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Kidney Disease

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CONTENTS

THE 31ST ANNUAL STONEBURNER LECTURE SERIES
Kidney Disease
Presented by the Division of Nephrology and the Department of Continuing Medical Education of the School of Medicine.
DONALD E. OKEN, M.D., *Guest Editor*

Introduction 110

Cancer and the Kidney 111
DONALD E. OKEN, M.D.

Glomerulonephritis 116
WILLIAM F. FALLS, JR., M.D.

Management of the Nephrotic Syndrome 124
DOUGLAS M. LANDWEHR, M.D.

On the Prevention of Acute Renal Failure (Vasomotor Nephropathy) 128
DONALD E. OKEN, M.D.

Pyelonephritis 132
WILLIAM F. FALLS, JR., M.D.

Evaluation of an Abnormal Urinalysis in the Asymptomatic Patient 140
DOUGLAS M. LANDWEHR, M.D.

The End-Stage Renal Disease Program (Adapted from Treatment of End-stage Renal Disease) 144
WILLIAM K. STACY, M.D.

Diabetic Nephropathy 148
BARRY B. KIRSCHBAUM, M.D.

COVER: X-ray of classical bilateral "staghorn" calculi, courtesy Dr. M. J. Vernon Smith, Professor of Surgery, MCV.

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INTRODUCTION

The 31st Stoneburner Lecture Series was planned to present an overview of some important aspects of clinical nephrology that we hope are of interest to a wide audience. The faculty for this symposium was drawn largely from the Medical College of Virginia Nephrology Division, and we were fortunate to have Dr. George E. Schreiner, Professor of Medicine at Georgetown University and a long-time friend, as our Stoneburner Lecturer.

Nephrology has grown to a full-fledged specialty in only 20 years; knowledge in the field has burgeoned, and our understanding of renal diseases has changed dramatically in that time. Renal transplantation is now a routine procedure and chronic dialysis programs abound. So routine have these therapeutic modes become that we may lose sight of their costly and awesome social implications.

The audience attending this lecture series came from several states and represented various medical disciplines. They entered freely into the discussion and thus contributed greatly to the value of the presentations. We offer thanks to them, to the lecturers whose presentations are summarized in this issue of the MCV QUARTERLY, and to the Department of Continuing Medical Education whose planning for this symposium was both thorough and efficient.

DONALD E. OKEN, M.D.
Professor of Medicine, and Chairman,
Division of Nephrology

Cancer and the Kidney

DONALD E. OKEN, M.D.

Professor of Medicine, and Chairman, Division of Nephrology, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia

Cancer of the kidney is associated with a bewildering array of extrarenal symptoms, and conversely, tumors far removed from the kidney produce intriguing renal functional abnormalities.

A variety of extrarenal complications are seen with hypernephromas, most of which rarely accompany Wilms tumors which grow rapidly and generally occur before the age of 7. Wilms tumors are quite susceptible to radiation therapy and surgery, and are to be strongly suspected when hypertension and an abdominal mass are found in a small child. Unless treated, they rapidly cause death and usually leave little opportunity for the patient to develop the striking extrarenal manifestations seen with hypernephroma.

Among the fascinating complications of hypernephromas (Table 1) is first, the extremely slow growth rate of a sizable minority of them. I have seen patients known to have hematuria for up to three years prior to the time that the tumor was found and, on reviewing the intravenous pyelogram done at the onset of hematuria, seen evidence that a renal mass had been present all along. Those tumors which do grow slowly may result in generalized amyloidosis both in the kidney and elsewhere. Another peculiarity of the hypernephroma, which is almost unique to this tumor, is the disappearance of metastases once the primary tumor has been removed. In only a few instances has there been histologic evidence that the "metastatic" lesions were indeed derived from a renal cell carcinoma. Nevertheless, the phenomenon of spontaneous regression of metastases seems well established and offers at least a gleam of hope for those in whom pulmonary metastases are found.

Perhaps equally remarkable is the finding of distant metastases many years after a renal cell carcinoma is removed surgically. The longest recorded survival between a diagnosis of renal carcinoma and the eventual death of a patient whose neoplasm was considered inoperable and left in place is 37 years.[1] Many patients have been reported to develop metastases 5, 10, and even 25 years after the resection of a hypernephroma. I have seen a patient who developed "solitary" metastases sequentially over a 19-year period before he succumbed. Unfortunately, while such cases stand out, metastases appear earlier in most patients and lead to death within two years in one third of patients.

Renal cell carcinoma also tends to extend via the renal vein lumen into the inferior vena cava. Such a circumstance is reported to occur in almost 10% of patients with hypernephromas,[2] and a substantial proportion of these tumors extends all the way up the vena cava into the right atrium.[3] The extending tumor usually is restricted to the venous lumen without penetration of the vessel wall and, as a result, is generally removable in its entirety. Surprisingly, such vascular involvement alone does not appear greatly to alter the prognosis at 5 or 10 years,[4] and extraction of the tumor mass is often both possible and desirable.

Fever, unexplained by infection, is a common concomitant of hypernephroma. Melicow and Uson[5] have reported that 16% of 577 cases of renal carcinoma presented with fever, often with weakness, anorexia, and weight loss, without any urologic symptoms whatsoever. A much higher percentage combined these systemic manifestations with hematuria, an abdominal mass, or pain. Thus, it is not

This paper is supported by USPHS Grant #AM 20132.

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TABLE 1
Peculiarities of Hypernephromas

1. Slow growth frequent
2. Disappearance of metastases (rare)
3. Cause of occult fever (FUO)
4. Renal vein/vena cava spread
5. Nonmetastatic hepatic dysfunction
6. Benign nephrohepatomegaly
7. Polycythemia, leukemoid reaction, eosinophilia
8. Heart failure
9. Spontaneous rupture of kidney

uncommon for patients with hypernephroma to present with "fever of unknown origin" and a baffling clinical picture. The fever may be low-grade and constant or intermittent and hectic, temperatures reaching 39.5 C (103 F) and higher.

First described in 1961,[6] a syndrome of nonmetastatic hepatic dysfunction (NHDS) accompanies the systemic abnormalities mentioned above in some 10% of patients with hypernephromas,[7] and presents with hepatomegaly which differs both functionally and histologically from the benign hepatomegaly frequently encountered with such tumors.[8] Here, biochemical abnormalities include elevated serum alkaline phosphatase concentrations, hypoalbuminemia, and hyperglobulinemia. Liver biopsy may reveal nonspecific inflammatory infiltrates, fatty deposition, degenerative and regenerative changes of liver cells, and areas of focal necrosis.[8] The syndrome may mimic metastatic disease of the liver from which it must be distinguished in that it is potentially reversible after nephrectomy is performed; recognition of NHDS may suggest a diagnosis of previously unrecognized hypernephroma.

Reviews of polycythemia generally include hypernephroma in the list of causes, but in fact, polycythemia has been associated with this tumor in only 1% to 4% of most reported series.[10] Actually, anemia is more the rule than the exception whether or not the patient has had significant hematuria.[11] Eosinophilia, thrombocytosis, leukocytosis, and even leukomoid reactions occur in significant association with hypernephromas.[12] Coupled with fever of unknown origin, or alone, such findings may present vexing diagnostic problems.

As in many other types of malignancy, thrombophlebitis accompanies renal cell carcinoma with some frequency. Varicocele, particularly when on the right, may be the first clue to the existence of a renal tumor.

Hypertension is recorded in more than 20% of the patients with hypernephroma and in some cases, at least, the hypertension has been cured by nephrectomy.[5] In others, hypertension is not surgically correctable, and it is difficult to be sure that the tumor was causally related. The renal tumor most clearly associated with hypertension is the "juxtaglomerular cell" tumor. Neoplastically benign, this growth, originating in macula densa tissue, produces huge amounts of renin with resultant secondary hyperaldosteronism and the complications attendant upon that condition. It is mentioned here as a rare but fascinating renal tumor which produces signs and symptoms which may erroneously suggest the existence of renal arterial stenosis or venous obstruction secondary to the spread of renal adenocarcinoma or the hyperreninism sometimes associated with Wilms tumors.[13]

Uncommon but life-threatening vascular complications of hypernephromas include high-output congestive heart failure and spontaneous rupture of the kidney with hemorrhagic shock. Heart failure is attributable to highly vascular metastases with arteriovenous communications analogous to those observed in Paget disease.[14] Spontaneous rupture produces massive retroperitoneal hemorrhage closely resembling a ruptured aortic aneurysm and is equally lethal.[15]

Renal Complications of Extrarenal Malignancies

Space does not permit a detailed discussion of the many abnormalities of renal function found in subjects with malignant diseases; however, I shall comment upon the fluid and electrolyte disorders which frequently occur (Table 2), and discuss the nephrotic syndrome associated with malignancy.

Hypercalcemia may result from bony metastases or the forced immobilization of acutely ill patients. Certain cases are the result of parathormone secreting tumors which function autonomously,[16] and a growing number of reports have called attention to the existence of prostaglandin-secreting tumors producing hypercalcemia which may be reversed with indomethacin.[17] The hypercalcemia caused by both hormone-secreting tumors is reversible with complete removal of the tumor. Persistence of hypercalcemia after the primary tumor is excised may reflect the other causes of hypercalcemia (see Table 2), or be the result of metastases which, like the parent tumor, also synthesize prostaglandins or parathormone.

Hypercalcemia, if severe, may have devastating

TABLE 2
Electrolyte Abnormalities with Nonrenal Malignancies

1. HYPERCALCEMIA—producing severe volume depletion and functional renal failure, nephrolithiasis or nephrocalcinosis:
   a. Metastases
   b. Corticosteroid withdrawal/adrenal insufficiency
   c. Prostaglandin-secreting tumors
   d. Forced immobilization
   e. Parathormone-secreting tumors

2. VOLUME DEPLETION AND HYPONATREMIA*—producing functional renal failure:
   a. Hypoadrenalcorticism of tumor replacement, amyloidosis, surgical ablation of the adrenals, disseminated intravascular coagulation (DIC).
   b. Excessive diuretic therapy for peritoneal metastases or mechanical edema.
   c. Rapidly developing ascites and edema
   d. Extrarenal electrolyte losses:secretory diarrheas, villous adenomas, drug Rx hyperemesis, intestinal obstruction, malabsorption and carcinoid.

* To be distinguished from the syndrome of inappropriate ADH secretion (CNS tumor/metastases, vasopressin-secreting tumors, vincristine/cyclophosphamide therapy, and tricyclic anticonvulsants) where renal function does not specifically become impaired.

3. VOLUME DEPLETION AND HYPERNATREMIA—with functional renal failure:
   a. Diabetes insipidus of pituitary replacement, brain metastases, urinary outflow obstruction.
   b. Impaired thirst mechanism—organic or functional results of cachectic illness.
   c. Kaliopenic and hypercalcemic nephropathy
   d. Nasogastric feeding—osmotic diuresis

4. KALIOPENIC NEPHROPATHY—with impaired concentrating capacity and susceptibility to pyelonephritis:
   a. Pernicious gastrointestinal electrolyte loss (see section 2)
   b. "ACTH"-producing tumors
   c. Juxtaglomerular cell tumors
   d. Improper diuretic therapy
   e. Lysozymuric and nonlysozymuric leukemias

effects upon the kidney, producing severe volume depletion and functional renal failure, nephrolithiasis with infection and urinary outflow obstruction, or severe tubulointerstitial disease due to nephrocalcinosis.

Volume depletion and hyponatremia are frequent complications which plague the patient with malignant disease. Generically, the concurrence of volume depletion and hyponatremia reflects a state in which both sodium and water are lost from the body in large amounts but the net sodium loss exceeds the water deficit. Causes include adrenal insufficiency owing to tumor replacement, adrenal amyloidosis, surgical ablation of the adrenals as a therapeutic adjuvant, and disseminated intravascular coagulation. Ill-advised sodium restriction with vigorous diuretic therapy in an attempt to minimize mechanical edema or ascites due to peritoneal metastases is a reasonably common cause of hyponatremic volume depletion. The rapid development of ascites and edema in sodium-restricted patients is another cause. Massive electrolyte losses may occur through the intestinal tract as a result of the hyperemesis associated with cancer chemotherapy, the secretory diarrheas [amine precursor uptake and decarboxylation (APUD) syndromes], mucus-secreting intestinal tumors, intestinal obstruction, or malabsorption. Massive fluid losses may be seen in the carcinoid syndrome. The severe volume depletion attendant upon these complications may produce major abnormalities in renal function unless corrected.

Hyponatremia may also be seen in the presence of extracellular fluid volume expansion—the so-called syndrome of inappropriate antidiuretic hormone (ADH) secretion. Causes include vasopressin-secreting tumors (especially of lung), primary or metastatic intracranial malignancies, vincristine or cyclophosphamide therapy to retard tumor growth, and the tricyclic anticonvulsants.[18]

Volume depletion may coexist with hypernatremia for a variety of reasons. Diabetes insipidus may result from tumor invasion of the pituitary gland, intracranial metastases, or urinary outflow obstruction. Nasogastric feeding of concentrated solu-

tions lacking in free water is a common cause of an obligatory solute diuresis. Impaired thirst due to either organic brain disease or as a functional result of a cachectic illness may contribute greatly to the development of hypernatremic volume depletion, a situation which is further aggravated if kaliopenic or hypercalcemic nephropathy is present.

Kaliopenic (hypokalemic) nephropathy is manifested by impaired concentrating capacity and an increased susceptibility to pyelonephritis. It may result from pernicious gastrointestinal electrolyte losses, hyperadrenal corticism secondary to an adrenocorticotropic hormone (ACTH)-producing tumor, juxtaglomerular cell tumors, or improper diuretic management. Major degrees of hypokalemia may be seen in patients with leukemia, especially those leukemias associated with lysozymuria.[19] Impaired concentrating capacity may well lead to serious volume depletion and secondary renal dysfunction.

Nonelectrolyte-related abnormalities of the urinary tract are listed in Table 3, but cannot be covered in detail in this brief review.

Nephrotic Syndrome Associated with Malignancy

An increasing number of reports amply document the association of the nephrotic syndrome with malignant tumors.[20] Some cases are the result of amyloidosis, others to renal venous outflow obstruction, and still others to probable immune mechanisms. Myeloma and lymphoproliferative disorders are among the most common tumor-related causes of amyloidosis, yet solid tumors also may cause amyloid deposition if their course is not an accelerated one.[22] Invasion of the renal veins and vena cava by hypernephromas or other tumors, and compression of venous structures by retroperitoneal nodes, tumor mass, or retroperitoneal fibrosis may produce mechanical edema and marked proteinuria but are uncommon causes of the nephrotic syndrome.

TABLE 3
Nonelectrolyte Renal Complications of Malignancies

1. Fanconi syndrome
2. Renal tubular acidosis
3. Hydronephrosis—obstructive renal failure
4. Renal amyloidosis
5. Urate nephropathy
6. Radiation nephritis
7. "Citrovorum rescue," antimetabolite nephropathy
8. Myeloma kidney
9. Renal hemorrhage, outflow obstruction
10. Cortical necrosis post-disseminated intravascular coagulation (DIC)
11. Tumor-related lupus erythematosus (especially with lymphoma)
12. Renal vein/arterial or vena caval occlusion
13. Vasomotor nephropathy—hemorrhage, sepsis, shock, and so forth
14. Nephrolithiasis/nephrocalcinosis
15. Obstruction of bladder outflow, ureters, or urethra by tumor invasion
16. Renal invasion by metastases
17. Benign nephromegaly, etiology unknown
18. Retroperitoneal fibrosis/tumor invasion, producing ureteral obstruction
19. Nephrotic syndrome
20. Acute papillary necrosis, pyelonephritis

Tumor-related nephrotic syndrome occurs with some frequency in the absence of either amyloidosis or venous obstruction, Hodgkin disease leading the list of causes.[21] Lymphosarcoma, chronic lymphocytic leukemia, and Burkitt lymphoma also have been associated with frank nephrosis.[21] Of the solid tumors, bronchogenic carcinoma has been the most often found. Malignancies of the stomach, colon, breast, skin, ovary, oropharynx, and kidneys have all been incriminated.

The majority of lymphoma-related cases have shown minimal glomerular changes on biopsy or postmortem study. Most other types of tumors have produced membranous, proliferative or mixed membranous and proliferative lesions. Reversal of the nephrotic syndrome after excision or chemotherapy of the primary tumor has been observed by many authors, the return of proteinuria signaling regrowth of the malignancy [21]

In this overview, I have tried to touch on the highly complex interaction between carcinomatosis and the kidney. The manifestations of this relationship are so diverse and numerous that it is well to remember the adage, "Many a medical reputation has been lost in the retroperitoneum." It is hoped that continued awareness of the protean manifestations of tumors relating to the kidney will help to preserve the reputations of all clinicians.

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Glomerulonephritis

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In this paper the histologic picture of the most common disorders usually classified under the heading of glomerulonephritis will be reviewed, and the subject of angiitis will be briefly addressed. A special effort will be made to relate renal biopsy findings to the immunologically mediated pathogenetic process which is thought to be operative in each case. Where it seems appropriate, a few comments will also be made on clinical and pathological correlations. The specific entities to be covered include: diffuse proliferative glomerulonephritis; focal proliferative glomerulonephritis; membranous glomerulonephritis; antibasement membrane antibody disease; rapidly progressive glomerulonephritis (crescentic disease); membranoproliferative glomerulonephritis; lipoid nephrosis (nil disease); focal, segmental, and global sclerosis; polyarteritis nodosa; hypersensitivity angiitis; and Wegener granulomatosis. Few comments will be made about therapy because that subject is covered elsewhere in this issue. The review will be concluded by a discussion of the prognostic value of information gleaned from careful biopsy evaluation.

Two types of immunologic injury to the kidney have been clearly defined in experimental models and are thought to have distinct clinical counterparts.[1] These are immune-complex mediated disease and antibasement membrane antibody disease. The former is the most common and will be considered first.

