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NEPHROLOGY FORUM

Acute oliguric interstitial nephritis

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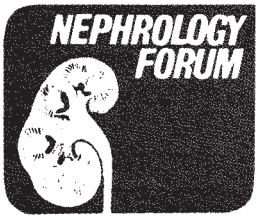
The *Nephrology Forum* is designed to relate the principles of basic science to clinical problems in nephrology.



Case presentation

A 58-year-old woman was admitted to the Cliniques Universitaires St-Luc for fever of 4 days duration. The patient, a laboratory technician in a medical research unit, uses methylcholanthrene at regular intervals and without gloves handles rats as part of her duties. She had been bitten by rats on several occasions, most recently 8 days earlier. Seven days prior to admission while on holiday in France, the patient ate a spoiled pate. Six days prior to admission, she became anorectic. Three days prior to admission, she noticed herpetic vesicles on her lips. On the same day, she also developed acute right lumbar pain and her temperature rose to 38.7° C. She treated herself with one tablet of cotrimoxazole. During the next 2 days, her temperature remained between 39.5° and 40.4° C despite the continued use of cotrimoxazole and acetylsalicylic acid. Because of persistent fever and right lumbar pain, the patient returned to Belgium and was admitted the following evening.

The physical examination revealed the following data: temperature, 39.5° C; pulse, 100 beats/min; blood pressure (supine), 110/80 mm Hg; chest, no rales; cardiac auscultation, Grade I/VI early systolic murmur; the tip of the spleen was palpated as well as the lower pole of the right kidney; the liver was not increased in size; the remainder of the examination was unremarkable.

Laboratory findings revealed the following: blood urea, 43 mg; serum creatinine, 1.4 mg/dl; serum sodium, 131 mEq; serum potassium, 3.6 mEq; total carbon dioxide content, 23 mEq/liter; hemoglobin, 15.6 g/dl; white blood cell (WBC) count, 5200/mm^3; serum lactate dehydrogenase (LDH), 619 U (normal, 140 to 300 U); creatinine phosphokinase (CPK), 31.5 U (normal, 3 to 65 U); serum glutamic oxaloacetic transaminase (SGOT), 36 U (normal, 6 to 30 U); serum glutamic pyruvic transaminase (SGPT), 16 U/liter (normal, 4 to 40 U/liter); serum bilirubin, 0.5 mg/dl. Results of urinalysis revealed the following: specific gravity, 1.015; pH, 5; no proteinuria, glucosuria, or sediment abnormalities. Several blood cultures and urine cultures, obtained during the first 24 hours, were sterile. ASLO titers were within normal limits. Paul-Bunnell, Widal and Wright reactions were negative. Serologic studies for the following agents were within normal limits or negative: 16 different serotypes of leptospirosis, toxoplasma, influenza A and B, parainfluenza I, II, and III, adenovirus, Q fever, Eaton Agent, Coxsackie B_1 through B_5, herpes, cytomegalovirus, EB virus, and hepatitis B.

During the first two hospital days, right lumbar and abdominal pain persisted and the patient vomited once. She was treated with acetylsalicylic acid administered intravenously, but she remained febrile. Several blood cultures obtained were sterile. In the evening of the second hospital day, her temperature fell to 37.8° C and remained below 37° C throughout the rest of her hospital course. The patient continued to be anorectic and vomited several times; persistent right lumbar and abdominal pain required the administration of pentazosin (Fortal®). Twelve hours after admission, a second urinalysis disclosed slight proteinuria (0.2 g/liter), 2 to 4 WBC per high power field (HPF), and a few hyaline and granular casts. Urine culture was sterile. During the first 24 hours, urine volume was 1050 ml. The urine contained: sodium, 3 mEq; urea, 13.3 g; and creatinine, 1185 mg/liter. On the morning of the third hospital day, blood analysis revealed: urea, 113 mg; creatinine, 3.6 mg; hemoglobin, 17 g/dl; WBC count, 14,100 mm^3 with 83% neutrophils and no eosinophils. A morning urine sample contained: protein, 19 g; glucose, 0.4 g/liter; 1 to 3 WBC and 10 to 15 red blood cells (RBC)/HPF. The 24-hour urine volume at that time was only 180 ml and it contained: sodium, 89 mEq; urea, 2.75 g; and creatinine, 485 mg/liter; 24-hour urine protein excretion was 1.9 g. The patient appeared to be slightly dehydrated, and 4 liters of saline were administered. On the fourth day, however, the patient remained oliguric (24-hour urine volume, 110 ml). Blood urea concentration increased to 180 mg, and serum creatinine concentration increased to 6.1 mg/dl. Echography revealed kidneys of normal size without evidence of obstruction.

