potassium, 9, 75, 77T, 78, 80, 81, 117, 121, 123, 187, 188, 190, 239, 246, 248, 271, 293, 293T, 304
PRA (Plasma Renin Activity), 95, 120, 121, 122, 178, 185, 186, 187
Prazosin, 102, 176
Predilution (hemofiltration), 230, 240, 241, 245, 247, 248
Prednisone, 158, 159, 161, 166, 195, 330, 331
Preeclampsia, 131-151, 213
Pregnancy, 4T, 5, 12, 13, 53, 59, 122, 123, 131-151, 213, 214, 214T, 215F, 216

Prerenal azotemia (Acute Renal Failure), 173, 193
Primaquin, 211
Probenicid, 53
Properdin, 27
Propranolol, 93, 94, 97, 103, 123
Prorenin, 187
Prostacyclin, 138, 139
Prostaglandin (PG), 68T, 71, 122, 176, 177
Prostatitis, 59
Protamine, 243
Protein diet, 4T, 11
Protein loading, 5
Protein meal, 10
Proteinuria, 9, 10, 33, 34, 35, 125, 131, 135, 143, 156, 157, 158, 161, 162, 191, 194
PTH (ParaThyroid Hormone), 69, 70
Pulmonary edema, acute, 100
Pyelonephritis, 8, 49, 305, 359, 362
Pyridoxine, 72
Pyrogen reactions, 286
Pyrophosphate, 78
Quinine, 211
Quinolones, 57, 59, 181T
r-HuEPO (Recombinant human erythropoietin) 264, 265, 266, 267, 268, 269, 270, 271
Ramipril, 116
Ranitidine, 181T
Raynauds phenomenon, 267
Recombinant human erythropoietin (See r-HuEPO)
Reflux (vesico-ureteric), 10, 54
Rejection (renal allograft), 36, 171, 179, 182, 184, 192, 194, 195, 325-344, 361, 362
Renal ablation, 5, 7, 8
Renal blood flow, 35, 71, 105, 174, 175, 176, 178, 181, 190, 194
Renal Carcinoma (in Magnetic Resonance), 353, 355, 356, 357, 359
Renal cysts (in Magnetic Resonance), 358
Renal failure, acute 116, 144, 171, 173, 186, 193, 227-259, 252T, 360
Renal failure, 33, 34, 36, 120, 121, 156, 157, 163, 164, 228, 263-277, 305
Renal growth 3
Renal hypertrophy, 3-19, 4T, 180
Renal lymphoma (in Magnetic Resonance), 356
Renal metastases (in Magnetic Resonance), 355, 357
Renal plasma flow, 8, 9, 177, 188, 191
Renal sarcoma (in Magnetic Resonance), 356
Renal vein thrombosis (in Magnetic Resonance), 362
Renin angiotensin system, 115, 115F, 116, 117, 122, 186, 187, 313
Renin, 95, 102, 115F, 116, 120, 121, 122, 178, 185, 186, 187, 191, 312T
Renotropin, 4
Renovascular hypertension, 116-117, 120, 121F
Replacement solution (in hemofiltration), 240, 241
Resistance, glomerular arteriolar, 174
Resistance, peripheral, 91, 93, 270, 284