Immune-Complex Glomerulonephritis

The pathogenesis of several glomerulonephritic patterns to be discussed subsequently seems to be of this type. In the classic immune-complex model, the following sequence of events is thought to occur: an antigenic substance gains access to the bloodstream and is delivered to immunologically competent cells which begin making antibody in response to the challenge; as antibody is released into the circulation, it combines with antigen to form complexes. Under certain circumstances of antigen excess, the complexes which are formed are small and soluble and are not phagocytized in the reticuloendothelial system; these activate the complement cascade via the classic pathway ($C_1 \rightarrow C_4 \rightarrow C_2 \rightarrow C_3$), and the entire aggregate of antigen, antibody, and complement components precipitates in the region of the glomerular basement membrane. The terminal components of the complement system include substances which increase vascular permeability and are leukotactic. An increase in the permeability of the capillary wall leads to leakage of protein into Bowman space and the influx of leukocytes may cause proteolytic destruction of portions of the glomerular capillary wall; in response to this assault, endothelial and mesangial cell proliferation occur. Thus, any antigen capable of stimulating an antibody response is a potential cause of immune-complex mediated injury. As we shall see, numerous inciting antigens have been identified, but the pattern of injury may vary considerably, probably depending on the nature of the antigen and the responsiveness of the host.[2]

Our understanding of the nature of immunologic injury to the glomerular capillary has been enhanced greatly by the development of immunofluorescent staining techniques. In this process a quick-frozen renal biopsy section is treated with a fluorescent-tagged antibody against a specific class of human globulin, complement component, or fibrinogen.

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Fig 1—Immunofluorescent microscopic preparation (anti-IgG) of a portion of a glomerulus from a patient with poststreptococcal glomerulonephritis. Note "lumpy-bumpy" pattern. (× 1500).

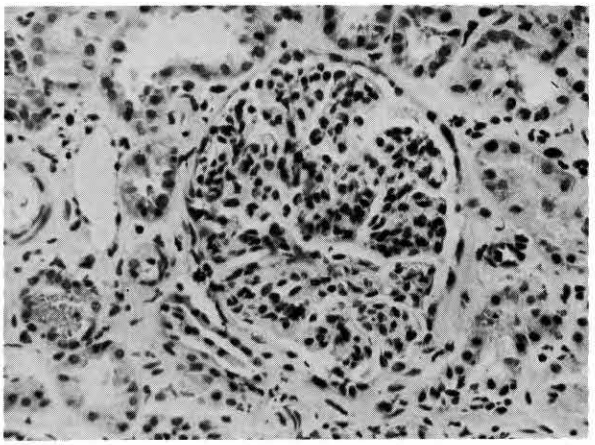

Fig 2—Light microscopic preparation (H & E) of a portion of renal biopsy from a patient with diffuse proliferative glomerulonephritis following streptococcal infection (×200).

When this preparation is viewed with fluorescent microscopy, a clear picture of the area of protein deposition is obtained. In the case of immune-complex mediated disease, a "lumpy-bumpy" pattern will be observed and is the hallmark of this type of injury.

Diffuse Proliferative Glomerulonephritis

Figure 1 is a photomicrograph of the immunofluorescent staining for IgG in a patient with acute poststreptococcal glomerulonephritis. Note the coarse, granular deposition of the immunofluorescent material in the area of the capillary basement membrane and the mesangium. Figure 2 is the light microscopic correlate of this lesion and shows the characteristic picture of diffuse, proliferative glomerulonephritis. The glomerulus is swollen and the capillary loops are occluded by proliferating mesangial and endothelial cells; there is marked hypercellularity and an influx of foreign inflammatory cells is noted. Figure 3 is a high-power view of an electron micrograph which demonstrates the classic appearance and location of the electron-dense deposits which are thought to represent the deposited complexes. Note that the deposits are quite large, "hump-like," and located in a subepithelial position; the foot processes in the area of the deposit have become fused. This phenomenon of foot process fusion has been found to correlate closely with the presence of proteinuria.

The immunofluorescent and light microscopic picture described above is typical of the aggressive type of immune-complex mediated disease characterized by poststreptococcal glomerulonephritis but is by no means specific to it. A similar light microscopic appearance may be seen in some patients with lupus erythematosus, bacterial endocarditis, nephritis associated with infected ventriculojugular shunts, cryoglobulinemic nephropathy, and other antigenic insults.[2] Diffuse proliferative glomerulonephritis secondary to lupus erythematosus can usually be distinguished from poststreptococcal disease because the electron-dense deposits in lupus are usually located on the subendothelial surface of the basement membrane (Fig 4) and discrete viruslike particles may also be evident.[2] The site of deposition in other diseases is

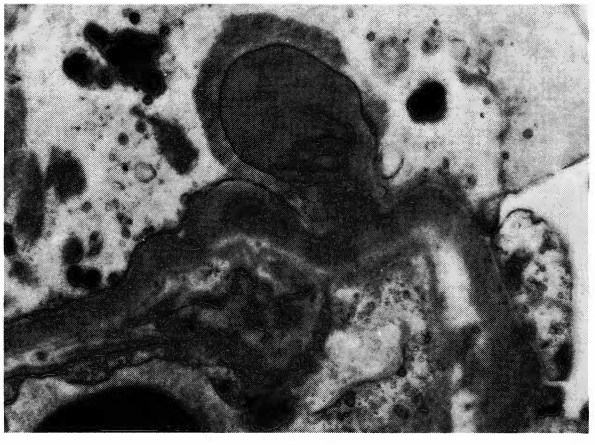

Fig 3—Electron microscopic preparation of a portion of a glomerulus from a patient with acute poststreptococcal glomerulonephritis. Note large subepithelial electron-dense deposit, "hump" (× 32,000).

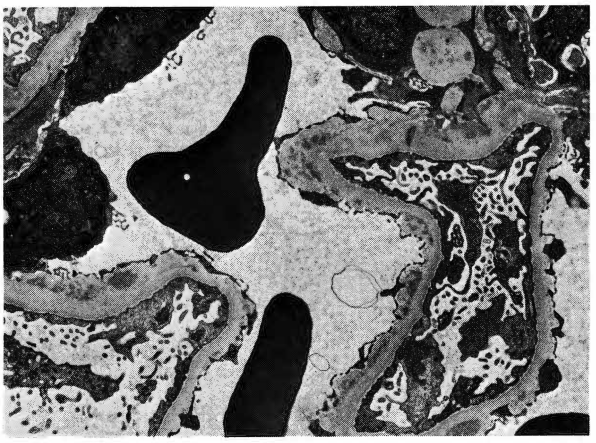

Fig 4—Electron microscopic preparation of a portion of a glomerulus from a patient with systemic lupus erythematosus and a diffuse proliferative lesion by light microscopy. Note large subendothelial deposits (× 10,000).

variable, but in many cases with proliferative lesions they are subendothelial.

In most cases of diffuse proliferative glomerulonephritis associated with lupus, one can find serologic evidence of activation of the classic complement pathway (low serum $C_{1q} \rightarrow C_2 \rightarrow C_4 \rightarrow C_3$).[2] Such changes are variable in other diseases with proliferative lesions and in some cases of poststreptococcal disease there may also be evidence of activation of the alternate complement pathway. In this circumstance C_3 is activated directly, bypassing the earlier components. A number of substances are known to activate C_3 directly. These include endotoxin, properdin, and IgA-containing complexes.

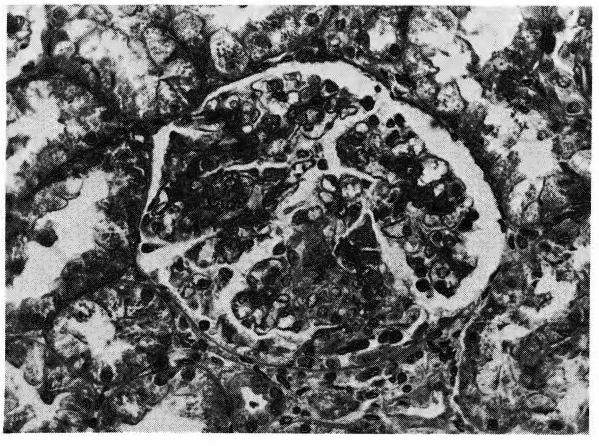

Fig 5—Light microscopic preparation (H & E) of a portion of a renal biopsy from a patient with systemic lupus erythematosus, showing a focal proliferative lesion (× 400).

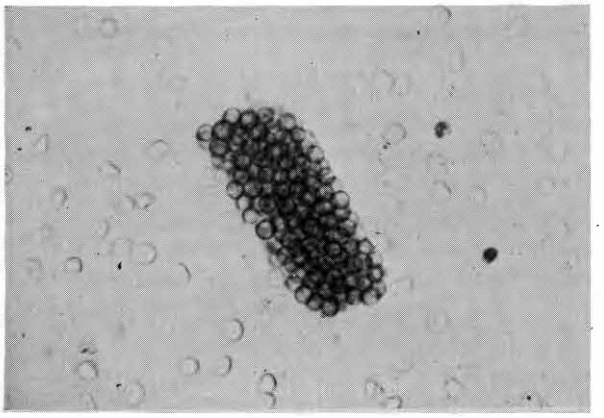

Fig 6—Red blood cell cast in urine sediment from a patient with poststreptococcal glomerulonephritis (× 1,000).

The course of immune-complex mediated proliferative glomerulonephritis is highly variable, depending on the disease process, and may well be related to the supply of antigen. In lupus erythematosus there is an inexhaustible supply of antigen in the form of various nucleoprotein derivatives including double-stranded DNA.[3] As a consequence, lupus glomerulonephritis tends to be an ongoing, progressive disease. On the other hand, poststreptococcal disease tends to be self-limited, particularly in children,[4] perhaps because of the rapid eradication of antigen from the body.

Focal Proliferative Glomerulonephritis

Another histologic pattern of immune-complex mediated glomerular injury is demonstrated in Figure 5. This is the pattern of focal (among glomeruli) and segmental (within a glomerulus) glomerulonephritis. By immunofluorescence the deposited globulins tend to be localized more within the mesangial region than along the capillary walls, and IgA may frequently be found along with other immune globulins and complement components. Evidence of alternate complement pathway activity may also be seen and it has been suggested that IgA-containing complexes may set this pathway in motion.[5]

Focal proliferative lesions may be seen in a wide variety of disorders including some patients with lupus erythematosus, Schönlein-Henoch purpura, and Berger disease (IgA nephropathy).[2]

Figure 6 is the photomicrograph of a red cell

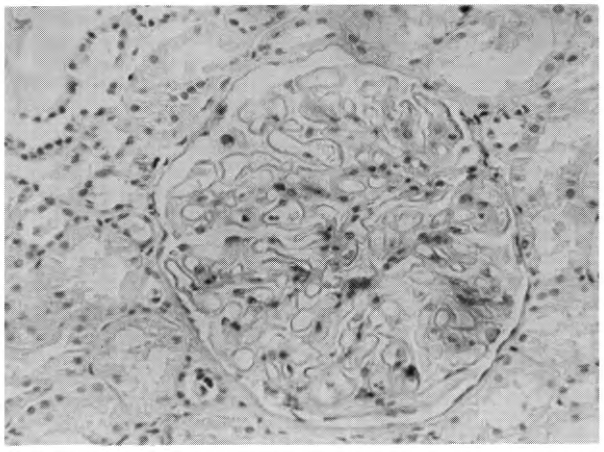

Fig 7—Light microscopic preparation (PAS) of a portion of a glomerulus from a patient with membranous glomerulonephritis (× 200).

Fig 9—Immunofluorescent preparation (IgG) from a portion of biopsy of a patient with antibasement membrane antibody disease. Note linear pattern of fluorescence. (× 1500).

cast. This structure is considered to be characteristic of inflammatory or necrotizing disease of the glomerulus. It is introduced at this time because, being the most characteristic feature of the urine sediment in patients with glomerulonephritis, it tends to correlate with the type of proliferative lesions which have just been described.

Membranous Glomerulonephritis

In each of the immune-complex mediated disorders mentioned above, the light microscopic picture demonstrated evidence of cellular proliferation and inflammation. Such is ordinarily not the case in membranous glomerulonephritis. Figure 7 demonstrates the typical light microscopic picture of this lesion. The only recognizable abnormality is thickening of the basement membrane. On immunofluorescent and electron microscopic study this membrane alteration is found to be secondary to finely granular deposition of immunoprotein along the subepithelial border of the basement membrane. In addition to IgG and IgM, complement components may be deposited. Why this deposition is not associated with the induction of an inflammatory reaction like that described above is unclear. In animal models similar lesions are associated with small, weak-affinity antibodies[6] and it is possible that this is also true in human disease.

A membranous pattern may be seen in a number of clinical states including: lupus erythematosus, drug intoxication (heavy metals, tridione, penicillamine), solid tumors (carcinoma of the lung and colon), sickle cell disease, hepatitis B infection, and as an idiopathic occurrence.[2] Patients with membranous nephropathy usually present with a nephrotic state characterized by edema, hypoalbuminemia, hypercholesterolemia, heavy proteinuria, and fat-filled macrophages in the urine sediment.

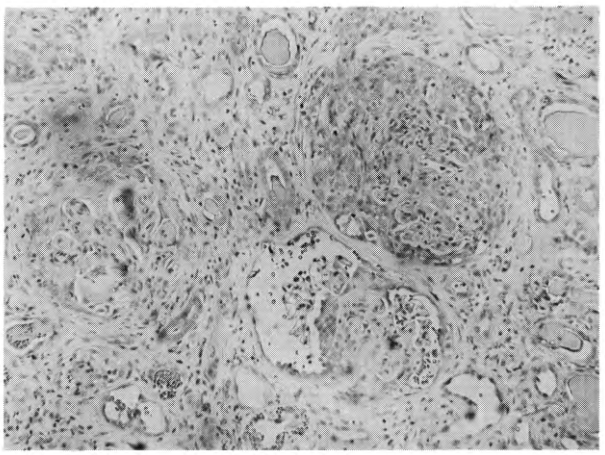

Fig 8—Light microscopic preparation (H & E) from renal biopsy of a patient with rapidly progressive glomerulonephritis. Note marked crescent formation by proliferating glomerular epithelial cells (× 80).

Antibasement Membrane Antibody Disease

The second, well-established type of injury to the glomerular capillary is that caused by circulating antibasement membrane antibody.[1] In this disorder antibodies, usually of the IgG class, develop against

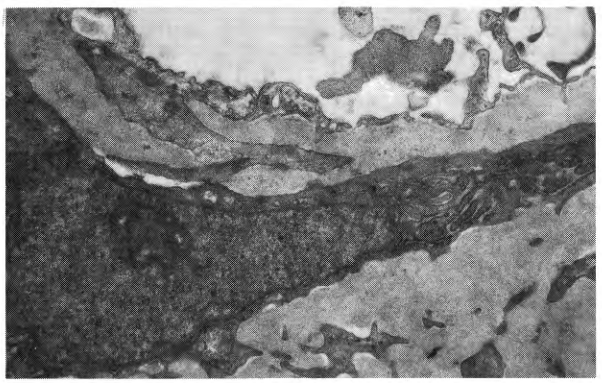

Fig 10—Electron microscopic representation of basement membrane reduplication in a patient with type I membranoproliferative glomerulonephritis. (× 14,000).

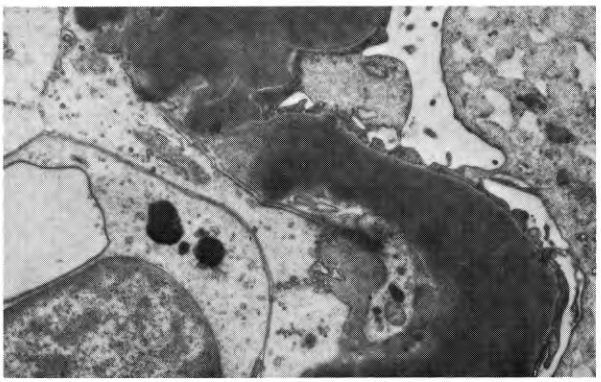

Fig 11—Electron micrograph from a patient with membranoproliferative glomerulonephritis type II. Note the homogeneous electron-dense deposit throughout the basement membrane. (× 15,000).

some antigenic component of the basement membrane. These abnormal antibodies enter the circulation and are carried to the kidney where they attach to antigens on the basement membrane. This reaction of antigen and antibody activates the complement cascade, probably via the classic pathway, and induces an inflammatory reaction in a manner analogous to that described earlier. Under certain circumstances there may be cross-reactivity of the glomerular antibasement membrane antibody with other basement membranes in the body, particularly the lung. It is this sharing of antigenic determinants that is thought to lead to lung hemorrhage and glomerulonephritis in Goodpasture syndrome.[7]

Rapidly Progressive Glomerulonephritis (Crescentic Disease)

A histologic picture of marked proliferation of both visceral and parietal epithelial cells, leading to extensive crescent formation (Fig 8) associated with a rapidly progressive, downhill clinical course may be seen under a number of different clinical circumstances.[8] It is classically seen in the kidneys of patients with Goodpasture syndrome and in this setting immunofluorescent staining invariably shows a linear deposition of antibody (Fig 9). A crescentic pattern may also be seen in patients with rapidly progressive glomerulonephritis without lung hemorrhage. In this circumstance only about 40% of the patients show an immunofluorescent pattern which is indicative of antibasement membrane antibody disease.[2] The remainder show a "lumpy-bumpy" fluorescent pattern indicative of an immune-complex pathogenesis. This is confirmed by electron microscopy which demonstrates electron-dense deposits. The common denominator of the crescentic pattern seems to be damage to the glomerular basement membrane of such a magnitude that fibrinogen and other components leak into Bowman space where the coagulation process is activated. This, in turn, stimulates proliferation of epithelial cells and attracts an influx of macrophages.[9] The picture of crescent formation and immune-complex deposition may also be seen in diffuse proliferative lupus and certain of the angiitic processes to be discussed later.