Six days after admission, anuria persisted; blood urea concentration was 228 mg, and serum creatinine concentration was 8.8 mg/dl. Intravenous urography revealed a slight but persistent nephrogram and a normal pelvicalyceal system visible on late films. A percutaneous renal biopsy was obtained immediately thereafter, and the results will be described later. One week after admission, IgA and IgM levels were elevated at 165 and 321%, respectively. IgE and IgG levels were normal. Serum com-

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plement was at the lower limit of normal. Ten days later, the same observations were made but in addition IgG levels had increased to 138%. No specific treatment was given. Two weeks after admission, the urine volume exceeded 400 ml/day for the first time and increased to normal levels thereafter. The patient underwent hemodialysis three times in the interim. Results of urinalysis 12 days after admission revealed protein content of 5 g/liter, 50 WBC/HPF, and 10 RBC/HPF. Sixteen days after admission, the 24-hour urine volume exceeded 1 liter, and protein and sediment abnormalities disappeared from the urine. Twenty days after admission, serum creatinine concentration was 1 mg and blood urea concentration was 33 mg/dl. Results of urinalysis were normal.

Discussion

DR. CHARLES VAN YPERSELE DE STRIHOU *(Professor of Medicine, Head, Renal Service, University of Louvain Medical School, Cliniques Universitaires St-Luc, Louvain en Woluwe, Brussels)*: I should like first to discuss the patient's presentation and the initial physical and laboratory findings. In brief, she suffered for 4 days prior to admission from intense right lumbar pain and elevated temperature, while not responding to cotrimoxazole therapy. Although deterioration of her general condition was the immediate problem on admission, renal failure soon appeared and progressed to oliguria and anuria. On admission, the patient appeared to be slightly dehydrated. Urinary sediment was normal and the urinary concentration of sodium was low, whereas the urinary concentrations of urea and creatinine were elevated. Infusion of several liters of saline, however, failed to restore renal function. Dehydration can thus be eliminated as the sole cause of renal failure. Urinary tract obstruction, suggested by the right lumbar pain and the lack of urinary sediment abnormalities, can be ruled out as well because neither echographic examination nor i.v. urography demonstrated any evidence for obstruction.

The diagnostic process thus inevitably leads to primary renal disease as the cause of the severe oliguria in this patient. Acute or subacute glomerulonephritis is unlikely because she did not initially have hypertension, edema, proteinuria, or any urinary sediment abnormalities, in particular hematuria and red cell casts. It is noteworthy, however, that 3 days after admission, a second urinalysis disclosed a high protein content and red blood cells, but not red blood cell casts. Acute ascending pyelonephritis is also unlikely because *(1)* the patient did not have chills or pyuria, *(2)* her temperature remained constant after the second hospital day, and *(3)* urine cultures were sterile. The findings of the urine cultures, however, should be interpreted cautiously because the patient received cotrimoxazole prior to admission.

The sudden onset of oligoanuric renal failure in a patient with symmetric, slightly enlarged kidneys certainly suggests acute tubular necrosis (ATN); the dense, persisting nephrogram observed on i.v. urography also supports this diagnosis, although in one series of 20 patients both signs were absent in 20% of the patients [1]. Several features, in this patient, however, are not common in ATN. A causal factor could not be identified: despite a detailed history, no toxic factors were discovered, and although an increase in temperature was seen early in her course, there was no evidence for septic shock. Slight lumbar pain may be present in ATN, but intense pain, which required potent analgesics in this patient, is not a usual finding. Lumbar pain is seen rarely, however, in toxic nephropathies such as that induced by carbon tetrachloride inhalation. Serum analysis failed to disclose any sign of hepatic dysfunction, rhabdomyolysis, or intravascular hemolysis. Finally, chemical analysis of the urine argues against a diagnosis of ATN on admission because the urinary sodium concentration was low, and the urine-to-plasma ratios for urea and creatinine were high. In a recent prospective study, Miller et al observed a urinary sodium concentration below 20 mEq/liter in less than 10% of the patients with nonoliguric ATN [2]. Similarly, a urine-to-plasma ratio for creatinine above 40 was observed in less than 10% of these patients. A combination of these two indexes, the "renal failure index" [(urinary sodium, mEq/liter)/(urine-to-plasma creatinine ratio)], was below 1 in only 6% of the patients with nonoliguric ATN, whereas in our patient this index reached 0.6. Taken together, these observations lead us to suspect another cause of acute renal failure, namely, acute interstitial nephritis (AIN).