Resistance, vascular, 91, 100, 105, 116, 121, 174, 176, 191
Reticulocytes, 265
Retroperitoneal hemorrhage (in Magnetic Resonance), 360
Retroperitoneal fibrosis (in Magnetic Resonance), 360
Retroperitoneal neoplasm (in Magnetic Resonance), 360
Rheumatoid arthritis, 194
Rheumatoid factor, 28
Rickettsia, 211
Rifampicin, 212
Roll-over test (in pregnancy), 133-134
Salt intake (in pregnancy), 141
Saralasin, 176
Scintigraphy, 362
Sclerosis, glomerular, 8, 10, 155, 193, 195
SCUF (Slow Continuous Ultrafiltration), 227, 228, 229, 231F, 234, 236
SDT (Single-dose treatment in urinary tract infection), 49-63
Seldinger technique, 228, 235
Sepsis, 210T, 212, 213, 214T, 218, 220, 234, 248
Septic abortion, 213, 214T, 216
Shigella dysentery, 210
Shunt (AV), 229, 230, 234
Sieving coefficient, 247, 249, 250
Single-dose treatment, (urinary tract infection) 49-63
Sjiogren syndrome, 194
SLE (Systemic Lupus Erythematosus), 194
Slow Continuous Ultrafiltration (See SCUF)
Snakes (ARF by), 210T, 211, 212
Sodium cellulose phosphate, 76T, 78-79
Sodium, 9, 68T, 70, 72, 73, 75, 76T, 78, 79, 81, 173, 177, 186, 190, 247, 282, 283, 284, 286, 287
Sonography, 357, 362
Spironolactone, 122
Stenosis, renal artery, 120, 361, 362, 364
Steroids, 34, 35, 69, 144, 156, 157, 158, 159, 160, 162, 163, 164, 165, 181T, 194, 326, 327, 330, 335
Stones, calcium oxalate renal, prevention, 67-85, 68T, 76-77T
Streptomycin, 53, 57
Struvite, 78
Sulfadoxine, 50, 52
Sulphafurazole, 53, 54, 57
Sulphonamides, 50, 52, 53, 55, 58, 181T
Sulphormethoxine, 50
Suppressor T cells (lymphocytes), 30, 158, 184
Surgical acute renal failure, 215-216
Sympathetic nervous system, 104, 176
T cells (lymphocytes), 30, 31, 157, 184, 325, 326, 327, 328, 329, 330, 334, 335, 336, 338, 340
Testosterone, 4T
Tetracycline, 52, 55, 57, 58
Thiazide, 68T, 69, 72, 75, 76T, 79, 80, 81, 123
Thrombocytopenia, 185, 327
Thrombosis, glomerular, 185

Thromboxane (TX), 138, 139, 176, 177
Thyphoid fever, 211
Thyroid, 4T, 313
Thyrotoxicosis, 70
Ticarcillin, 181T
Total Parenteral Nutrition, 229
TPN (Total Parenteral Nutrition), 4T, 8, 12, 13
Transplant, renal (in Magnetic Resonance), 361, 364
Transplant, 210T
Transplantation, corneal, 192
Transplantation, bone marrow, 171, 185
Transplantation, liver, 171, 185
Transplantation, heart, 171, 187, 180, 187, 192
Transplantation, renal, 8, 171, 176, 178, 179, 180, 182, 185, 187, 188, 192, 193, 212, 268, 325, 331
Transplant donor, 8
Triglycerides, 94
Trimetazidine dihydrochloride, 34
Trimethoprim, 51, 52, 55, 57, 58, 181T
Tubuloglomerular feedback system, 176
Tumor (in Magnetic Resonance), 348, 349F, 353, 354F, 355, 356, 357
TX (Thromboxane), 138, 139, 176, 177
Ultrafiltrate (in continuous renal replacement therapy), 243, 246
Ultrafiltration (in continuous renal replacement therapy), 228, 234, 243F, 244, 245, 247, 248, 249, 250
Ultrafiltration, Slow Continuous (See SCUF)
Ultrafiltration coefficient (glomerular), 174
Urate, 9, 75
Urea, 240, 241, 250, 281, 283, 289, 290, 291, 292T, 293, 303
Uric acid nephropathy, 217
Uric acid, 71, 72, 73, 75, 77T, 80, 123, 132, 143, 188, 217
Urinary tract infection, 49-63, 68T, 72, 78, 211
Urinoma (in Magnetic Resonance), 360, 362
Urokinase, 35
Uveitis, 192, 195
Vasopressin, 4T
Verapamil, 89, 90, 91-97, 98, 100, 101, 104, 172, 181T, 188, 189
Vesico-ureteral reflux, 10
Viral hepatitis, 211
Virus, 28
Vitamin B12, 291, 292T
Vitamin D, 69, 70, 71, 78
Water diuresis, 177, 190
Wilm's tumor (in Magnetic Resonance), 356-357
WT32, 334, 339