Glomerulonephritis in Which the Pathogenesis is Not Clearly Defined: Membranoproliferative (Mesangiosclerotic Glomerulonephritis)

Great interest is currently being focused on lesions included under this heading[10]; its classification is in a state of almost daily flux. On light microscopy the glomeruli from patients with this type of lesion show a lobular pattern which is associated with an increase in both the cellular and acellular components of the mesangium. This type of lesion may be seen in a variety of disease states including lupus erythematosus and non-resolving poststreptococcal glomerulonephritis. It is nonspecific in and of itself. Typical membranoproliferative lesions have also been described in children and adolescents who usually present with a nephrotic syndrome accompanied by varying numbers of red blood cells and red blood cell casts in the urine sediment. Early on, attention was drawn to the fact that many of these children had low levels of circulating C_3 and some had evidence of

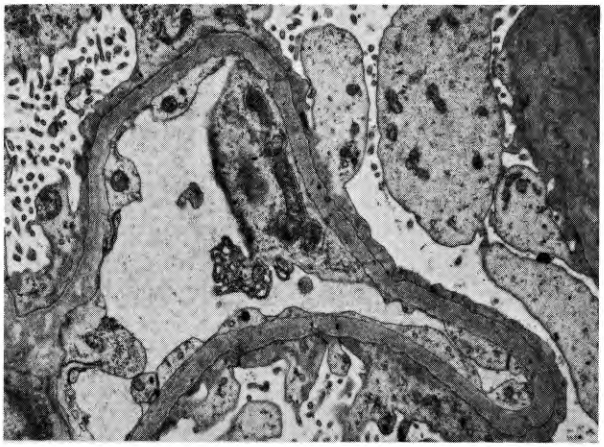

Fig 12—Electron microscopic preparation of a portion of a renal biopsy from a patient with "nil disease." Note normal-appearing basement membrane, the absence of deposits, and the presence of fused foot processes (× 14,000).

activation of the alternate complement pathway as manifested by the presence of properdin in the glomerular mesangium.[2] Careful evaluation of biopsies with silver staining techniques revealed extensive reduplication of the basement membrane. Electron microscopic study confirmed this finding and suggested that the new basement membrane was laid down by proliferating mesangial cells burrowing beneath the cytoplasm of the endothelial cells (Fig 10). Subsequent evaluation of a larger number of cases has revealed the presence of some IgG deposits and early-reactive complement components in the mesangium. These patients have been classified as having membranoproliferative glomerulonephritis, type I

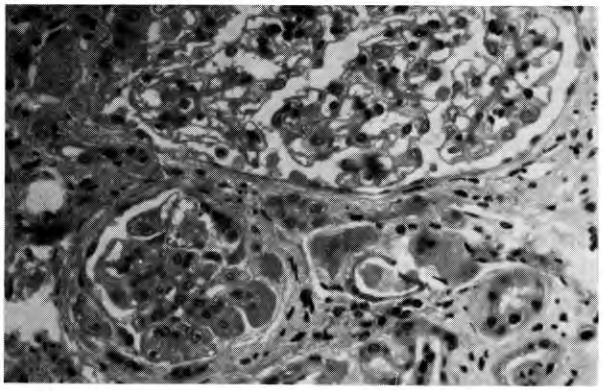

Fig 13—Light microscopic representation (PAS) of renal biopsy section from a patient with focal, segmental sclerosis. Note the peripheral hyaline lesions in lower glomerulus while upper glomerulus is relatively spared. (× 200).

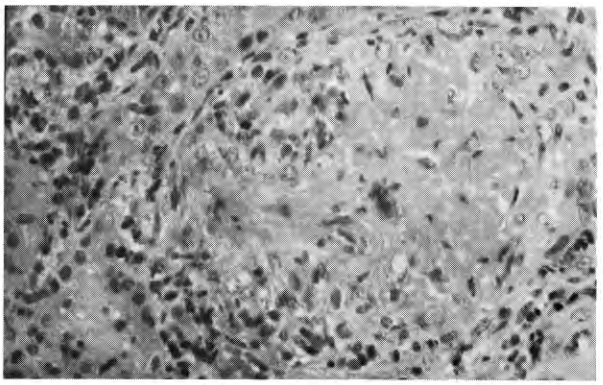

Fig 14—Light microscopic view of necrotic glomerulus (H & E) from a patient with Wegener granulomatosus. (× 500).

and are thought to have a variant of a classic immune-complex mediated disease. At present there is no clue as to the nature of the inciting antigen or antigens.

Membranoproliferative glomerulonephritis, type II, on the other hand, seems to be a more specific, homogeneous disease entity, albeit poorly understood. This disorder is also seen more frequently in younger individuals who usually present with a nephrotic syndrome. The light-microscopic biopsy picture is indistinguishable from the lobular pattern with basement membrane reduplication seen in type I. A distinctive dense deposition involving all of the basement membranes is seen with electron microscopy (Fig 11),[10] however, and positive immunofluorescent staining is seen only for complement. The staining is intense and seems to involve the same areas as the electron-dense deposits. These abnormal histologic changes accompany a blood chemical picture which is characterized by low C_3 levels, normal early-reacting complement components, and the presence of an abnormal circulating globulin component which is capable of activating C_3 directly (C_3 nephritic factor).

Type II membranoproliferative glomerular nephritis is felt to be mediated via alternate pathway complement activation alone. For reasons that are not clear, type II disease has been observed with some frequency in patients with partial lipodystrophy and glomerulonephritis. Both type I and type II may show recurrence in the transplanted kidney.

Lipoid Nephrosis of Childhood (Nil Disease)

Most young children who have a nephrotic syndrome display no recognizable abnormality on light

or immunofluorescent microscopy of their renal biopsy. The only recognizable change is fusion of the epithelial cell foot processes (Fig 12) which can be observed on electron microscopic section. This histologic pattern correlates with an essentially normal urine sediment. If cellular elements are present in more than very scant numbers, some other process must be considered. A similar lesion has been noted to occur in some patients with active Hodgkin disease and to disappear with successful treatment of the underlying disorder. This observation, taken in conjunction with the recognition that Hodgkin disease is a T-cell related malignancy, has invited speculation that the idiopathic nephrotic syndrome of childhood may also be a manifestation of abnormal T-cell function.[11] Such conjecture is interesting but entirely unproven.

Focal, Segmental, Global Sclerosis

Those young children with a nephrotic syndrome who have neither a spontaneous remission nor a favorable response to steroid therapy probably have this disorder. In most cases the initial involvement is deep in the juxtamedullary glomeruli, and centrifugal progression occurs throughout the entire cortex. In the focal lesion, some glomeruli are involved by segmental areas of mesangial sclerosis or hyalinization which are easily noted on light microscopy (Fig 13). Immunofluorescent studies may show spotty, nonspecific staining for IgG and complement, and electronmicroscopy demonstrates an increase in mesangial matrix material with an occasional mesangial deposit. In patients with global sclerosis the changes are similar but involve the entire glomerulus. The etiology of this disorder is uncertain, but an immune-complex mechanism is suggested by the finding of immunoglobulins in the sclerotic lesions and its occurrence in association with hepatitis B infection.[12]

Angiitis

The angiitic processes are probably immunologically induced and for our purposes may be divided into three groups, depending on the size of vessels involved and the presence or absence of granulomatous change.

Polyarteritis nodosa: Histologically this disorder is characterized by necrotizing, inflammatory lesions of medium-sized and large arteries. The hallmark of this process in the kidney is the presence of ischemic necrosis and infarction. Deposits of immune globulin, complement, and fibrin may be seen with immunofluorescent stains of the vessel walls. Clinically, patients with this disturbance present with a picture of hypertension, mononeuritis multiplex, central nervous system disturbances, and progressive renal insufficiency with an active urinary sediment.

Hypersensitivity angiitis: This is an angiitic process which involves small vessels including arterioles, venules, and the capillary loops of the glomerulus. Segmental necrosis of glomerular tufts may be seen on light microscopy and there may be nonspecific deposition of immune globulin and complement noted by immunofluorescence and light microscopic studies. Vasculitis of the skin is a frequent accompaniment of the renal lesions. This type of angiitis has been reported as a manifestation of hypersensitivity to a number of drugs. Hepatitis B infection has also been described in association with this disorder.[13]

Granulomatus arteritis: Wegener granulomatosis, the prototype of this disturbance, is characterized by the presence of necrotizing granulomas in the respiratory tract and a necrotizing, proliferative lesion of the renal glomerulus (Fig 14). Immunoglobulins and fibrin are deposited in a nonspecific glomerular pattern and crescents may be seen with frequency. Although thought to be of immunologic origin, the antigenic stimulus for this disease is unknown.[14]

Prognosis of Immunologically Mediated Renal Injury

The question, Why do a biopsy? frequently arises. Information from tissue examination should be of value in determining the proper diagnosis, prognosis, and treatment. We have pointed out the diagnostic value in the histologic review above. The prognostic information to be gained may be substantial and is outlined below.

As noted earlier, the course of a patient with an immune-complex mediated diffuse proliferative lesion is variable and relates to the underlying disease process. In those patients with an idiopathic lesion or in lupus the prognosis is usually poor. Patients with membranous lesions secondary to a recognized antigen which can be withdrawn or eradicated frequently show remission or improvement. Thirty percent of patients with an idiopathic nephrotic syndrome secondary to membranous nephropathy may have a spontaneous remission whereas the course of the remainder tends to be indolently downhill with a continued nephrotic syndrome. Patients with crescentic disease either related to an antibasement membrane

antibody or to circulating immune complexes do poorly. The prognosis in both types of membranoproliferative lesions is one of slow progression to end-stage disease in 10-12 years. The prognosis in nil disease is excellent with a high incidence of spontaneous remissions. Focal and global sclerotic lesions are associated with a slow but inexorable deterioration in renal function. The prognosis for untreated polyarteritis nodosa and Wegener granulomatosis is very poor. A similar prognosis is seen with small vessel angiitis unless it is drug-related in which case withdrawal of the offending agent may be accompanied by improvement.

In summary, the histopathology of the more common glomerulonephritic and angiitic lesions which may be seen on renal biopsy has been reviewed. Their diagnostic and prognostic implications have been discussed. Undoubtedly, the future will bring alterations in the presently outlined classifications as our understanding of the underlying immunologic pathogenetic mechanisms expands.

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Management of the Nephrotic Syndrome

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The nephrotic syndrome represents one of the major clinical problems in nephrology. It is usually defined as the constellation of clinical findings which includes edema, massive proteinuria, low serum albumin, high serum cholesterol, and the presence of oval fat bodies in the urine.[1] However, if we focus on the primary disturbance in the patient, that is, massive proteinuria, the nephrotic syndrome may be defined more simply as the clinical and metabolic consequences of persistent and massive proteinuria. The other manifestations listed in the classic definition are all inconstant and secondary to this loss of protein and may be found in other clinical disorders. Proteinuria is considered massive when it is greater than 3.5 mg/kg body weight per day, and persistent when present for many weeks or months. For diagnosis of the nephrotic syndrome, 24-hour urine protein excretion must be measured; a spot measurement is inadequate because some patients with massive proteinuria produce occasional specimens with little or no protein.

In understanding potential causes of the nephrotic syndrome, it is useful to recognize two general categories of disease.[2,3] One is the nephrotic syndrome associated with systemic illnesses. The other is not associated with a recognizable systemic process, and thus reflects only intrinsic renal disease. The most common systemic diseases associated with the nephrotic syndrome are diabetes mellitus, systemic lupus erythematosus, malignancy and amyloidosis. Additionally, there is a large variety of other diseases less commonly associated with the nephrotic syndrome. Many of these involve immune and toxic reactions related to drugs, as well as infectious and environmental agents. Although these entities are uncommon, it is important to recognize them, as removal of the drug or toxin, or definitive treatment of the infection, is a fundamental part of the management of these patients. Drugs shown to be associated with the nephrotic syndrome include the antiepileptic drugs paradione and tridione, anticoagulant agents, and penicillin. Forms of allergic reactions associated with the nephrotic syndrome include those following bee sting or exposure to poison oak or poison ivy. Chronic infections which are known to be complicated by the nephrotic syndrome include syphilis, malaria, hepatitis and toxoplasmosis.

There are several intrinsic renal diseases which cause the nephrotic syndrome. Recognition of these depends on characteristic morphologic findings in the renal biopsy specimen. The first is the clinicopathologic entity referred to as nil disease or lipoid nephrosis.[2] As implied in the term nil disease, there is little, if any, change in the normal architecture of the kidney when examined by light microscopy; however, electron microscopy does disclose changes of epithelial foot process fusion. Nil disease is the predominant cause of the nephrotic syndrome in children, particularly between ages 2 and 5 years; it is a less common cause in adults, accounting for approximately 15% of adult cases of primary nephrotic syndrome.

The second intrinsic renal disease which causes the nephrotic syndrome is a condition termed idiopathic membranous glomerulopathy[2] and it is found most frequently in adults. This term refers to the morphological changes of diffuse thickening of the basement membrane of all glomeruli. Within and to

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the outside of the basement membrane are found desposits which have been shown to contain immunoglobulins and serum complement components. They are thought to result from the deposition of circulating complexes of antigen and antibody, and are responsible for injury to the glomerulus which results in heavy proteinuria. Membranous glomerulopathy accounts for approximately 40% of the primary nephrotic syndrome in adults. It is relatively uncommon in children in the United States.

A third intrinsic renal disease which causes nephrotic syndrome is termed membranoproliferative glomerulonephritis.[3] In this disease the mesangial or supporting cell of the glomerulus is affected. Although the cause of this disease is not understood, immune deposits may be found in the mesangial area. This is an uncommon cause of nephrotic syndrome in adults but is perhaps the most common cause in patients aged 10 to 20 years. Prognosis for this disease is not good as its course commonly leads to renal failure.

The fourth intrinsic disease recognized as causing the nephrotic syndrome is termed focal sclerosing glomerulonephritis.[2,3] As this pathologic term indicates, the lesion involves a process which at first is confined only to parts of individual glomeruli. Again, the cause is unknown, although immune deposits are found in the areas of scarring. Like membranoproliferative glomerulonephritis, this disease also frequently results in renal failure.

In managing patients with the nephrotic syndrome, it is useful to bear in mind the pathophysiology of the syndrome. Although the most frequent concern is with the development of massive edema, it should be remembered that such edema is a consequence of massive loss of protein into the urine. This in turn leads to depletion of intravascular albumin and reduction of plasma oncotic pressure. In turn, fluid escapes from the vascular compartment into the interstitial tissue. As a compensatory response to the fall in plasma volume, there is decreased salt and water excretion by the kidney which may further increase the accumulation of edema. If intravascular albumin depletion can be prevented or reversed, significant problems with edema and fluid retention will not develop. As albumin depletion is caused primarily by loss through a leaky glomerulus, the first approach, if possible, should be to reverse the albumin leak. As we shall see later, this is regularly accomplished only in nil disease in which the leak is predictably corrected by steroids. In other conditions in which the albumin leak is not remedial, metabolic considerations should be first and foremost in management. A high-protein and high-caloric diet can result in significant repletion of intravascular albumin.[5] To the extent that albumin loss can not be matched by increased dietary protein, then salt restriction and diuretics may be necessary to prevent undue accumulation of edema. From a practical standpoint, the diet of the nonazotemic patient should contain a minimum of 100 gm of high-quality protein and approximately 3,500 calories for the average nephrotic adult. At times, protein intake of 2-3 gm/kg of body weight will be required. Since many of these patients are anorectic and have been grossly malnourished for some time, the diet may have to be increased gradually until these goals are accomplished. This will require persistent and close cooperation between the patient, the physician, and the dietitian.

If serum albumin remains severely depressed despite optimal intake of protein, it is probable that salt and water restriction, as well as diuretics, may be necessary for control of severe edema. One must remember that, although there may be massive accumulation of edema, there is at the same time potential for significant intravascular volume depletion. Therapy designed to reduce edema accumulation may further reduce intravascular volume, and potentially result in shock. Judicious use of salt restriction and diuretics is necessary in order to achieve the appropriate balance in which severe accumulation of edema is prevented without unduly jeopardizing intravascular volume. In general, this involves sodium restriction of approximately 40-60 mEq/p day. Diuretics should be adjusted so that edema is not reduced to the point where postural changes in blood pressure and pulse occur. Although this may involve some trial and error, one can usually arrive at a body weight in which massive edema is prevented but not at the expense of severe volume depletion.

The nephrotic syndrome may also be complicated by increased susceptibility to infection. Prior to the introduction of steroid and antibiotic therapy, pneumococcal pneumonia and/or peritonitis was a major cause of death in nephrotic children. This is at least in part because of loss of immunoglobulins in the urine. In addition, protein malnutrition and edematous tissue may contribute to reduced host defenses. It is not always possible to prevent the loss of immunoglobulins in the urine of patients with persistent, heavy proteinuria, but massive edema and malnutri-

tion are potentially correctable. It is most important that the physician be alert to early signs of infection in these patients so that they are treated definitively and aggressively.

An increased thromboembolic tendency is an additional potential complication of the nephrotic syndrome. Although the mechanism is not clearly understood, there are data to suggest that a hypercoagulable state may exist in association with the nephrotic syndrome. Care should be taken that other factors, such as venous stasis, which predispose to thromboembolism, be avoided in order to minimize this risk. It is also important that those providing medical care for these patients be especially attuned to this problem, so that definitive diagnosis and treatment may be accomplished at the earliest possible time. There appears to be no basis for use of anticoagulant agents except in documented episodes of pulmonary embolus. For unclear reasons, there seems to be a predilection for the formation of clots within the venous system of the nephrotic kidney. Again, it appears that anticoagulants are not indicated except in the occurrence of a pulmonary embolus.

It has been conclusively demonstrated that patients with long-standing nephrotic syndrome may develop accelerated atherosclerotic disease, leading to an increased risk of coronary artery disease and acute myocardial infarction; this appears to be related to prolonged hyperlipidemia. There is an inverse relationship between serum albumin and serum lipid levels. Any maneuver which improves the serum albumin level, such as correction of protein malnutrition, can be expected also to lower serum lipid levels. Treatment with clofibrate does not appear to be highly effective in treating hyperlipidemia associated with the nephrotic syndrome and may be associated with severe side effects if the dosage is not reduced to correspond to the reduced serum albumin levels.

The most fundamental concern in management of the nephrotic syndrome should be the correction of increased glomerular protein leakage. If protein loss can be reversed, all secondary problems will resolve. Two general considerations relate to abnormal protein leakage. First, the physician should be aware that the nephrotic syndrome could be a manifestation of some reversible systemic process. Any drug, toxin, or allergen which could potentially cause the nephrotic syndrome should be removed, if possible. Systemic diseases associated with the nephrotic syndrome, such as malignancy and chronic infections, should be identified and treated definitively. Even when malignancy is not curable, reduction in tumor mass may lead to resolution of the nephrotic syndrome.