Acute interstitial nephritis is probably less rare than is believed currently. In a recent series of 976 patients with acute renal failure, Richet et al performed renal biopsy in 218 patients in whom the diagnosis was not clear-cut [3]. Pure AIN was observed in 29 patients—that is, 14%. An almost identical proportion has been reported by Wilson [4]. Over the last few years, we have been more aggressive in performing renal biopsy in acute renal failure because the biopsy results provide clues not only to AIN but also to other unsuspected glomerular or vascular diseases. Richet argues that renal biopsy is indicated in all patients with acute renal failure under the following conditions: *(1)* when accompanied by systemic manifestations such as a cutaneous

rash, arthralgias, unexplained temperature, raised level of blood eosinophils; *(2)* when the expected diuresis does not occur within the usual time limits; *(3)* when renal failure is subacute and associated with atypical urinary features [3]. In his series of biopsies, Richet reported only a few perirenal hematomas [5]. They were encountered only in vascular renal diseases and led to nephrectomy in three patients. The frequency of this complication, though low, justifies a cautious approach to renal biopsy in acute renal failure and requires rigorous control of the hemorrhagic tendency and hypertension commonly associated with acute renal failure. Dr. Cosyns, would you report the findings of the renal biopsy?

DR. J. P. COSYNS *(Department of Pathology, Cliniques Universitaires St-Luc, Louvain en Woluwe, Brussels)*: The renal tissue obtained by needle biopsy was composed of 25 glomeruli and a large portion of medulla. Except for one hyalinized glomerulus, the glomeruli showed only minimal abnormalities—that is, a few polymorphonuclear neutrophils in some capillary lumina and some swelling of the epithelial cells. The vessels were normal. There was considerable congestion of the intertubular capillaries with areas of interstitial hemorrhage and there were nucleated cells in the vasa recta. There was no interstitial fibrosis. There was, however, diffuse interstitial edema and cellular infiltration predominantly in a large subcapsular area, in the boundary zone and in the medulla (Fig. 1). The infiltrating cells were mainly lymphocytes, mononuclear cells, a few plasma cells, and rare polymorphonuclear neutrophils. There were no eosinophils. The tubular architecture was normal except for spotty tubular loss without atrophy and some dilatation in the cortex. Some epithelial linings were flattened and showed increased cytoplasmic acidophilia and nuclear density. These findings were obvious in the upper medulla, in the midportion of the cortex where a few mitoses were seen, and in the severely infiltrated subcapsular area where there was some tubular loss and rare atrophic tubules. In this area, the staining of the tubular basement membranes by PAS and PASM was very weak (Fig. 2). No overt rupture was seen. The inflammatory cells were in close relation with the altered basement membranes. A few inflammatory cells were visible between tubular epithelial cells but not in the tubular lumen. Rare eosinophilic proteinaceous casts but no granular or pigmented casts were seen. Finally, rare crystalline deposits resembling calcium oxalate were present in the lumen of cortical tubules. Direct immunofluorescent staining failed to reveal IgG, IgA, IgE, fibrinogen or the third component of complement (C3). A few plasma cells fixed the anti-IgM antiserum. The electron microscopic examination revealed a normal glomerulus, interstitial edema, and well-differentiated tubules.

The microscopic study allows us to exclude glomerular or vascular disease. We are dealing either with ATN or AIN. This differential diagnosis is not always easy for the pathologist since shock-induced ATN with a prominent cellular interstitial reaction and AIN may be histologically similar [6]. Ooi et al [7] have described a tubular lesion named "tubulitis" defined as the infiltration of acute or chronic inflammatory cells, or both, in the peritubular regions or between the lining epithelial cells, with or without disruption of the tubular basement membrane. This lesion is not specific to AIN since it has also been observed by the same group in a patient with ATN following abortion. Furthermore, agents such as cephalothin [6, 8] or gentamicin [9] may produce either ATN or AIN. It is noteworthy that the lesions observed as a consequence of adverse reaction to certain drugs such as glafenin have been termed acute tubulo-interstitial lesions [10]. These lesions seem to be representative of an "intermediate phase" between ATN, following an episode of shock, and AIN. In light of current data, observers are questioning whether these lesions should be classified as ATN with prominent interstitial cellular infiltration, or more properly as true AIN [3]. Nevertheless, in view of the clear findings of interstitial cellular infiltration, particularly in the important subcapsular area, I believe this patient has AIN. We should remain cognizant, however, both of the lack of well-defined histopathologic criteria in AIN and of the small sample of renal tissue obtained by needle biopsy, which is not necessarily representative of the whole renal parenchyma [11].

DR. C. VAN YPERSELE: We and Dr. Cosyns thus conclude that this patient has AIN. I should like to comment further on a few unusual aspects of this patient's course, and then proceed to a discussion of the possible cause of AIN in this patient.

Intense lumbar pain has been reported in several patients with AIN [12–15]. It is probably due to the distention of the renal capsule by interstitial edema, evidenced sometimes by an increase in renal size [16, 17]. Interestingly, in two patients with antibiotic-induced interstitial nephritis [16, 18] the lumbar pain was unilateral, as it was in our patient. A dense immediate nephrogram has also been observed in another patient with antibiotic-induced interstitial

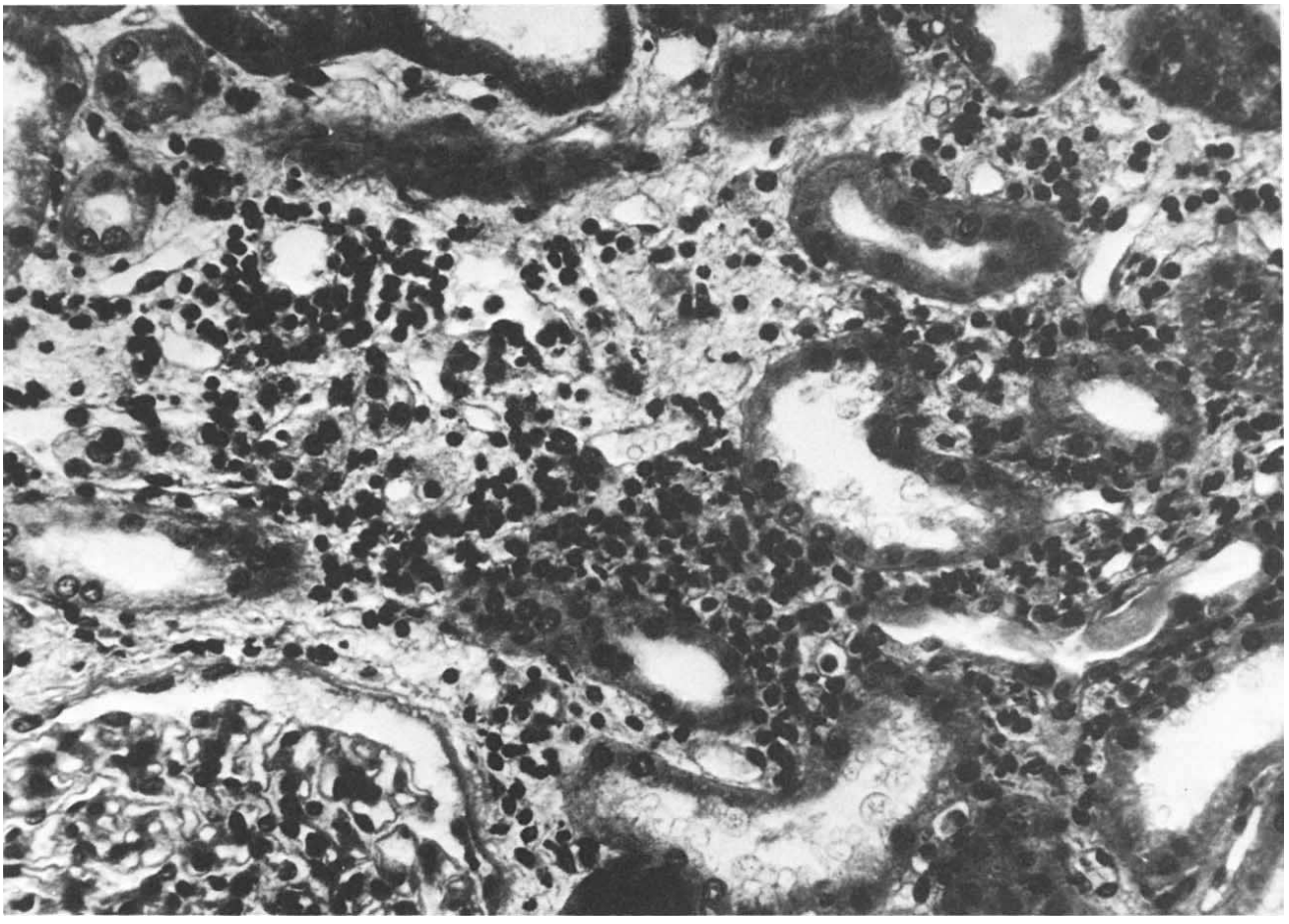

Fig. 1. *Subcapsular area with considerable degree of interstitial edema and cellular infiltration.* There is some tubular loss but no glomerular abnormalities (Trichrome ×390).

nephritis [19]. These cases viewed together suggest that i.v. urography does not help in distinguishing between ATN and AIN.