The second approach to treatment of glomerular protein leakage involves the use of steroids and immunosuppressant agents. It has been shown conclusively in only one disease, nil disease, that these agents can predictably reverse glomerular leakage of protein; for the rest there is little evidence of efficacy of such agents. In nil disease, treatment with prednisone, in doses of 40-60 mg/day/m^2 body surface area in children and 1 mg/day/kg body weight in adults, will result in a significant reduction in the level of proteinuria within 7 to 28 days. In general, children will respond quickly, and their proteinuria will fall off rapidly to undetectable levels. Adults tend to respond more slowly and less completely but will usually have less than 1 gm of protein excretion per day within the first 28 days of treatment. After clearing or significant reduction in the level of proteinuria, treatment is usually switched to an alternate-day regimen and the steroids reduced and subsequently discontinued over the next two to three months. Immunosuppressant agents, such as cyclophosphamide, may be useful in some patients with nil disease who have frequent relapses upon cessation of steroid therapy. Recent evidence suggests that these agents may prevent or reduce the frequency of such relapses.

In addition to the beneficial effect of steroids and immunosuppressant agents on the proteinuria of nil disease, there is also a recent and ongoing interest as to whether these agents may prevent or slow the rate of progression of renal failure in glomerulonephritis associated with the nephrotic syndrome. The severe glomerulonephritis of systemic lupus erythematosus, as well as idiopathic membranous and membranoproliferative glomerulonephritis, are diseases whose prognosis may be improved by these agents; however, studies supporting such conclusions have not been adequately controlled and remain controversial.

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On the Prevention of Acute Renal Failure (Vasomotor Nephropathy)

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Acute renal failure following severe trauma, shock, transfusion reactions, poisoning, and sepsis is characterized by prolonged oliguria, increasing azotemia, isosthenuria, and a sodium concentration of 40-90 mEq/L. Despite the availability of intensive medical and surgical care, potent antibiotics, and dialysis, this syndrome still carries a mortality rate of approximately 50% and once established cannot be reversed by any known medical regimen. It is, however, often preventable, and the purpose of this paper is to evaluate the efficacy of the various prophylactic measures currently in vogue.

In searching for means of preventing acute renal failure, we should consider three pathophysiologic mechanisms involved that, historically, have received the greatest attention:

1. The passive backflow theory,
2. Tubular obstruction, and
3. Vasomotor factors.

According to the passive backflow theory, glomerular filtrate is formed at a normal or close to normal rate but is absorbed quantitatively and nonselectively across injured tubular epithelium. The tubular obstruction theory presupposes that cell swelling and tubular debris occlude the tubule lumen, raise intratubular pressure to the point that filtration is seriously reduced, and/or augment the driving force for passive backflow of the filtrate formed. The vasomotor theory suggests that acute renal failure is the result of a primary failure of glomerular filtration because of decreased glomerular capillary filtration pressure with or without reduced permeability of the filtration surface.

The renal cortical blood flow of human subjects with acute renal failure has been found almost invariably to be greatly decreased.[1-4] If this decrease in blood flow relates only in part to an increased preglomerular vascular resistance as seems evident from angiography,[5] glomerular filtration must be maximally suppressed. Although the possibility of inulin leakage casts some doubt on the validity of inulin clearance measurements which would confirm such a near cessation of filtration, micropuncture studies of experimental animals with acute renal failure have provided unequivocal proof that glomerular filtration does, indeed, fail.[6] By and large, experimental models reveal proximal tubular pressure to be distinctly low, not elevated as might be suggested by the tubular obstruction theory. Although tubular leakage of glomerular filtrate has been described by some authors, tubular absorption has, for the most part, been shown to be markedly decreased, rather than increased as suggested by the passive backflow theory.[7] Perhaps the most telling argument against this theory can be derived from studies of chronically salt-loaded rats poisoned with mercuric chloride. Such animals, allowed 1% saline solution in place of tap water for a month prior to mercury injection, are almost perfectly protected from renal failure. Their blood urea nitrogen concentrations and whole kidney inulin clearance values are close to normal 24 hours after the injection of mercury. Nevertheless, their kidneys show tubular necrosis which is just as severe

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as that displayed by their water drinking counterparts with virtually no renal function.[8] If the passive backflow theory is not applicable to kidneys with evident necrosis of the entire terminal portion of the proximal tubule, it is highly unlikely to be the major determinant of other types of acute renal failure in which tubular damage is far less severe. It is thus well to remember that the degree of tubular injury in the kidneys of patients with acute renal failure is highly variable. Finckh,[9] Sevitt,[10] and others have pointed out that classical acute renal failure may be found without any significant tubular injury, and that no correlation exists between the duration or severity of renal insufficiency and the degree of tubular injury which can be demonstrated. Similarly, acute renal failure in man may coexist with scant, if any, evidence of tubular obstruction with casts.[9] In sum, the overwhelming bulk of evidence presently affirms that acute renal failure relates to a primary cessation of glomerular filtration.

Recently, Flores et al[11] have proposed that filtration failure is caused by endothelial and renal interstitial cell swelling. Such swelling was said to be reversible, and renal failure prevented, by administering massive doses of mannitol. According to the data in that report, however, renal failure was not prevented by mannitol administration, merely somewhat blunted. In our laboratory, closely following the technique used by Flores, we could find no significant effect of mannitol therapy.[12] Nor have we found a beneficial effect of hypertonic mannitol solutions in myohemoglobinuric acute renal failure other than that which could be achieved by volume expansion with saline or plasma alone.[13] Mannitol clearly increases renal blood flow and helps maintain glomerular filtration in dogs subjected to limited hemorrhage[14]; however, as their renal function generally returns to normal when renal perfusion pressure is restored after hemorrhage whether mannitol is given or not, one cannot presume from such studies that mannitol prevents acute renal failure. Aortic cross-clamping has also been reported to cause renal failure which is preventable with mannitol,[15] but several investigators studying far larger numbers of animals have been unable to duplicate any renal abnormalities at all in similarly treated animals not given mannitol.[16,17]

A number of clinical reports have suggested that mannitol prevents acute renal failure in man, although no prospective study of the efficacy of such treatment has appeared. Such a study would, however, be difficult indeed. Assuming a 1% overall incidence of renal failure in the total population of patients at risk after surgery, burns, trauma, or hemorrhage (a deliberate overestimate), at least 2,000 patients would need to be treated and a comparable number employed as controls before a statistically meaningful comparison of the two groups could be made. Powers et al[18] have estimated that the syndrome occurs in 0.1% of patients at risk, a more realistic figure that would necessitate the inclusion of perhaps 20,000 patients in any controlled study of the efficacy of a prophylactic measure. While patients subjected to aneurysmectomy develop renal insufficiency more often than others subjected to less traumatic surgery, they still have a low risk of renal insufficiency unless the aneurysm has ruptured. In reviewing 1,659 cases of lower aortic surgery performed in ten centers, Kountz et al[19] found an overall incidence of renal failure of only 3.8%. While the physician may be reassured that none of 20 or 50 patients subjected to major surgery and treated with mannitol will develop acute renal failure, there is little basis for assuming that mannitol infusions are responsible for his good luck. Similar considerations apply to the use of furosemide as a prophylactic agent.

The rationale for mannitol's usage rests with the suggestion that it maintains renal blood flow, reduces renal cell swelling, washes out tubular debris, serves to expand vascular volume, and induces urine output if filtration still persists. This is an impressive list of potential benefits, but the bulk of controlled experiments show cell swelling and tubular obstruction not to be critical to the development of acute renal failure. The syndrome can be induced readily in rats with congenital diabetes insipidus, excreting (and drinking) a volume equal to 80% of their body weight each day.[20] Thus, the maintenance of urine volume and washout of tubular casts is not critical to the prevention of acute renal failure, whether this is achieved with furosemide or with mannitol. A response to either agent proves that acute renal failure does not yet exist, as urine can only be formed when filtration is ongoing.

Whether renal failure develops or not depends largely on the type, as well as on the severity, of the underlying injury sustained. Shock, for example, is a major factor. While brief and modest hypotension may, at times, lead to renal failure, the syndrome is far more likely to occur if shock is of long duration or poorly controlled. Volume depletion also plays a sig-

nificant pathogenetic role, adequate volume replacement being the most important single therapeutic modality available for the prevention of renal shutdown. The adequacy of fluid therapy cannot be merely assumed, however, but requires documentation of adequate weight gain, appropriate changes in urinary sodium concentrations and osmolality, and where needed, measurement of central venous pressure and blood volume. Sepsis may predispose to renal insufficiency not only on the basis of toxemia, but also by the activation of intravascular coagulation.[21] With prompt and vigorous treatment of fluid volume deficits, the restoration of cardiac output to reasonable levels, and vigorous treatment of sepsis, the incidence of acute renal failure has become far lower than in previous times, a reduction which is as apparent in centers where mannitol and furosemide are not used as "preventive agents" as in those where they are.

While acute renal failure owing to trauma and shock is far less prevalent nowadays, a new threat has emerged with the widespread use of the aminoglycoside antibiotics. These agents are excreted essentially unchanged primarily by the kidney. Any impairment of glomerular filtration rate (GFR), whether because of organic disease or as a functional result of heart failure or dehydration, causes accumulation of these agents to a level which may be nephrotoxic. Unlike the idiosyncratic reactions to other antibiotics that occur in a very small percentage of the population, renal toxicity can be expected in any patient exposed to abnormally high concentrations of aminoglycosides. The setting in which these agents are used is one that so frequently results in some compromise in renal function that toxic levels are easily attained. Unlike other forms of acute renal failure, that following aminoglycoside overdosage may be irreversible.

How can we prevent this common and very serious complication? First, the aminoglycosides should be used only when less toxic antibiotics cannot be substituted. Second, renal function should be followed closely if these agents are to be given. Various formulae are used as guides to appropriate gentamicin dosage in the face of reduced renal function, and not one seems clearly superior to the others. All, however, rely on the reasonably accurate assessment of renal function. Normal serum creatinine concentrations in non-gravid adults range from 0.6 to 1.6 mg%. Thus, a value of 1.2 mg% in one patient may be normal; in another, it may be twice normal and indicative that the GFR is reduced by one half. If one abruptly loses all renal function, the serum creatinine obtained two days later will be perhaps 3 mg% and will rise progressively thereafter. It certainly would be erroneous to assume that a creatinine concentration of 3 mg% in such a patient means that the GFR is one third of normal and administer gentamicin (or the other aminoglycosides) accordingly, when, in fact, the GFR is almost nil. The way out of the dilemma is to routinely measure the serum creatinine concentration of any patient receiving these drugs on the day after treatment is started. Any significant increase should prompt a repeat determination 12 or 24 hours later, as should any circumstance likely to lead to worsening renal function. As serum creatinine concentrations truly reflect renal function only when they are stable, it is imperative that serum antibiotic levels be monitored to serve as the guide to dosage if the creatinine concentrations are rising.

Nephrotoxic renal damage may be superimposed on preexisting renal impairment and, as previously stated, may be irreversible. Only by treating the aminoglycosides with the greatest respect and closely monitoring the renal function of patients receiving these drugs can overdosage and the resultant renal failure be avoided.

To summarize, the best evidence available at present indicates that acute renal failure represents a sustained and severe decrease in GFR. Tubular factors are thus of secondary importance, and the term "acute tubular necrosis" (ATN) is not pathologically appropriate. Vasomotor nephropathy seems a better term, and one we have adopted for this syndrome[22] which in many circumstances is largely preventable by the prompt and vigorous restoration of fluid deficits and cardiac output, as well as the treatment of sepsis. Unfortunately, such therapy may be only marginally successful in some instances (for example, overwhelming sepsis, acute hemorrhagic pancreatitis), but there is scant evidence that either mannitol or furosemide protects patients from renal failure. Rather than relying on such agents, efforts should be made to maintain normal fluid volume and cardiac output in all cases at risk of vasomotor nephropathy.

Renal failure owing to gentamicin and other aminoglycoside antibiotics is a result of improper attention to dosage relative to a patient's renal function. Close attention to renal function can largely

eliminate this common cause of renal failure.

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Pyelonephritis

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The purpose of this paper is to review current thinking about pyelonephritis. Pyelonephritis may be defined as a "bacterial infection of the kidney which affects the parenchyma, the pelvis, and the calyces. It occurs in two forms, acute and chronic."[1]

Clinically, acute pyelonephritis is characterized by the symptoms of dysuria, frequency, urgency, chills, fever, and flank pain. The urine sediment contains numerous white blood cells, bacteria, and white blood cell casts (Fig 1). A quantitative culture of the first voided urine in the morning yields a growth of greater than 10^5 colonies per ml. Renal histologic examination reveals an acute interstitial inflammatory reaction with polymorphonuclear leukocytes and microabscess formation (Fig 2). If the infection remits either spontaneously or with antibiotic therapy, the involved areas may heal with formation of a contracted, fibrotic scar. In contrast to the acute infection, chronic pyelonephritis may be totally asymptomatic. Examination of the urine sediment usually shows changes similar to those in acute disease except that the quantities of cells and casts may be less remarkable. The classic pathologic picture of chronic pyelonephritis includes interstitial infiltration by mononuclear cells, scarring, tubular dilatation (thyroidization) and periglomerular fibrosis (Fig 3). The typical chronic pyelonephritic kidney is shrunken, contains multiple scars, and is atrophic.

The pathologic picture of pyelonephritis is not entirely specific, particularly in the chronic state where other processes which cause an interstitial inflammatory reaction may give a similar appearance. An incomplete list of nonbacterial causes of chronic interstitial nephritis includes: analgesic abuse, other drug toxicity, tuberculosis, sarcoidosis, gouty nephropathy, hypercalcemic nephropathy, and ischemic vascular disease.[2] Initially, these disorders may be suspected because of the presence of sterile pyuria, but later, superimposed bacterial infection may cloud the picture.

Bacteria invade the kidney by two principal routes: hematogenous and retrograde.[3] Hematogenous spread occurs infrequently, but when it does, it is the means whereby most staphylococcal and streptococcal infections are initiated in the kidney. These infections may be severe and associated with multiple abscess formation. Most bacterial infections of the kidney are caused by gram-negative organisms that reach the kidney via retrograde spread from the lower urinary tract; the natural habitat of the majority of these organisms is the gastrointestinal tract from which they spread to the urethra and then into the bladder and up the ureters. Approximately one fourth of all bacterial infections involve the urinary tract, but only a portion of these ascend above the bladder to the renal parenchyma.

Several factors are now recognized as being of major importance in the pathogenesis of urinary tract infection, the first of which is sex. There is clearly a higher incidence in females at all ages but particularly in the childbearing years. Only in later life with the advent of prostatic hypertrophy and associated obstructive uropathy does the incidence tend to increase in the male. The increased incidence in females probably relates to the shorter urethra, the absence of the antibacterial action of prostatic fluids, and trauma during intercourse. Recently it has also been recognized that disturbances in the bacterial resistance of the vaginal vestibule secretions may be the factor

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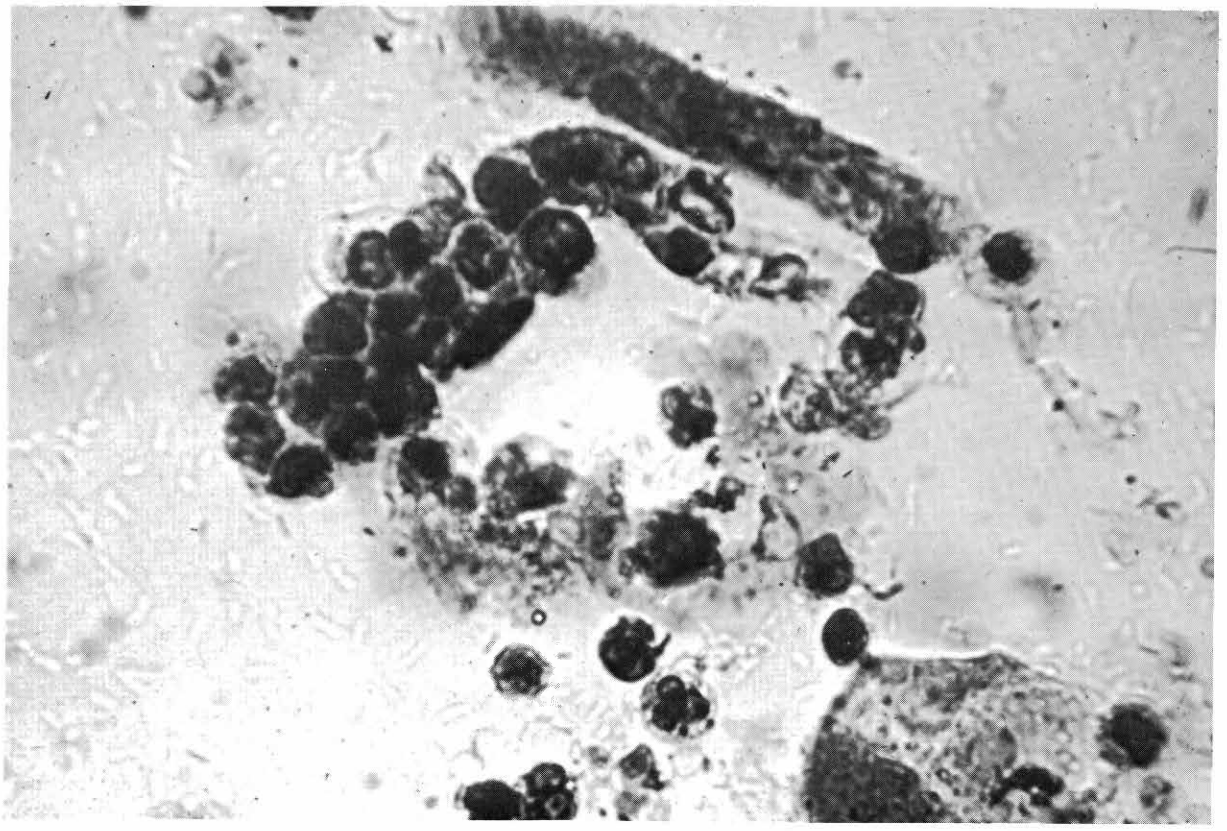

Fig 1—Urine sediment from a patient with acute pyelonephritis, showing white blood cells, a white blood cell cast, a granular cast and numerous bacteria (× 1,000).

which initially allows bacterial colonization of the urethra in females.[4]

Instrumentation of the urinary tract is frequently associated with introduction of bacteria into the bladder. Unfortunately, the instrumentation is usually undertaken for evaluation of an anatomically abnormal tract. Bladder urine is normally sterile. When pathogenic organisms are introduced into the bladder of a normal, unobstructed animal or man, they are rapidly cleared because of the combined effects of the bacteriostatic properties of normal urine, the dilution of organisms by voiding, and the resistance of the bladder mucosa to bacterial colonization.[5] On the other hand, in the obstructed state there is a residual pool of relatively stagnant urine; the bacterial clearing mechanisms are no longer operative and infection ensues. In this context neurogenic bladder dysfunction may have the same propensity to infection as overt obstructive uropathy.

In recent years numerous studies have indicated that ureteral reflux is probably the most important factor which allows for initiation and perpetuation of renal parenchymal infection. Congenital reflux becomes a problem in early childhood and is usually caused by an abnormal placement of the ureter in the bladder wall.[6] In the immature kidney it is likely that even sterile reflux may result in calyceal scarring and contracture of the parenchyma. This type of reflux carries an ominous prognosis and frequently requires surgical correction. Acquired reflux (Fig 4) may appear in older individuals and may be related to bladder infection, adjacent bladder diverticulae, or neurogenic mechanisms.[7] When reflux is severe, it may be associated with intrarenal reflux in the polar regions of the kidney. Some authorities think that this may be the cause of atrophic pyelonephritis.[8]

Dilatation of the ureters, because of pressure from the expanding uterus, and the smooth muscle

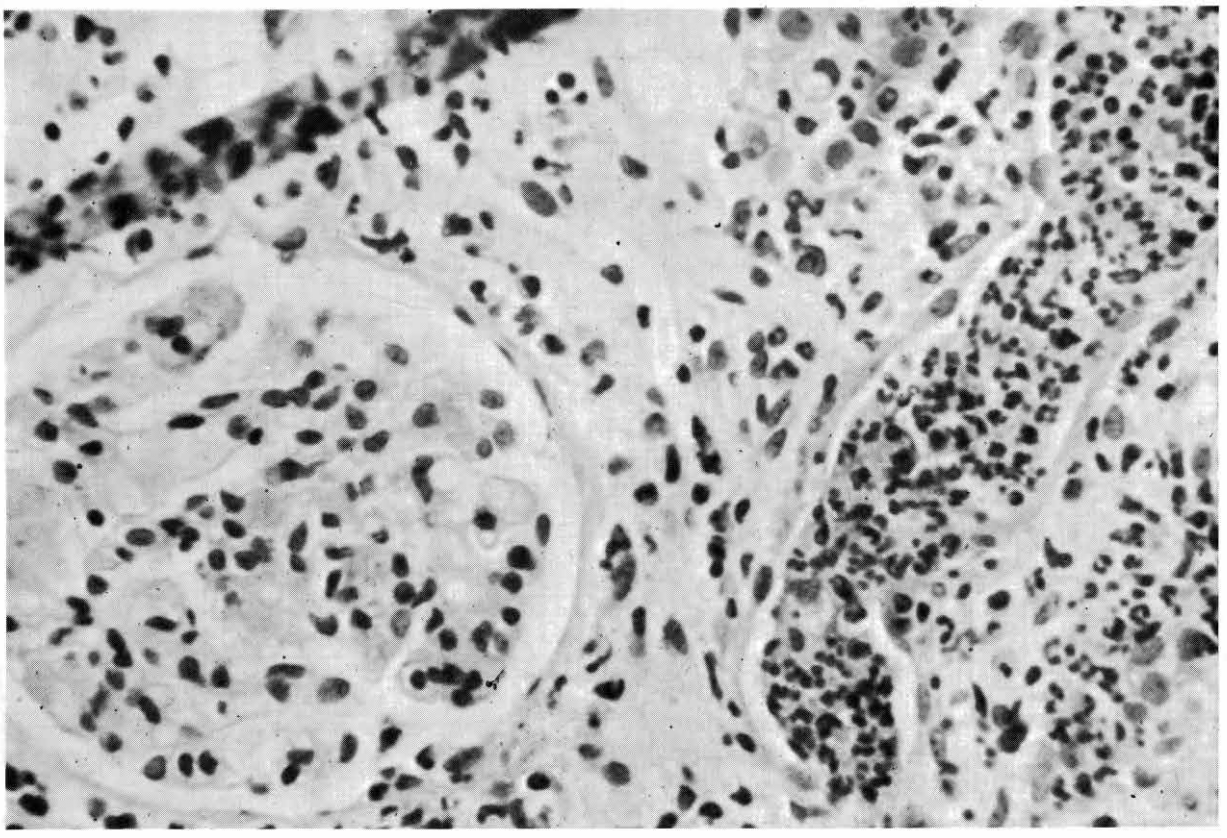

Fig 2—Light microscopic representation (H & E stain) of a renal biopsy section, showing the picture of acute pyelonephritis. Glomerular architecture is relatively well maintained, but there is a marked interstitial inflammatory reaction with both polymorphonuclear and mononuclear leukocytes. A white blood cell cast fills the collecting duct on the right. (× 80).

relaxing effects of high estrogen concentrations, may predispose to the development of pyelonephritis in pregnancy.[3] Fully 30% of pregnant patients with asymptomatic bacilluria will have an episode of acute pyelonephritis during a given pregnancy if left untreated.[9]

Controversy continues to surround the issue of whether or not diabetes mellitus predisposes to the development of pyelonephritis, and recent evidence suggests that its incidence is higher in diabetic women.[10] Clearly, when pyelonephritis develops in a diabetic patient, the infection itself is more likely to be severe.

The cortex appears to be relatively resistant to bacterial colonization, and most parenchymal infections begin in the medulla where increased susceptibility to infection probably relates to the lower blood supply to the medulla, the hypertonicity of the medullary interstitium which depresses phagocytosis, the high level of ammonia which interferes with activation of the complement system, and the tendency for granulocytes to emigrate from the medullary area.[3]

Eighty-five percent of new urinary tract infections which develop outside the hospital are caused by *Escherichia coli* organisms and the remaining 15% by other organisms, most of which are also gram-negative.[11] When infection develops in the hospital setting or occurs after instrumentation, the bacterial flora is likely to be different and is usually composed of gram-negative organisms with a greater degree of bacterial resistance than *E coli.*

The main danger of bacterial infection of the kidney relates to its complications. There are a number of these and one which has generated much recent interest about its pathogenesis is atrophic pyelonephritis.[8] It is now clear that this condition develops in early life, is associated with high grades of reflux, and may terminate in end-stage renal disease at an early

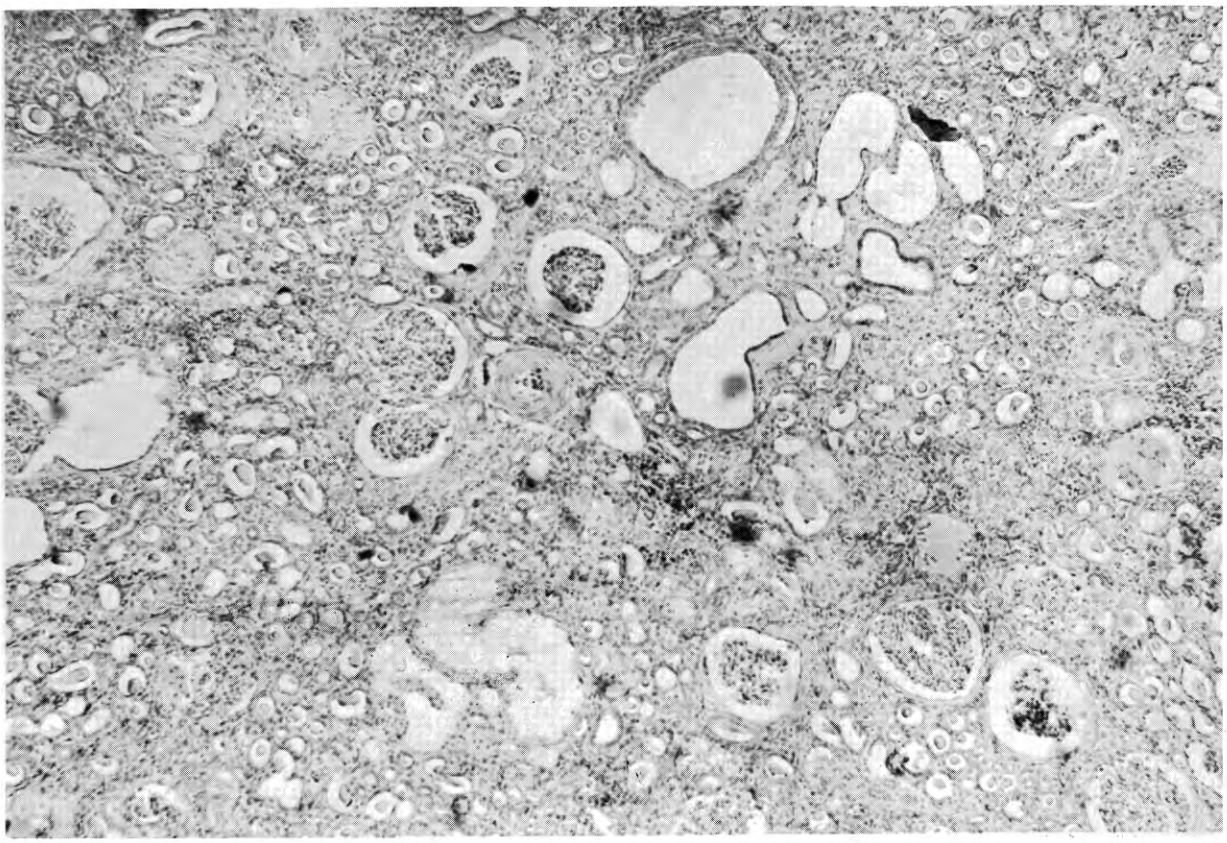

Fig 3—Light microscopic autopsy section (H & E stain) from a patient with chronic pyelonephritis. Marked interstitial inflammatory reaction in association with scarring, tubular dilatation, and periglomerular fibrosis is present. Secondary arteriolar thickening has also occurred (× 20).

age if the reflux is not corrected. It has been suggested that the small shrunken kidney seen in later life may be the result of atrophic pyelonephritis in childhood.

Papillary necrosis may be one of the most devastating complications of urinary tract infection, particularly if it occurs in diabetes mellitus with obstruction. This constellation of disturbances was formerly associated with a high frequency of sepsis and death, but it is seen less frequently since the advent of modern antibiotic therapy. At the present time it is more likely that papillary necrosis may present insidiously with slow deterioration in renal function, perhaps in conjunction with the passage of small pieces of papillary tissue in the urine. Contemporary studies[12] suggest that this latter picture may be seen more frequently with another underlying disease such as analgesic abuse or sickle cell disease, rather than as a manifestation of pyelonephritis (Fig 5).

Struvite stone formation is another common complication of urinary tract infection and is caused by infection with urea-splitting organisms, particularly those of the proteus species. This type of infection is seen all too frequently in patients with obstructive uropathy or neurogenic bladder dysfunction. Under either of these circumstances a continuous cycle of stone formation-infection-stone formation may develop. The composition of most "staghorn" calculi which develop in an obstructed, infected urinary tract is struvite. Infection is virtually impossible to clear from the urine in this situation.

Perinephric abscess is an infrequent but important complication of urinary tract infection because its onset may be insidious and it may be associated with remarkably minimal changes in the urine sediment. It may present as a fever of unknown etiology, and the use of modern radiographic techniques, such

Fig 4—Voiding cystourethrogram in a patient with acute cystitis and bilateral reflux. Moderate ureteral dilatation is present and the contrast medium refluxes into the calyceal system. The left calyceal system is also clearly dilated.

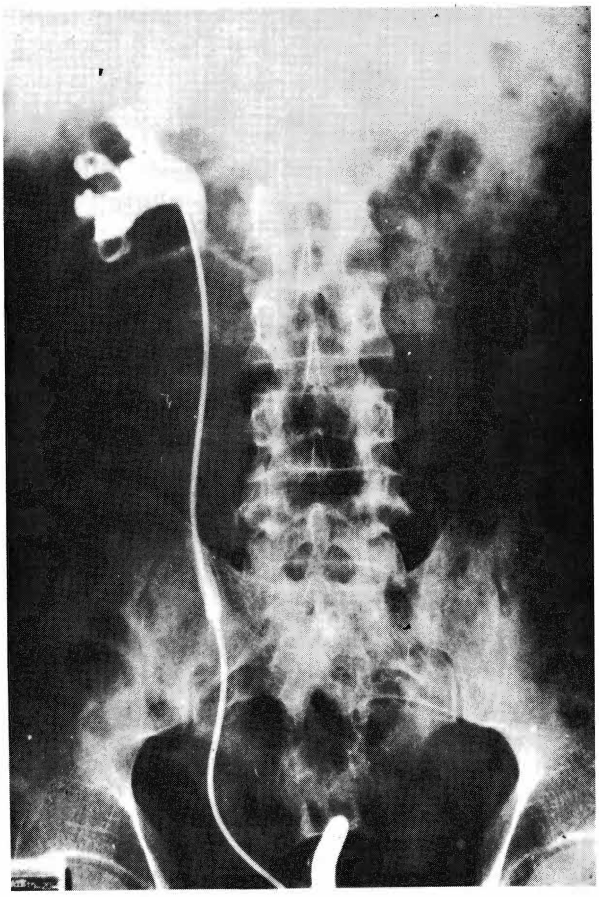

Fig 5—Retrograde urogram in a patient with papillary necrosis secondary to analgesic abuse. There is marked distortion of the calyceal system on the right. Necrotic, papillary debris is present in several calyces, displacing the contrast medium and giving rise to the characteristic "ring" sign.

as gallium scanning and CT scanning, may be of great diagnostic aid. In addition, sonography of the retroperitoneum and abdomen may be of diagnostic help.

Gram-negative sepsis remains a frequent complication of urinary tract infection and may be associated with instrumentation or the presence of an indwelling urethral catheter; therapy requires aggressive treatment with measures to support the circulation while administering a bactericidal antibiotic.

Whether or not chronic pyelonephritis predisposes to the development of severe hypertension continues to be a subject of debate. Some evidence in both children and adults would suggest that the chronically scarred kidney may be associated with activation of a pressor hypertensive mechanism;[13] however, most patients with chronic infection remain normotensive or, at worse, mildly hypertensive. Perhaps a more important aspect of the association is the fact that progression of pyelonephritis, like that of any other type of renal disease may be accelerated by the presence of superimposed hypertension; therefore, elevated blood pressure in a patient with pyelonephritis should be treated vigorously.

A number of disturbances in relation to pregnancy have been correlated statistically with the presence of urinary tract infection. The most notable of these are anemia and decreased birth weight of the fetus. After a period of skepticism about the relationship of these abnormalities to infection, recent studies have confirmed their association.[9] As mentioned ear-

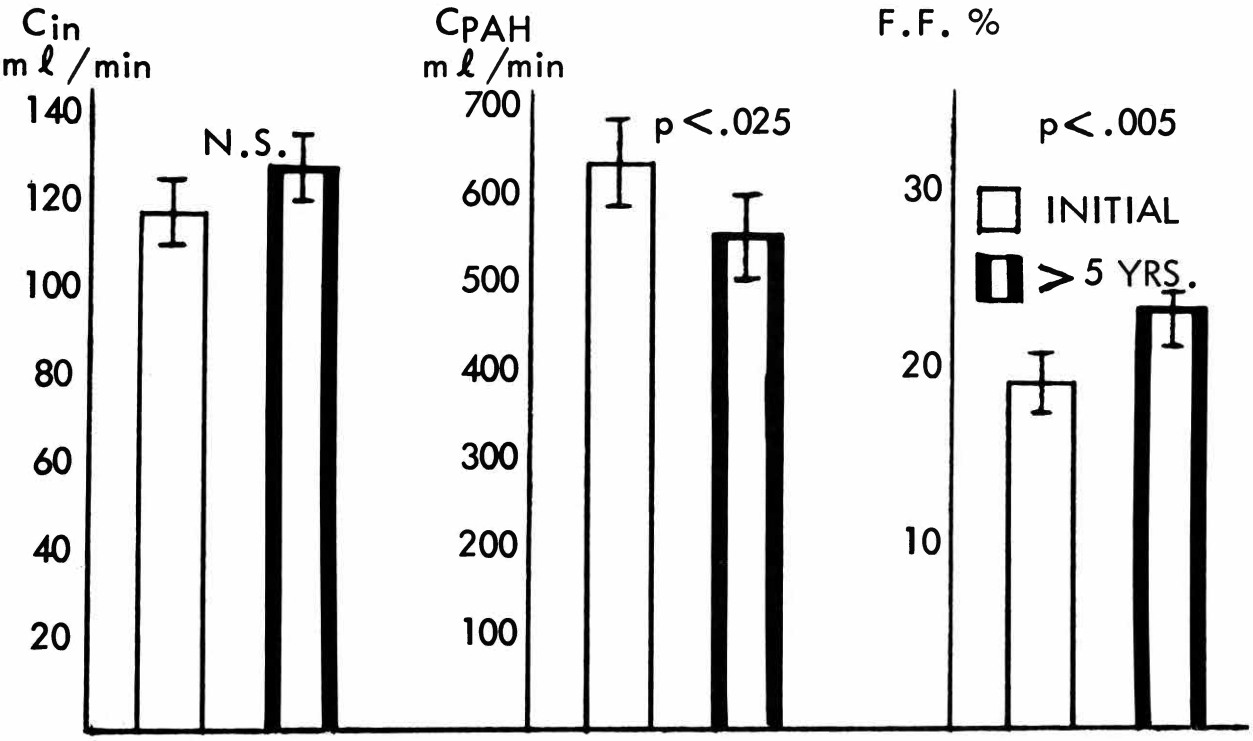

Fig 6—Comparison of mean ± SEM values for C_{in}, C_{PAH}, and FF between initial measurements early after injury and similar determinations after more than five years in 18 patients with spinal cord injuries and persistent bacilluria.

lier, there is a high incidence of acute pyelonephritis in pregnant females with bacilluria, and this condition, clearly, should be treated.[9]

For years pyelonephritis was considered to be a major cause of end-stage renal disease. Careful evaluation of patients entering dialysis and transplant programs, however, has indicated that this is not the case.[14] It is likely that many of the cases of interstitial nephritis which were thought to be caused by infection were in actuality the end result of one of the other causes of interstitial disease mentioned earlier. Present estimates would suggest that no more than 15% of the patients reaching end-stage disease have infection as the primary cause of renal failure and virtually all of these are complicated by the presence of stones, reflux, or other anatomic disturbance.