The "prerenal" characteristics of the urine observed at the onset of renal failure in our patient continue to be puzzling. Indeed, the limited data available suggest that the results of chemical urine analysis in AIN are identical with those seen in ATN. It is possible however that at its earliest stage AIN behaves differently. In acute ureteral obstruction, it has been demonstrated that the urine sodium concentration decreases, whereas the concentrating power of the kidney is preserved [20]. Two patients with obstructive renal failure in whom the sodium concentration was initially low have been observed [21]. It is thus possible that the results in our patient indicate an incipient intrarenal obstruction. Whatever the interpretation, it should be remembered that when the patient became oliguric, the results of urine chemistries were compatible with ATN.

What are the possible causes of AIN in our patient? Acute interstitial nephritis is a very heterogenous condition but two major causes have been identified: drugs and infection. Our patient had not taken any drugs save acetylsalicylic acid and cotrimoxazole. Acute interstitial nephritis has been attributed to sulfonamide toxicity [22], and cotrimoxazole does contain a sulfonamide derivative. Further, acute reversible deterioration of renal function after administration of cotrimoxazole has been reported in 20 patients [23, 24]; in 2 of those patients, renal biopsy showed ATN with an interstitial reaction [23]. Two instances of cotrimoxazole-induced AIN have been reported; one patient had an increased serum concentration of IgE, and another patient had many eosinophils in the urine [18, 25]. In our patient, however, cotrimoxazole toxicity does not seem to be the cause of the disease. Indeed, the amount taken was much lower than that in reported observations of acute renal failure from