Information about the natural history of urinary tract infection in man is still incomplete. As noted above, end-stage renal disease in the absence of an anatomic or neurologic defect in the urinary tract is rare despite the frequency of culture-proven bacilluria. We have recently attempted to define more clearly the association of chronic bacilluria and deterioration in renal function by a prospective analysis of the changes in inulin clearance (C_{in}) and PAH clearance (C_{PAH}) in a group of patients with persistent bacilluria (spinal cord injury patients). C_{in} is an accurate measure of the glomerular filtration rate and C_{PAH} indicates the renal plasma flow.

Figure 6 demonstrates that at a mean period of five years after the initial determinations, a statistically significant reduction in mean C_{PAH} from an initial value of 643 ml/min shortly after injury to 556 ml/min at the time of study had occurred in 18 study patients. Over the same period, there was no significant change in C_{in}; there was also a significant reduction in the filtration fraction (FF). This index reflects the ratio of C_{in}/C_{PAH} and is an indicator of the state of perfusion in the kidney. Diseases which produce renal ischemia may be associated with a low FF. Each of the study patients had a neurogenic bladder and persistent bacilluria. A number had experienced one or more severe complications such as renal stones, reflux, or sepsis. Yet, at the time of study, all had adequate urinary drainage. These data suggest that there may be insidious damage occurring to the

kidneys of these patients; however, barring superimposition of some other insult, renal failure is unlikely to be the cause of their death.

There will always be differences of opinion about the work-up and therapy of patients with urinary tract infection. Outlined below are some principles which are generally applicable to these issues:

1. A quantitative culture, colony count, and antibiotic sensitivity determination should be performed in all pregnant women and in all individuals suspected of having a urinary tract infection.
2. A patient with the typical clinical picture of acute pyelonephritis or gram-negative sepsis should be treated with a bactericidal antibiotic to which the organism is sensitive for at least 10 days.
3. Radiographic studies including an intravenous pyelogram and voiding cystourethrogram should be done after the first episode of acute pyelonephritis in the adult male and in all children. Similar studies should be done in any female with recurrent infection or an elevated serum creatinine. Further urologic evaluation should be done in all patients in whom these studies identify a structural abnormality. Surgical correction of obstruction and severe reflux should be undertaken. Mild reflux in children may be observed during a period of antibiotic therapy and can be expected to disappear in 50% of cases by age 6 years and in 65% by age 14 years.[6]
4. The clinical picture of cystitis and asymptomatic bacilluria may be treated with bacteriostatic agents. If recurrence occurs, the above-mentioned radiologic studies should be done. If these are negative, prophylactic or suppressive therapy may be tried. In the future, tests for antibody coating of bacteria may be helpful in differentiating upper tract infection with renal parenchymal involvement from lower tract infection.[15]
5. Reculture should be done after the completion of therapy for a urinary tract infection and on several occasions over the next two years to determine the presence of recurrence or reinfection.

In summary, current thoughts about the pathogenesis, natural history, complications, and management of pyelonephritis have been reviewed. It is now clear that chronic urinary tract infection in the absence of some anatomical disturbance or complication seldom leads to renal failure. Efforts should therefore be directed toward discovering and correcting derangements in the anatomical integrity of the urinary tract at an early stage of infection.

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Evaluation of an Abnormal Urinalysis in the Asymptomatic Patient

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Physicians are occasionally presented with the problem of evaluating a patient who has an abnormal urinalysis[1] but who has no other sign or symptom of genitourinary (GU) tract disease. For example, patients may present with hematuria, pyuria or slight proteinuria, but they may have no other clinical or laboratory abnormality to suggest glomerulonephritis, renal failure, urinary tract infection, obstruction, hypertension, or stones. There are a wide variety of lesions which may produce such isolated abnormalities,[2,3] and a rational approach is indispensable in preparing an efficient and definitive diagnostic plan.

The urinalysis may be abnormal because of the presence of red blood cells, white blood cells, or excessive amounts of albumin. To understand the diagnostic possibilities of such abnormalities it is useful to begin by considering the sensitivity of the routine urinalysis (Table 1). Detection of the presence of only 1+ albuminuria requires albumin in a concentration of 30 mg/100 ml. In the case of red cells and white cells in a centrifuged urine specimen, our limits of detection extend to recognition of a single cell under the microscope. Let us next consider the quantity of each of these elements in a single milliliter of blood. Blood normally contains 4 gm of albumin per 100 milliliters, which is equivalent to 40 mg/ml. White blood cells number approximately 10,000/mm^3 of blood, which is equivalent to 10 million/ml. Similarly, 5,000,000 red blood cells per mm^3 of blood is equivalent to 5 billion/ml. Let us assume that some abnormality in the GU tract leads to the loss of 1 ml of blood (a relatively small amount) into the urine each day. Assuming a modest urine volume of 1,000 ml/day, let us then examine what would be the concentration of the individual components of the urine relative to the limits of detection. In the case of albumin, 40 mg from 1 ml of blood distributed in one liter of urine would result in a concentration of only 4 mg/100 ml. This is well below our detection limit of 30 mg/100 ml for a 1+ measurement. White cells from 1 ml of blood distributed in 1,000 ml of urine would result in a concentration of 100,000/10 ml. If one takes 10 ml of that urine, as with the standard urinalysis, centrifuges it and resuspends the sediment, all 100,000 white cells are potentially identifiable; with red blood cells, there would be an even higher number of identifiable units in the urinalysis.

There are certain important conclusions concerning the routine urinalysis which can be drawn from the above consideration: on one hand, it is evident that we can detect small amounts of bleeding into the urine by the presence of red blood cells; on the other hand, relatively large amounts of blood, 20-40 ml/day, depending on urine volume, must be present to give detectable albuminuria. Such quantities would contain large numbers of red blood cells and thus result in gross hematuria. Albuminuria, detected on the routine urinalysis and accompanied by only microscopic hematuria, could, therefore, not reflect simple bleeding in the GU tract. Albumin can be separated from blood cells only in the glomerulus and, thus, glomerular abnormalities must exist if there is detectable albuminuria in the routine urinalysis in the absence of gross hematuria.

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TABLE 1
Sensitivity in Detection of Abnormalities of the Urinalysis

	Albumin	Pyuria	Hematuria
Limits of detection	30 mg/100 ml	1 WBC/HPF	1 RBC/HPF
Content in 1 ml blood	40 mg/L (4.0 gm/100 ml)	10,000,000 (10,000/mm^3)	5,000,000,000 (5,000,000/mm^3)
Concentration when 1 ml blood mixed with 1 liter urine	40 mg/L (4.0 gm/100 ml)	10,000,000/L 100,000/10 ml	5,000,000,000/L 50,000,000/10 ml

In view of the above considerations, let us now consider the evaluation of the patient with an abnormal urinalysis. Asymptomatic albuminuria, with or without microscopic hematuria, indicates glomerular leakage of protein. As we are considering asymptomatic albuminuria, this would involve only mild degrees of protein loss. Proteinuria greater than 3.5 gm/day would not be asymptomatic or isolated, since it would be accompanied by manifestations of the nephrotic syndrome. Causes of asymptomatic albuminuria may be divided into functional and pathological disturbances. It is referred to as functional when it is not permanent and when it occurs in association with other temporary physiological disturbances. Examples of this include albuminuria which occurs with fever, exacerbations of congestive heart failure, or severe exertion. Another kind of functional proteinuria is that which is detectable in certain persons after prolonged standing. Such postural or orthostatic proteinuria usually involves excretion of less than 1.5 gm of protein per day. Long-term follow-up of most patients with postural proteinuria have indicated a good prognosis; however, in somewhat less than 10% of cases, postural proteinuria is associated with unequivocal glomerular disease, and here the prognosis is more guarded.

Asymptomatic albuminuria also occurs as a predecessor of serious disease in some patients and is termed pathologic proteinuria. In general, certain forms of glomerulonephritis, such as idiopathic membranous and focal sclerosing glomerulonephritis, may initially present with isolated asymptomatic proteinuria. After a period in which there are no other signs or symptoms of renal disease, proteinuria either increases to nephrotic levels or progressive renal failure begins.

Having spoken of this entity as isolated and asymptomatic proteinuria, we are presupposing that the patient has already had a careful clinical and laboratory evaluation which has not disclosed other significant nephrologic abnormalities. No further evaluation or treatment is indicated. Renal biopsy does not contribute importantly other than providing a more definitive prognosis. At the present time even those types of pathologic proteinuria which may initially present as asymptomatic proteinuria do not appear to be amenable to therapy.

Pyuria may be defined as the presence of more than four white blood cells per high-power field from a carefully collected urine specimen. It is usually attributable to infection in the GU tract; however, on rare occasion, it may occur in the absence of classical infection and without other abnormalities in the urinalysis. In these circumstances pyuria deserves special consideration. Tuberculous infection of the GU tract, as well as infection with fungi, should be considered. Nephritis associated with systemic lupus erythematosus is a recognized cause of a urinalysis which contains abnormal numbers of white blood cells in the absence of other signs and symptoms of renal disease. Rejection of the transplanted kidney and other forms of interstitial nephritis may also on occasion present initially with asymptomatic isolated pyuria.

Evaluation of asymptomatic pyuria should be undertaken when it is demonstrated in repeated urinalyses from carefully collected urine samples. Cultures for tuberculosis are indicated and intravenous pyelography may be useful in demonstrating the characteristic lesions of GU tract tuberculosis. In the immunosuppressed patient or in the patient with recognized systemic fungal diseases, special cultures for fungi should also be done. A careful clinical and laboratory search for evidence of systemic lupus erythematosus should be carried out and agents such as antibiotics and diuretics, which may potentially produce an interstitial nephritis, discontinued. Treatment, of course, is dictated by the specific diagnosis.

TABLE 2
The Most Frequent Causes of Asymptomatic Hematuria

Urinary tract infection
Stones
Prostatic disease
Tumors:
25% incidence with gross hematuria
2% incidence with microscopic hematuria
Glomerulonephritis
Interstitial nephritis
Cystic kidney disease
Papillary necrosis
Tuberculosis
Hemorrhagic states
Vascular malformations

Hematuria is the most troublesome and potentially serious problem when it is encountered as an isolated finding in the asymptomatic patient. Abnormal numbers of red blood cells may enter the urine anywhere in the kidney or urinary tract, and may be caused by such diverse lesions as glomerulonephritis, benign and malignant masses, cysts, infection, and hemorrhagic states.[4,5] The most frequent causes of asymptomatic hematuria are presented in Table 2. The incidence of each of these entities varies considerably with the age, sex, and racial background of the patient. Although there is a significant incidence of neoplastic lesions with microscopic hematuria, a tumor etiology is even more likely in the presence of gross hematuria.

Evaluation of asymptomatic hematuria should begin with a review of some aspects of the patient's history. The patient should be questioned about the timing of the hematuria. When it occurs upon initiation of voiding, an anterior urethral bleeding site is suggested. When hematuria is only evident at the termination of voiding, a site near the posterior urethra, bladder neck, or trigone is more likely. Hematuria equally present throughout urination usually has a source above the level of the bladder. Recurrent episodes of either gross or microscopic hematuria, in association with upper respiratory tract illnesses, immunization, or exercise, suggest glomerulonephritis. Symptoms of stone disease and infection should be sought. Polycystic kidney disease and sickle cell disease frequently produce hematuria and may be suggested from a careful review of the patient's family history. Unusual bleeding other than in the GU tract, as well as the use of anticoagulant medications, may lead one to suspect an underlying coagulopathy.

Careful performance of the urinalysis by the responsible physician is also important. As noted above, when microscopic hematuria is accompanied by qualitatively detectable albuminuria, a glomerular origin is likely. Red blood cell casts can only form within the tubules of the kidney and indicate a renal origin for hematuria. Early morning urine, as well as urine obtained after exercise, should be examined since red cell casts may be more prevalent under these circumstances.

As outlined in Table 3, special studies may be required in the evaluation of hematuria. An intravenous pyelogram should be obtained in most cases; it is especially useful for demonstrating mass lesions in the GU tract, as well as stones and papillary necrosis. Cysts may be further evaluated with sonography if there is any question as to malignancy; absence of internal echoes means that a cyst is probably benign. Cyst puncture under sonographic control allows aspiration of fluid for cytological study, as well as instillation of contrast media. Demonstration of an irregular cyst wall strongly suggests a renal cell carcinoma.

When no cause for hematuria is apparent from the intravenous pyelogram, or when a lesion requires further definition, cystoscopy should be carried out. This may permit direct visualization of bleeding sites and, with great care, may allow sampling of urine from individual ureters. Additionally, retrograde pyelography may disclose lesions not demonstrable by an intravenous pyelogram.

In cases in which cystoscopy, as well as intravenous pyelography, fails to disclose a source for hematuria, renal arteriography should be considered. In this way masses too small to demonstrate by the

TABLE 3
Special Studies for Asymptomatic Hematuria

1. INTRAVENOUS PYELOGRAM	tumors, cystic disease, stones, papillary necrosis.
2. SONOGRAM	simple cyst vs tumor.
3. CYSTOSCOPY (RETROGRADE PYELOGRAPHY)	lower GU tract lesions, evaluation of ureteral urine.
4. RENAL ARTERIOGRAPHY	cyst vs tumor, occult tumors, vascular malformations.
5. RENAL BIOPSY	glomerulonephritis, interstitial nephritis.

previous techniques may be localized. Additionally, vascular malformations leading to hematuria may be demonstrable only with arteriography. When arteriography does not disclose an abnormality and when no bleeding is found from the lower urinary tract by cystoscopy, hematuria is probably caused by interstitial renal disease or glomerulonephritis. Interstitial nephritis may result from commonly used drugs such as diuretics and antibiotics. Such agents should be discontinued and the patient followed closely to determine whether the hematuria resolves. Glomerular lesions are probably the most frequent cause of isolated hematuria of renal origin in the asymptomatic patient who has no lesion demonstrable by pyelography or arteriography. In general, glomerular lesions which produce only hematuria and are not associated with other systemic abnormalities have an excellent prognosis. They may occur at any age but are more frequent in children and young adults. However, other more severe forms of glomerulonephritis may occasionally present with asymptomatic isolated hematuria. Such disease processes include hereditary glomerulopathies, collagen vascular disease, and unresolved poststreptococcal glomerulonephritis. Thus, a diligent search for nonrenal signs and symptoms of these diseases, as well as appropriate laboratory tests, should be carried out.

In the patient with hematuria of renal origin and normal renal arteriography, it may be important to establish a definitive diagnosis by renal biopsy. If this is not done, hematuria may recur or persist, and physicians caring for these patients in the future may be concerned over neoplastic lesions which might have been missed in previous investigations. Frequently these concerns lead to multiple, unnecessary arteriographic and cystoscopic procedures. Percutaneous renal biopsy in most such patients will provide a definitive diagnosis and thus obviate further invasive diagnostic procedures. Additionally, the biopsy may be useful in providing prognostic data on the potential severity of the glomerular lesion.

As can be seen from the above discussion, evaluation of an abnormal urinalysis from an otherwise healthy individual involves consideration of a large number of potential diagnoses. If the meaning of individual abnormalities in the urinalysis is not carefully considered, valuable time may be wasted and inappropriate and expensive procedures may be performed. The general principles discussed above, however, allow for a rational and effective approach to this problem.

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The End-Stage Renal Disease Program

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By the mid 1960s it had been clearly demonstrated that the lives of people with total, permanent kidney failure could be indefinitely prolonged with the artificial kidney and that an acceptable proportion of kidney transplants would be successful. The extraordinary cost of this form of therapy, however, prohibited its application to the majority of patients. A strong lobby of health care providers and consumers sought government assistance and in the spring of 1972 Congress passed Public Law 92-603 (Section 2991) which provided for payment of 80% of costs for management of end-stage renal disease (ESRD) for all persons eligible for Social Security benefits, regardless of their ability to pay. This law established what is, in effect, a national health insurance program for people with end-stage renal disease and it may well be a model for future national health insurance programs.

Until early 1977, the ESRD program was administered through the Bureau of Health Insurance of the Social Security Administration and the Bureau of Quality Assurance of the Public Health Service; after that the responsibility for all administrative activity was consolidated in the newly formed Health Care Financing Administration (HICFA).[1] Primary responsibility for medical matters was assigned to the Health Standards and Quality Bureau and fiscal matters to the Medicare Bureau.

To facilitate administration at the local level, the nation was divided into 32 ESRD networks by the Secretary of Health, Education and Welfare according to established referral patterns, modalities of services offered, and population (Fig 1).[2] The network boundaries do not necessarily follow state or other government lines. Virginia is divided among three networks. The large central portion of the state and the whole of West Virginia make up Network 30. The Virginia counties of Scott and Washington are in Network 18 with Tennessee, Alabama, and Mississippi. Four northern Virginia counties, Arlington, Fairfax, Loudoun, and Prince William, have been included in Network 23 with the District of Columbia and five Maryland counties. This division of Virginia was considered consistent with established referral patterns and medical communications; funding for the establishment of these networks was made available in August 1977, and all of them are now active. Network 30 was organized in 1977 as a free-standing, non-profit corporation called the ESRD Network Coordinating Council of the Virginias, with offices in Richmond.