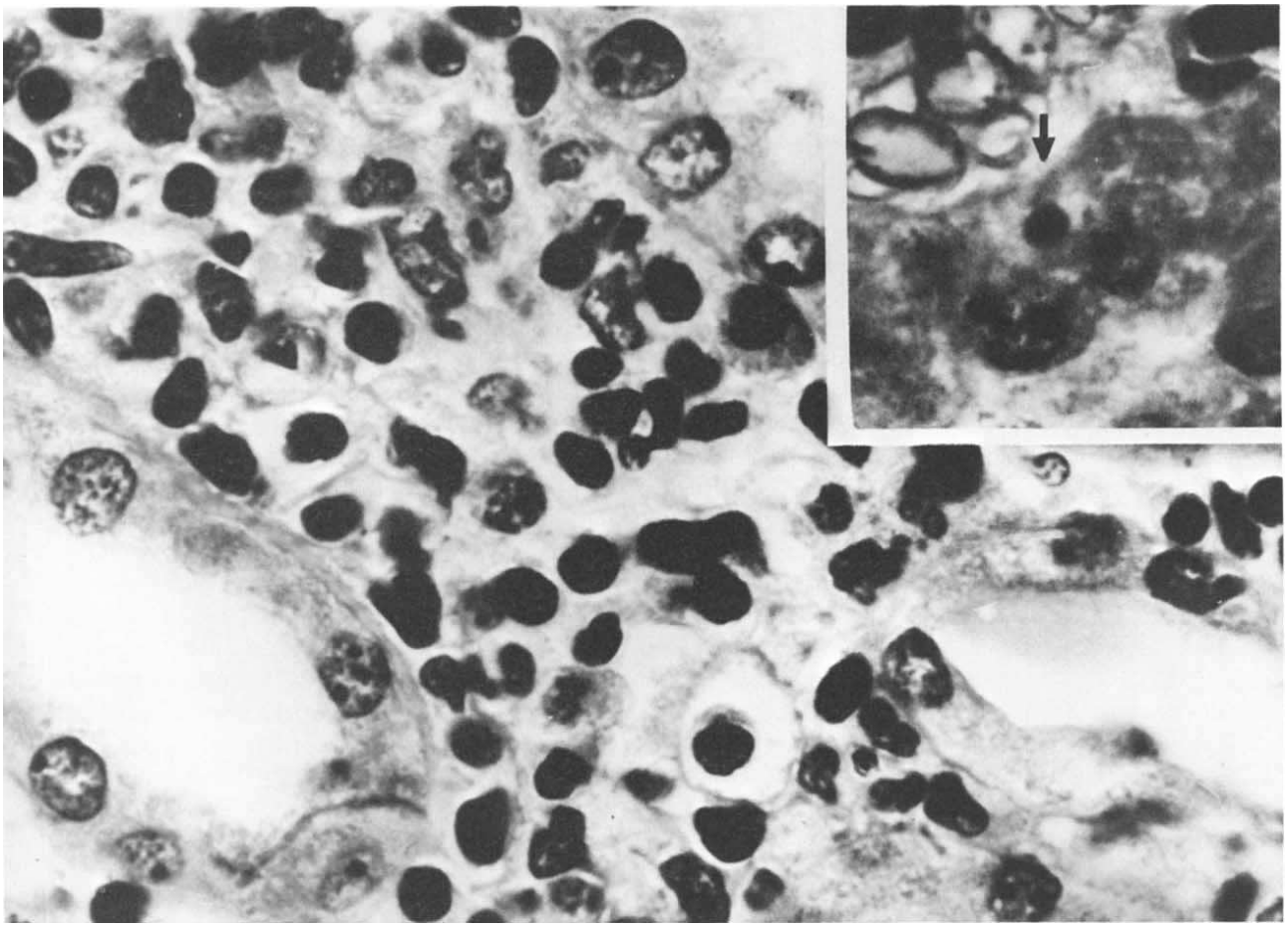

Fig. 2. *Weakly-stained tubular basement membranes in the interstitial areas infiltrated by chronic inflammatory cells, chiefly by polymorphonuclear leukocytes* (trichrome, ×625). Insert shows inflammatory cells (*arrow*) infiltrating between the tubular epithelial cells and the tubular basement membrane (trichrome, ×1560).

this agent. Furthermore, the symptoms of fever and lumbar pain antedated intake of the drug.

The presence of an infection responsible for the fever is suggested by the history, the elevated WBC count, and the evolution of serum protein changes; that is, the early increase of IgM and IgA followed 10 days later by an increase in IgG concentration. The fact that the serum complement concentration remained at the lower limit of normal during this inflammatory reaction suggests that complement was consumed by circulating immune complexes. The concentration of immune complexes, as measured by the Cambiaso method [26], was initially at the upper limit of normal but fell subsequently. These findings should be interpreted with caution as the detection of immune complexes depends very much on the technique used; results may be negative with some techniques and positive with others. Although our observations are suggestive of an infectious disease, we must acknowledge that no causal agent could be identified. Blood and urine cultures were consistently sterile, antistreptolysin titers were normal, and the antibodies against a multitude of microbial species were normal. The spontaneous decrease in temperature suggests a viral infection. This hypothesis is further supported by the striking occurrence of acute renal failure in two additional patients, both working in the same laboratory and manipulating rats, within the 3 months preceding this patient's illness. Similarities can be seen among all three patients. Dr. Vandenbroucke, would you present briefly the history of these other two patients?

DR. J. M. VANDENBROUCKE *(Physician, Renal Service, Cliniques Universitaires St-Luc, Louvain en Woluwe, Brussels)*: As Dr. van Ypersele mentioned, a few weeks prior to admission of the patient under discussion today, we observed an identical clinical picture in two people working in the same laboratory as this patient. The first patient, a

37-year-old man, works with rats and pigeons. He suffered, a few days after his wife, with an influenza-like syndrome and was treated with phenacetin and doxacycline. Three days later, he had an episode of vomiting, and 2 days later, he had chills and a temperature of 39° C. At that time, the patient complained of heavy lumbar pain, predominantly on the right side, and urine volume decreased. His physician found proteinuria; the next day, urinalysis disclosed the protein content to be 17 g/liter with moderate leukocyturia. Serum creatinine concentration reached 6.5 mg/dl and the patient was admitted to the hospital. Physical examination revealed hypertension (200/120 mm Hg) and bilateral flank pain. Blood analysis disclosed an accelerated erythrocyte sedimentation rate (E.S.R.) and an increased concentration of fibrinogen: creatinine concentration was 9.2 mg; blood urea was 135 mg/dl; enzymes were normal; WBC count was normal without eosinophils. Results of urinalysis revealed: protein content, 0.4 g/liter; sediment, 3 to 6 WBC/HPF, 2 to 4 RBC/HPF; urine culture, sterile. An i.v. urogram showed kidneys of increased size with parenchymatous edema; excretion was symmetric but slight; there was no evidence of obstruction. During the hospital course, daily urine volume remained above 1.5 liters; there was no fever, and renal function returned rapidly to normal with no specific treatment.