The governing body of the network is the Network Coordinating Council (NCC). Federal regulations require that each approved ESRD care facility provide a representative to this body and that all health care disciplines concerned with ESRD be represented including physicians, nurses, social workers, dietitians, technicians, and administrators. Consumers must also be represented but not as a majority.

The objective of the network is to assure that all persons with ESRD have access to appropriate care. The coordinating council is concerned with monitoring the quality of care and encouraging the appropriate distribution and utilization of ESRD care facilities. To avoid duplication of effort and conflict of interest, working agreements are being developed between the networks and other agencies with similar objectives including Professional Standards Review Organizations (PSRO) and Health Systems Agencies (HSA).

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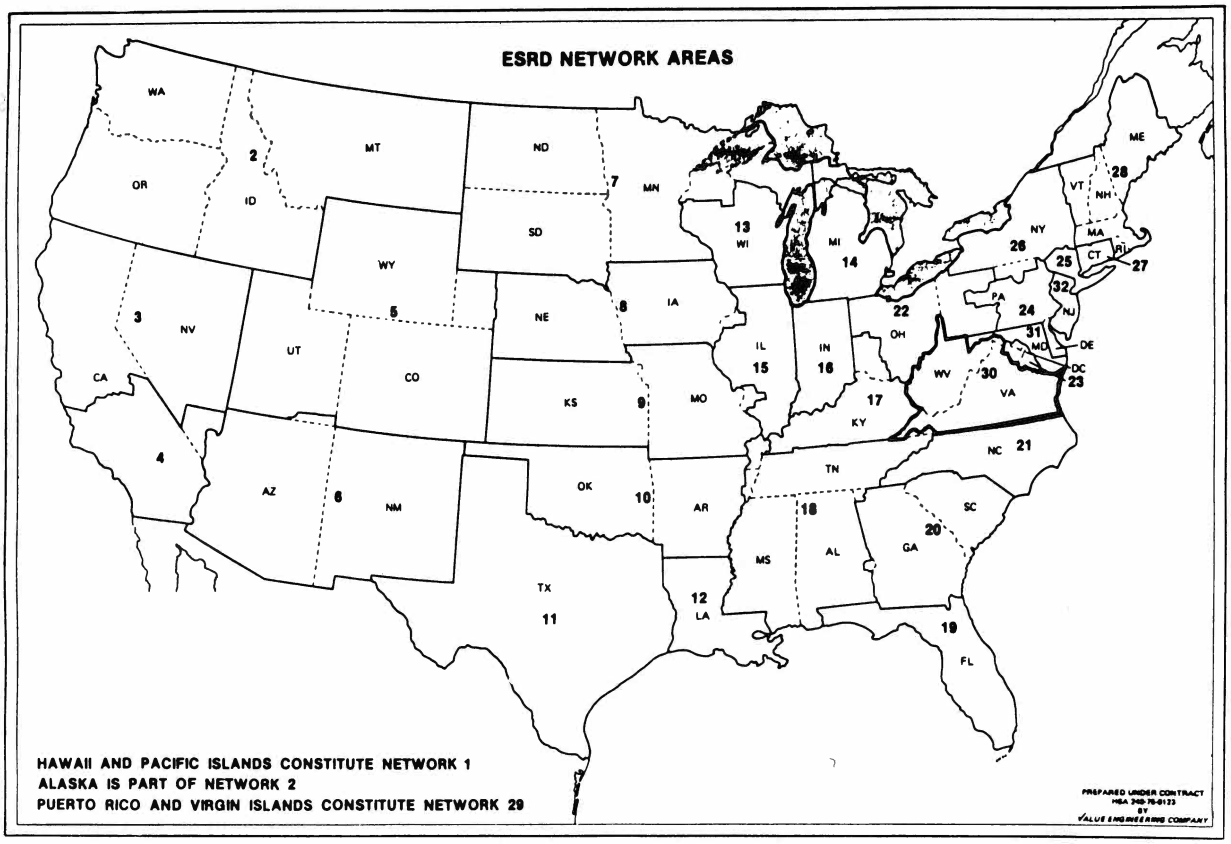

Fig 1—ESRD networks as designated by the Department of Health, Education and Welfare. Most of Virginia is in Network 30.

Each network is required to have a Medical Review Board (MRB) to supervise the appropriateness and quality of care of ESRD patients. The Medical Review Board is appointed by the NCC and consists of a nephrologist, transplant surgeon, registered nurse, social worker, and three additional physicians. Standards of care are recommended by the MRB for approval by the NCC. It is expected that this procedure will allow the establishment of high standards of care acceptable to all health care providers. Compliance is voluntary and the NCC has no powers of enforcement. The Network 30 MRB is completing the first medical audit of dialysis patients, and an ongoing review program is planned that will consider all aspects of ESRD patient care.

The distribution and utilization of medical care facilities have recently been the subjects of considerable discussion and government attention at all levels; the ESRD program is no exception. The authorizing legislation requires the establishment of minimal utilization rates of both dialysis and trans-

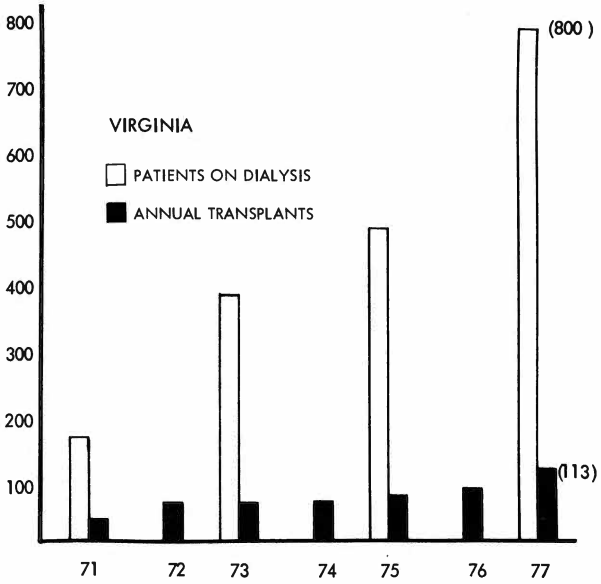

Fig 2—Dialysis and transplantation activity in Virginia. Accurate dialysis data not available for 1972, 1974, and 1976.

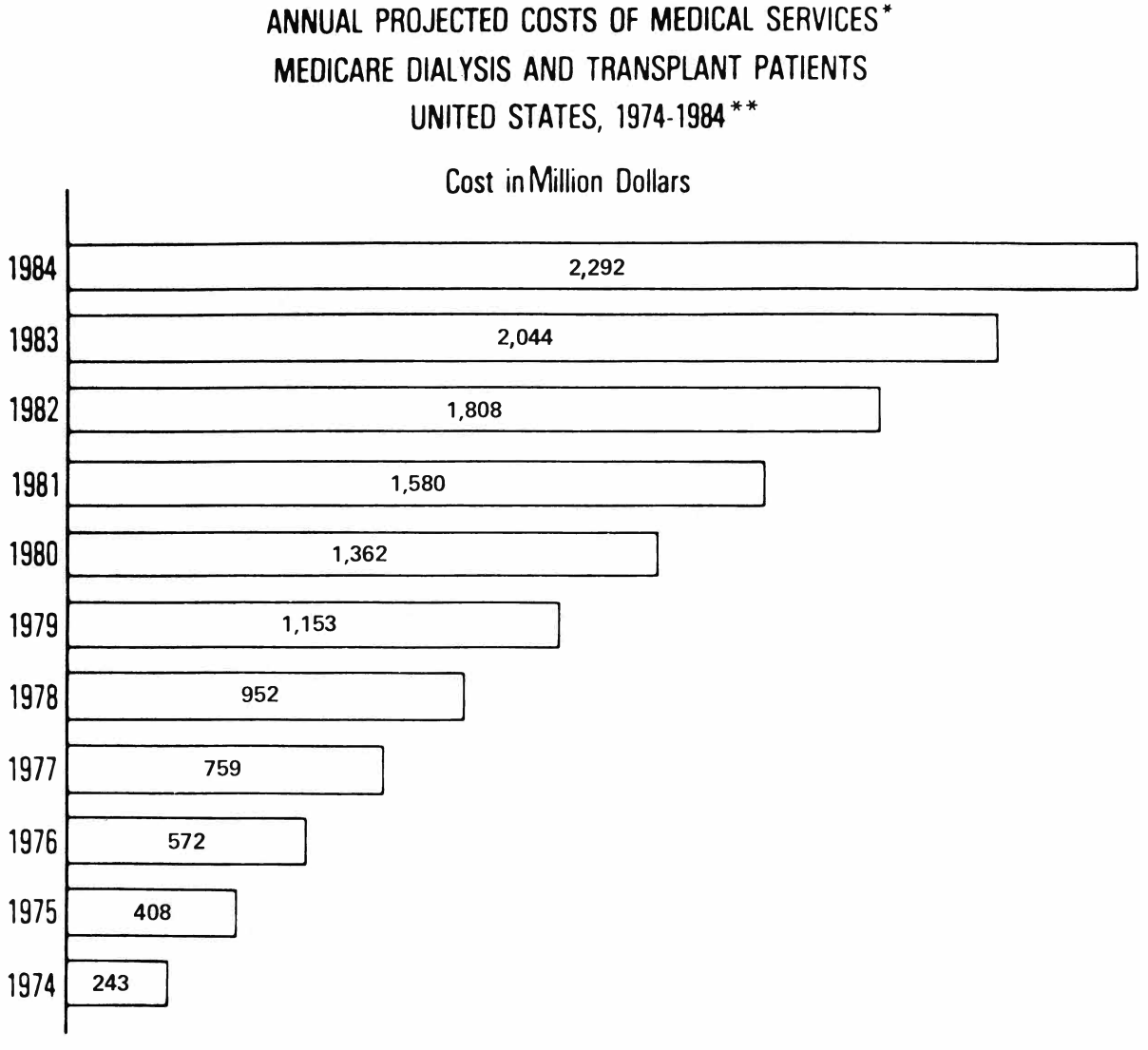

Fig 3—Projected costs of the ESRD program. Estimates provided by the Health Care Financing Administration, Office of Financial and Actuarial Analysis–Medicare.

plant facilities. These rates have now been established and all facilities must be in compliance to receive payment for services. The NCC has no authority to regulate utilization or distribution of facilities, but it is expected that it will provide consultation to HSAs and state health departments in these matters.

A national End-Stage Renal Disease Medical Information System (ESRD MIS) is being developed to collect data on the types of facilities and services provided and on the course of illness of patients with ESRD. It is anticipated that the data generated will provide basic information to assess and evaluate the quality of care provided to ESRD patients and the type of information needed for effective health care delivery planning. This system replaced the Human Renal Transplant Registry and the National Dialysis

Registry. Unfortunately, this new system has been slow in starting and only limited data regarding ESRD patients have been published since the other registries ceased operation in 1976.

As expected, the number of patients receiving ESRD care has rapidly increased since 1972. According to the National Dialysis Registry, there were only 2,426 patients receiving dialysis in the United States in 1970.[3] By June 1977 the Social Security Administration estimated that 33,371 persons were receiving dialysis treatment in over 800 facilities under the ESRD programs.[2] Transplantation activity has increased also but not quite so rapidly.[4] The growth of dialysis and transplant activity in Virginia has generally paralleled that of the nation (Fig 2).[5] There are approximately 27 dialysis facilities and 4 transplant programs [University of Virginia, Medical College of Virginia, VA Hospital (Richmond), Eastern Virginia Medical School] in this state. The basic needs of the patient population are being met. There remain, however, some areas where the distance to a facility is unacceptably long. This is particularly true in the south central and southwestern portions of the state, but it is expected that units will soon be organized in these poorly covered areas. Considerable effort is being made to increase transplant activity, particularly by improving cadaver organ procurement.

The ultimate size of the ESRD program is difficult to predict. It has been estimated that 50-75 new ESRD patients per million population per year will be candidates for treatment. This may well be a low estimate, since practically all patients are now considered candidates for some form of treatment. The Social Security Administration predicts 55,900 patients will be receiving treatment by 1982.[2]

The cost of this program is staggering. According to the most recent projections, expenditures for 1978 will approach $1.0 billion and will be $3.0 billion annually by 1984 (Fig 3).[2] The cost of maintaining a chronic dialysis patient who receives dialysis in a center approaches $25,000 per year. A saving of $8,000 to $10,000 annually is realized if the same patient performs self-dialysis at home. The cost of a successful transplant is approximately $25,000 the first year and $1,000 to $3,000 each year thereafter.[6] It is very likely that legislation will be passed in 1978 that will provide incentives for both health care providers and consumers to employ the less expensive alternatives. Changes in reimbursement procedures are also expected. These measures will help, but important changes in the artificial kidney and considerable improvement in transplant results will be required before major cost reductions are possible.

In summary, a national health insurance program for people with permanent failure of one organ system is well established. Appropriate care for most Americans with ESRD is readily available and affordable. The program, though effective and growing rapidly, is extremely expensive and cost containment is the major concern of health care providers and the government. The mechanism of administration of this program may well be the model for future national health insurance programs.

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Figure 2 is abstracted from *The Renal Program of Virginia 1977.*

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Diabetic Nephropathy

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Any discussion of morbid events in diabetes is going to emphasize cardiovascular and peripheral vascular problems. Renal disease accounts for a relatively small percentage of the mortality in diabetes; yet the overall incidence of diabetes mellitus in the population so greatly exceeds that of the various types of glomerulonephritis that it has become one of the most common causes of end-stage renal failure in this country. It is difficult to assign exact numbers because the figures in the medical literature vary considerably; however, it is estimated that in the United States today there are some 10 million people who are known to be diabetic, who would be found to be diabetic if tested, or who during the course of their lives will develop overt diabetes. In autopsy series of diabetics the prevalence of glomerulosclerosis has varied from 15% to 82%, with a mean of approximately 30%. This figure will vary depending on how carefully the kidneys are studied, particularly with respect to the use of special stains for identifying glomerulosclerosis; the incidence will also increase with the proportion of juvenile to adult onset diabetics included in the sample. Renal failure is listed as the cause of death of 6% to 12% of diabetics, and its incidence is increased seventeenfold in the diabetic population as compared to the nondiabetic. These figures are probably applicable to those diabetics who have many complications and who require referral to major medical centers for treatment. In terms of the general diabetic population renal failure is probably in the range of 1% to 2%. This means that the prevalence of glomerulosclerosis is severalfold higher than the prevalence of renal failure, and that simply finding the lesion on biopsy does not indicate that kidney function itself has been impaired or that there will be any abnormalities present on urinalysis. As a cause of end-stage renal failure, diabetes now accounts for some 15% to 25% of all new cases.

Five years' survival after onset of proteinuria in diabetics compared to age-matched controls is 65% opposed to 73% for diabetics who do not develop proteinuria and 83% for non-diabetics. This does not mean that these people are dying of renal disease but that proteinuria heralds increased mortality from all causes. For juvenile diabetics it is extremely unusual for proteinuria to develop before 10 years' duration of the disease or to appear after a protein-free interval greater than 30 years. This means that there are essentially two populations of juvenile diabetics with regard to the kidney; those who will have their disease for an unlimited amount of time and never develop renal complications, and those who during the period between 10 and 30 years will note the onset of renal problems. Finally, in juvenile diabetes mellitus, azotemia defined as BUN in excess of 30 mg percent implies end-stage renal failure within three years. An important point to note is the rarity of a decline in the glomerular filtration rate before the onset of proteinuria when the cause is diabetic nephropathy. Once renal failure does ensue it has been calculated that the glomerular filtration rate falls at an average rate of 1 ml/min each month. With other forms of renal disease, hypertension greatly accelerates the rate of decline in the glomerular filtration rate, an important point in treatment.

Diabetic nephropathy and microangiopathy are the main topics under discussion here, but there are several other factors which contribute in varying de-

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MCV QUARTERLY 14(3):148–152, 1978

gree to the progression of renal failure in diabetics. As there is no therapy for diabetic nephropathy itself, these other factors assume an importance in line with their response to treatment. Infection, in particular pyelonephritis and papillary necrosis, becomes an extremely important factor in the management of the diabetic. This is true because the autonomic neuropathy that may complicate diabetes favors development of a neurogenic bladder with high residual urine which may lead to reflux up the ureter, if the urine is infected, this reflux will result in secondary pyelonephritis and subsequent papillary necrosis with rapid loss of renal function. In patients who already have some type of renal failure, infection, even without involvement of the renal parenchyma, can result in a further decline in renal function. One of the theories that has been advocated to explain this is that certain types of bacteria can attach themselves to the cells of the ureter and thereby compromise the peristaltic action of the ureter which is important in propelling urine from the renal pelvis into the bladder. This results in a type of functional obstruction which acts in the same way as a true obstruction. Treatment of these patients with antibiotics to eradicate the bacteriuria improves ureteral peristalsis and renal function as well.

Diabetes is also frequently complicated by hyperlipidemia and hyperuricemia. Uric acid crystals are a cause of interstitial nephritis, and high uric acid levels which lead to increased uric acid excretion can set the stage for uric acid calculi, obstruction, and subsequent infection. In the evaluation of a diabetic patient, the potential adverse effect of uric acid should be considered as this cause of renal failure is subject to therapy either by alkalinization of the urine or the use of allopurinol.

A number of cardiovascular problems will also contribute to the declining glomerular filtration rate. Hypertension has already been mentioned; this can accelerate the vascular degenerative changes in the kidney, leading to nephrosclerosis which in turn can accelerate the hypertension, creating a cycle which may be interrupted if the hypertension is successfully controlled through the careful use of antihypertensive medication. Another complication of hypertension is its deleterious effect on the myocardium, leading to hypertensive cardiomyopathy and congestive heart failure. This will have an adverse effect on renal function, for as the kidney is damaged secondary to diabetes or other processes and as the vascular disease in the kidney progresses, autoregulation of blood flow in the face of a reduced cardiac output is compromised; thus low-output congestive heart failure will result in prerenal azotemia superimposed on the preexisting renal failure. In general, this situation is handled by the combination of digitalization and diuretics; however, it is worth pointing out the problems associated with excessive use of diuretics in these patients. They may get too dehydrated, a factor that will superimpose a prerenal type of azotemia upon their already preexisting level of renal failure. A compromise has to be worked out in terms of controlling the symptoms of congestive heart failure without, at the same time, contributing further to the impairment of renal function. Diabetics are prone to develop atherosclerosis, and particularly those patients who have extremely severe atheromatous disease of the aorta are subject to embolization to the renal vessels. This can present as episodic elevations of blood pressure associated with fluctuations in the level of renal function reflected by BUN and creatinine and accompanied by microscopic or even gross hematuria, depending on how much of the kidney is damaged or destroyed by infarction.