Two weeks later, the second patient was referred to us for treatment of acute renal failure with massive proteinuria. The clinical history was similar: intense lumbar pain, predominantly on the right, at the beginning; a few days later, development of fever and vomiting; and proteinuria accompanied by hematuria. On admission, the patient was febrile, normotensive without symptoms of hypervolemia, but had hepatosplenomegaly and an enlarged, tender right kidney. Laboratory examination revealed: an accelerated E.S.R. and increased concentration of fibrinogen in the blood; serum creatinine, 3.4 mg; blood urea, 104 mg/dl; LDH, 764 U; SGOT, 93 U; SGPT, 74 U. Hemogram was normal: WBC count, 9200/mm^3 with monocytosis (15%) but with no eosinophils. Urinary protein was 7.3 g/liter initially but rapidly decreased; microhematuria also disappeared rapidly. During the first two hospital days, the patient was oliguric; subsequently the daily urine volume increased, exceeding 1.5 liters, with a simultaneous decrease in serum creatinine concentration to normal.

In neither of these two patients did we find an etiologic factor for the acute renal failure: toxicologic research was negative, serology was negative for leptospirosis and toxoplasmosis. Only in the first patient did we observe a rise in titer for the Coxsackie B_4 antibodies of questionable significance—1/128 to 1/512 and later 1/128. Immunoglobulin studies showed a transient increase in IgA concentration.

DR. C. VAN YPERSELE: The striking similarity in the courses of these three patients indeed suggests the presence of an infectious agent which to date we have not been able to identify.

I should now like to turn to a more in-depth discussion of the pathogenesis of AIN. Heptinstall defines AIN as an acute inflammatory lesion of the interstitium occasionally associated with tubular lesions but without glomerular involvement [6]. This pathologic picture is observed in a great variety of clinical renal disturbances, ranging from simple proteinuria with only slight alterations of the urinary sediment to acute renal failure. It may have various immunologic manifestations and may occur in a variety of circumstances, which suggests that AIN is the common endpoint of diverse diseases acting through different mechanisms. To the restrictively defined AIN of Heptinstall, one should add the acute interstitial lesions that may accompany glomerular or vascular diseases. It is probable that AIN, like glomerulonephritis, will be divided into a variety of subgroups in the future.

Experimental acute interstitial nephritis. I plan to review the various clinical conditions associated with AIN, but first I will summarize the experimental immunologic manipulations that may induce AIN. Three different mechanisms have been identified: the *first* relies on immune complexes, the *second* on antitubular membrane antibodies, and the *third* on the induction of delayed hypersensitivity.

Two models of AIN demonstrate the *first* mechanism: The repeated injection of homologous cytoplasmic tubular (HCT) antigens [27] or the repeated administration of heterologous bovine albumin (HBA) [28] in the rabbit result in the development of interstitial nephritis characterized by mononuclear infiltration and tubular lesions. In the HCT antigen model, the glomeruli are spared, whereas in the HBA model they are involved. On immunofluorescence, granular IgG and C3 deposits are seen along the tubular membrane. In the HBA model deposits are also located along the glomerular basement membrane. The lesions in the HCT antigen model result apparently from the in situ combination of cytoplasmic tubular antigens slowly diffusing from tubular cells with circulating antibody

brought by blood flow to the basal membrane. In the HBA model, immune complexes of bovine albumin and antibovine albumin antibodies are carried through the circulation into the glomeruli and along the tubular basement membrane. From these models, we may conclude that immune complexes may provoke acute interstitial reaction whether they are formed within the interstitium or are located there secondarily.

The *second* mechanism is demonstrated by experiments in which purified rabbit tubular membranes are injected into the guinea pig [29]. Acute interstitial nephritis develops subsequently and is characterized by cellular infiltration of plasmocytes, mononuclear cells, macrophages, and giant cells, which provoke tubular lesions. On immunofluorescent examination, linear deposits of IgG and C3 are observed along the tubular basement membrane. This model of AIN is due to the development of circulating antitubular basement membrane (anti-TBM) antibodies, which have been identified in the circulation. Furthermore, injection of guinea pig serum induces the disease in nonimmunized recipients [30]. This reaction requires the activation of complement, at least through the alternate pathway [31–33], and probably also requires the presence of intact bone marrow cells in the recipient [34]. When the disease is transferred to a nonimmunized recipient, the injected antibody initiates the tubular lesion, but subsequently the recipient develops autoantibodies, thus amplifying the initial reaction [35]. From this model, we conclude that anti-TBM antibodies may provoke interstitial nephritis mediated by complement activation and marrow cells, which might suggest cellular immunization as well. These anti-TBM antibodies may be generated either by the injection of heterologous TBM or by the liberation of autologous hidden tubular membrane antigens.