The actual role of platelets in renal disease is still largely uncertain, although there is strong circumstantial evidence that platelets may be an important factor in the decline in renal function not only in diabetes but in glomerulonephritis as well. However, the abnormal properties of platelets in diabetes increase the level of suspicion that they have a major role in the pathogenesis of the renal disease.[1] In the laboratory, platelets are studied by incubating them with various agents such as adenosine diphosphate, epinephrine, and collagen, which induce aggregation. The Table shows that the percent aggregation of platelets in diabetics to all three aggregating agents exceeds the control sample; moreover, platelets from diabetics aggregate at a lower concentration of these agents than the control sample. The reason for this is not exactly clear, but there is current evidence for a disturbance of prostaglandin synthesis by the platelets of diabetics. The Figure shows the synthesis of immunoreactive prostaglandin E following the addition of a precursor of prostaglandin synthesis, arachidonic acid. Diabetic platelets show enhancement of prostaglandin formation following addition of the precursor. Thus with the evidence that platelets are more sticky in the diabetic and aggregate more easily, the possibility has been raised that within the microcirculation of the kidney, platelet aggregation occurs and leads to occlusion of the small blood vessels,

TABLE
Percent Aggregation Four Minutes After the Addition of Each of the Aggregating Agents

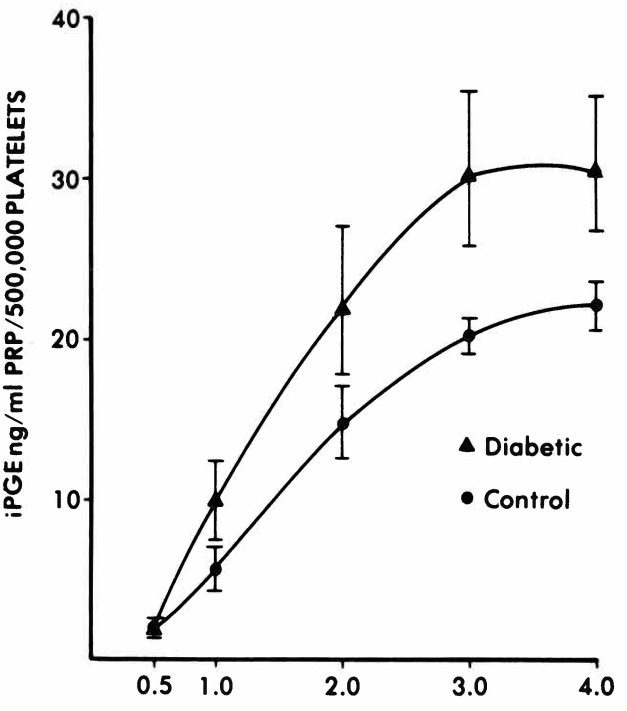
Aggregating Agent	Aggregation (%) Controls	Diabetic Subjects	P Value*
ADP:			
1 μM	22 ± 7†	80 ± 4 (9)‡	<0.001
2 μM	69 ± 4	88 ± 4 (9)	<0.005
5 μM	76 ± 4	86 ± 3 (9)	NS§
Epinephrine:			
1 μM	39 ± 8	82 ± 5 (10)	<0.001
2 μM	60 ± 6	85 ± 3 (9)	<0.01
5 μM	66 ± 6	84 ± 2 (10)	<0.005
Collagen:			
1 μg/ml	53 ± 10	80 ± 3 (8)	<0.05
2 μg/ml	69 ± 8	84 ± 4 (8)	NS
10 μg/ml	77 ± 8	86 ± 3 (8)	<0.05

* Difference between % aggregation seen in the platelet-rich plasma obtained from control and that in diabetic subjects.
† Mean ± SEM.
‡ Figures in parentheses denote no. of subjects
§ Not significant.

resulting in glomerular ischemia and glomerulosclerosis. There is some further evidence that involves platelets: thromboglobulin, a protein which is derived from the platelet, has been found to be increased in the circulation of those diabetics who have microangiopathy. There are also tests for the presence of circulating platelet aggregates, and those diabetics who have the most severe small vessel disease are also the ones who show the highest levels of these circulating platelet aggregates. A recent study[2] reported on the efficacy of sulfinpyrazone in the prevention of morbid events in patients who have severe coronary artery disease. There are active studies in progress to evaluate antiplatelet drugs in a variety of diseases that affect blood vessels, particularly coronary artery disease, atherosclerosis, and different types of renal disease.

Amyloidosis is always listed as associated with diabetes mellitus. Certainly the onset of nephrotic syndrome or heavy proteinuria in a patient with long-standing diabetes does raise the possibility that secondary amyloidosis may be present. With respect to immunologic factors which crop up in consideration of almost every type of renal disease, immunoglobulins and complements are found within the glomerulus of the diabetic kidney. Their presence in a rather nonspecific pattern together with several other serum proteins has been interpreted not to represent a specific immunologic event such as immune complex disease or anti-glomerular basement membrane (anti-GBM) disease. Still, there are some lines of evidence which do not exclude completely the idea that immunologic problems are present in the diabetic and may be contributing to the renal disease. It was recently reported that juvenile diabetes mellitus can be viewed as a genetic disease transmitted as an autosomal recessive gene.[3] More interesting, perhaps, is the close association of the diabetic gene with the HL-A locus. This area of the chromosome is concerned with a variety of immunologic responses, and many other diseases which have a close association with the HL-A locus have been more firmly established as being the result of an immunologic abnormality. Based on this there is still speculation that the diabetic may have altered immunologic responses and that this in turn may lead to primary or secondary renal damage.

Drug-induced disease of the kidney, while not confined to the diabetic, may assume increased signficance for these patients. There have been several reports of acute renal failure following the use of iodine contrast agents; for the most part, this can be prevented in the nondiabetic population by avoiding dehy-



Figure—Time course for the production of iPGE in platelet-rich plasma (PRP) from exogenous arachidonic acid (0.5mM). The values are the mean ± SEM for nine subject pairs.

dration which is part of the preparation of patients for radiologic examinations. Diabetics, however, tend to develop acute renal failure with a greater frequency than nondiabetics; moreover, avoiding dehydration does not seem to be protective. This suggests that something about the diabetic kidney predisposes it to damage in the face of a quantity of hyperosomotic material. The question arises whether the diabetic kidney is more susceptible to other nephrotoxic agents such as the aminoglycoside antibiotics and a host of other medications which have potential nephrotoxicity. The lack of a definite answer suggests that in the management of diabetics both diagnostic and therapeutic agents should be selected for their reduced incidence of nephrotoxicity.

Several studies have attempted to identify factors of importance in determining the development and progression of diabetic nephropathy. The data to be presented were derived from a small number of patients with biopsy-proven glomerulosclerosis who were followed for several years at which time a repeat biopsy was performed.[4] As far as the type of diabetes is concerned, of the 11 adult onset diabetics, 9 showed no progression of their glomerulosclerosis, and 2 became worse. In contrast, of the 6 juvenile diabetics, 1 showed no change and 5 showed progression of the disease. With regard to blood glucose control, 6 of the patients maintained good sugar control for the whole length of the study and none of the 6 showed progression of their glomerulosclerosis. By contrast, 13 patients were rated to be poorly controlled and 10 of them showed a progression of their renal lesions. In respect to the age of onset of these diabetics, patients in the group that showed no change were considerably older at the time of the onset of their diabetes than were those in the group that became worse. Obviously these three variables are not independent since, by and large, in older patients the adult onset type of diabetes can easily be managed by diet and weight reduction. But the results do suggest that blood glucose control may be important in terms of slowing down or averting the development of glomerulosclerosis.

There appear then to be at least three phases in the renal disease that accompanies diabetes. The first is a pre-proteinuria phase. Phase 2 is marked by the onset of proteinuria, and phase 3 would be development of azotemia. Several groups have tried to study the question, Is there anything abnormal about the kidney in the pre-proteinuric phase?, that is, before proteinuria becomes manifest and at a time when the other renal function tests are also normal.[5] If glomerulosclerosis progresses slowly with time, there might be a gradual increase in the excretion of albumin in the urine as the function of the duration of the diabetic process until such time as the amount of albumin in the urine definitely reaches an abnormal quantity. In a study of 97 young male diabetics who were followed from 1-19 or more years after the diagnosis of diabetes, there was no increase in albumin excretion throughout this period of time. Those who develop proteinuria are clearly distinguished from those who do not. Because strenuous exercise increases albumin excretion, a group of 13 juvenile diabetics were exercised at a rate which had not affected urinary albumin levels in 9 normal controls. The diabetics showed a statistically significant increase in protein excretion that returned to baseline after stopping the exercise. Another element that has been examined is the excretion of low molecular weight proteins by diabetics; these represent proteins that are considerably smaller than albumin and are freely filtered at the glomerulus. Almost none, however, appear in the urine because most of these filtered proteins are reabsorbed by the cells of the proximal tubule. In the pre-proteinuric phase, diabetics show an increase in excretion of low molecular weight proteins. These results, together with additional information on albumin excretion, suggest that the metabolic state of diabetes can adversely affect renal cell function so that when the diabetic is poorly controlled, the cells are less able to reabsorb filtered proteins, including albumin.

In addition to studies on patients, there have been attempts to gain information about diabetes through the use of animal models. Diabetes may be induced in animals either by removing the pancreas or by destroying the insulin-producing cells with a chemical such as streptozotocin. These animals then develop hyperglycemia and over the next several months their kidneys will show the kind of lesions that are present in humans: namely, there is an increase in the mesangial matrix and an increase in the degree of glomerulosclerosis together with deposition of immunoglobulins and complement. If the kidneys from a diabetic animal are transplanted into a normal animal, the diabetic changes rapidly disappear. On the other hand, if kidneys from a normal animal are transplanted into a diabetic animal, diabetic changes will develop. When pancreatic tissue is successfully transplanted into the diabetic animal, then coincident with the rise in insulin level, there is striking improve-

ment in the appearance of the diabetic kidney. This indicates that the changes seen in the glomerulus are at least initially reversible and that metabolic control of blood glucose, or at least the presence of insulin in appropriate quantities to keep the blood glucose normal, is a contributing factor to the development of diabetic changes.

The outline for therapy of diabetic kidney disease calls for the best blood glucose control circumstances will permit. Antihypertensive therapy has to be emphasized together with optimal management of congestive cardiac failure in order to maintain a high cardiac output and avoid prerenal azotemia. The patient should be evaluated for obstruction and for urinary tract infection. Nephrotoxic agents should be avoided as much as possible. As for vascular complications, anticoagulation offers little value as, by and large, patients who have renal disease also have retinal disease which is aggravated by these drugs. The antiplatelet drugs, based on available evidence, are quite promising, although unproven at the present time. As far as the treatment of end-stage renal disease in the diabetic is concerned, the same four modalities are open to these patients as anyone else: living related transplants, cadaver transplants, hemodialysis and peritoneal dialysis. Because of technical advances, greater experience in dealing with diabetics, and earlier acceptance of diabetics into end-stage renal failure programs, the prognosis has improved considerably during the past couple of years.[6] Transplantation from a living related donor seems to be as good in diabetics as in the general population, so that this would seem to be the treatment of choice for a diabetic with end-stage renal disease. The results with cadaver kidney transplantation tend to be poorer than those of the general population and until we have some better methods of managing cadaver kidney transplants in general, this is probably the least promising mode of therapy for the diabetic. Hemodialysis is the treatment that will be applied to the majority of these people. The problems are in establishing a suitable blood access site because of severe vascular disease and the requirement for anticoagulation during dialysis which frequently leads to a deterioration of vision. Many nephrologists now feel that the treatment of choice if a living related donor is not available is peritoneal dialysis; the major problem here is peritonitis as well as the necessity for using high-glucose containing solutions in the peritoneal cavity which can lead to severe degrees of hyperglycemia, but the complications associated with bleeding in the eye are avoided and vascular access is not necessary.

The table and the figure are reproduced with permission from the *New England Journal of Medicine* (297:1306–1310, 1977).

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Correction Notice: On p. 66 of the MCV/Q, 14:2, 1978, *Management of Urological Problems in Primary Care,* the second sentence in the footnote should have read, "An acceptable substitute is Protargol Urethral suppositories (1%) which can be made-to-order in pharmacies."

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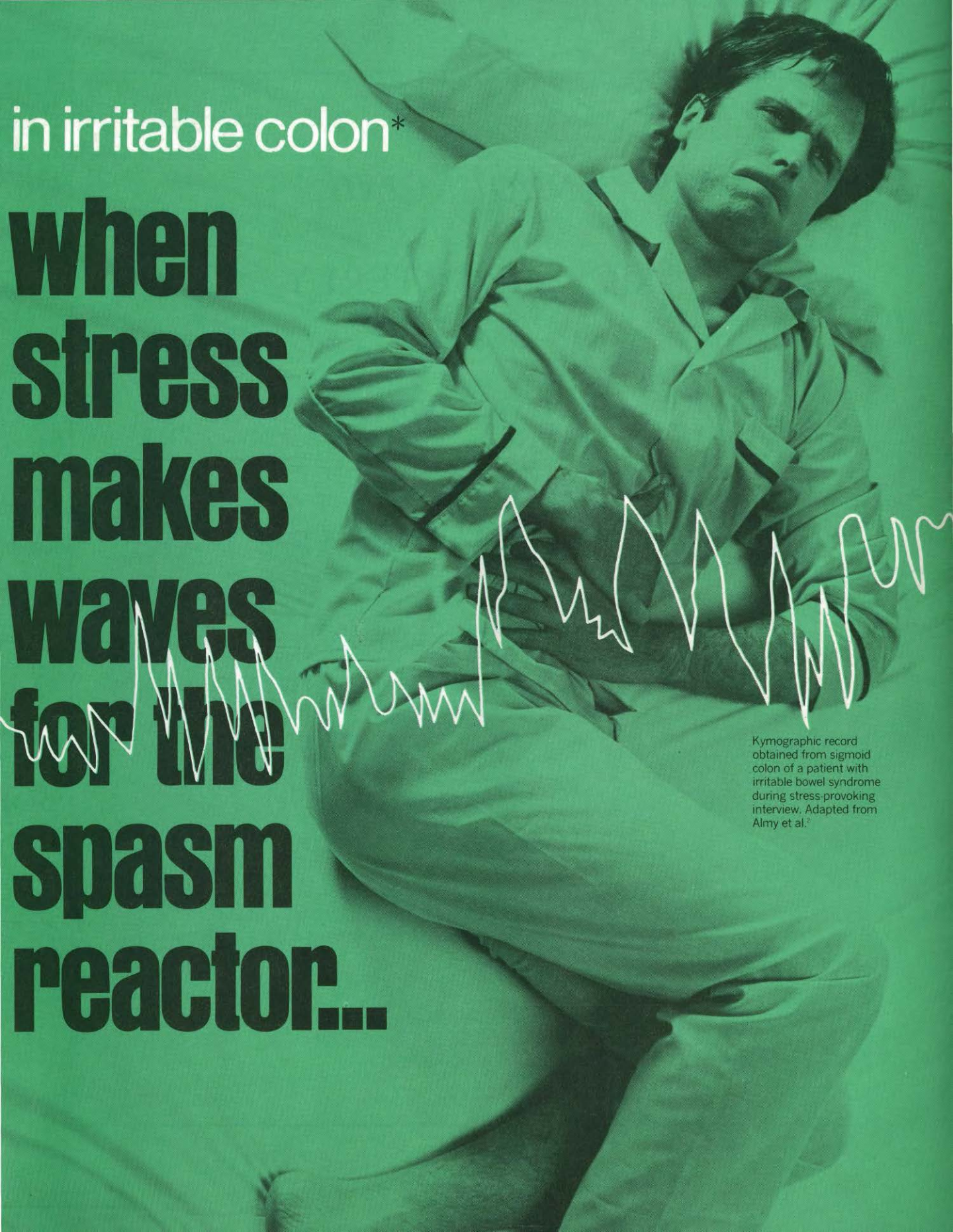

Kymographic record obtained from sigmoid colon of a patient with irritable bowel syndrome during stress-provoking interview. Adapted from Almy et al.[2]

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*Indications: Based on a review of this drug by the NAS/NRC and/or other information, FDA has classified the following indications as possibly effective: adjunctive therapy in the treatment of peptic ulcer; the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

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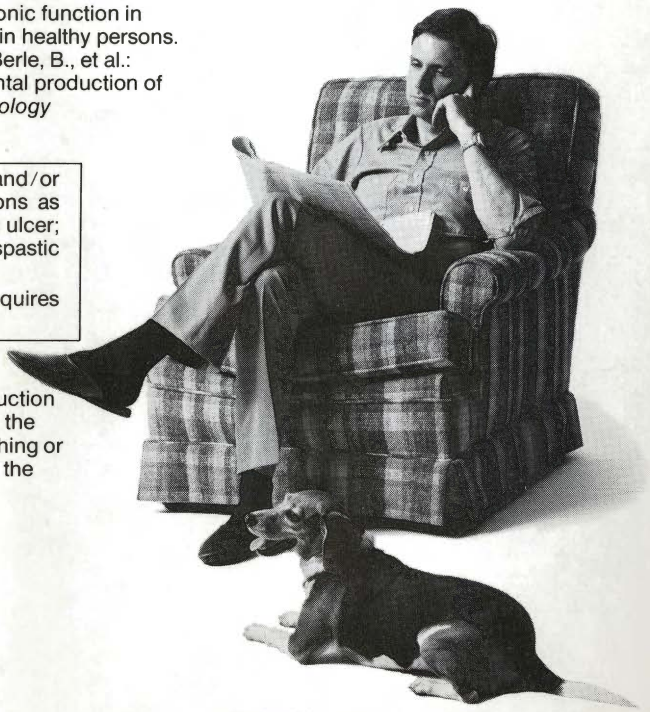

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