The *third* mechanism relies on delayed hypersensitivity. Guinea pigs or rats are injected with bovine gamma globulin (BGG) at a rate appropriate to stimulate delayed hypersensitivity [36]. Aggregated BGG is then injected into the subcortical region of the kidney. Immediately, there is an intense mononuclear cell infiltration, which destroys the tubular components. This type of interstitial reaction is certainly due to delayed hypersensitivity because it is transferable by lymphocytes but not by the serum of the donor. Furthermore, no circulating anti-BGG antibodies are demonstrated and no immunoglobulins are present in the kidney [37]. This model demonstrates therefore that delayed hypersensitivity may result in AIN if the stimulating antigen is located within the kidney.

Clinical acute interstitial nephritis. How can these mechanisms intervene in human disease? I will comment only briefly on the interstitial lesions associated with glomerular diseases. Immune complexes, probably DNA and anti-DNA, are observed along the tubular basement membrane in more than half the patients with lupus nephritis [38]. Other immune complexes along the tubular basement membrane have been reported in cryoglobulinemia [38] and renal transplants [39, 40]. Linear anti-TBM antibody deposits have been observed in rapidly progressive glomerulonephritis with antiglomerular basement membrane (anti-GBM) antibodies [38, 40] and in renal transplants [41, 42]. These observations illustrate the pathogenic role of humoral immunity in the genesis of AIN. It is noteworthy that in renal transplants the same immune challenge may result in two different types of lesions. A detailed analysis suggests that in addition to these two antibody-mediated lesions some cellular-mediated lesions—delayed hypersensitivity—are also involved.

In order to review AIN that is unaccompanied by glomerular lesions, I will follow Richet's classification [43]. This classification is based on the type of cells infiltrating the kidney: polymorphonuclear or mononuclear cells.

Acute interstitial nephritis with massive infiltration of polymorphonuclear cells and formation of microabscesses is induced by septicemias, occasionally of urinary origin. Urinary protein excretion reaches 2 to 3 g/liter and is accompanied by pyuria. Renal insufficiency is usually progressive, may be severe, and is only slowly and partially reversible. No immunoglobulins are seen in the kidney, and circulating anti-TBM antibodies have not been detected. Resolution of this type of AIN requires a careful search for the cause of the septicemia and its prompt treatment [44]. This variety of AIN was observed in 6% of the 218 patients with acute renal insufficiency biopsied by Richet [3].

Acute interstitial nephritis with mononuclear cell infiltration is more heterogenous and may be provoked either by drugs or infection. A drug may be toxic by itself, as demonstrated by the dose dependency of the lesions. This mechanism has been invoked to account for the important interstitial lesions occasionally observed after administration of polymyxin E, cephaloridine, cephalothin, and glafenin [13, 17, 45–47]. Interestingly, the acute renal failure provoked by these substances may be accompanied solely by minimal tubular lesions with-

out cellular interstitial infiltration, a picture identical to that of ATN.

In other instances, drugs act apparently through immune mechanisms: AIN is evoked by a normal dose of the drug, sometimes simultaneously with extrarenal manifestations of an immunologic conflict. The list of incriminated drugs is very long, but the most frequently mentioned are: methicillin, phenytoin, phenindione, rifampin, sulfonamides, and less frequently, cephalothin, glafenin, and diuretics (see Table 1) [8, 48]. The delay between the administration of the drug and the onset of renal lesions varies from a few hours to several weeks.

The clinical picture is heterogenous. Frequently, the onset of renal failure is acute and associated with hematuria, which is sometimes macroscopic, whereas a few series reveal consistent pyuria with a large number of eosinophils. Occasionally, however, renal failure develops slowly without urinary manifestations: the kidney may be increased in size with associated severe lumbar pain, or in some patients, the kidneys may be normal in size or only slightly enlarged. Renal failure is variable in severity and may require hemodialysis. Withdrawal of the offending drug is usually accompanied by improvement in renal function, providing further evidence for a cause-and-effect relationship. Readministration of the drug can lead to another episode of renal insufficiency [13, 48]. Total healing is frequent, but occasionally persistent chronic renal failure has been reported [8, 18, 49–51].

The existence of an immunologic conflict is suggested by systemic clinical manifestations such as fever, cutaneous rash, and arthralgias. These are by no means always present. An increased number of circulating eosinophils is often observed after administration of methicillin [18, 52, 53] or diuretics [48, 54, 55], in sporadic cases [56, 57], and rarely after administration of drugs such as rifampin [8], glafenin [13], or cephalothin [58]. On biopsy, lymphocytes, plasmocytes, and mononuclear cells are present in abundance, often but not always accompanied by eosinophils. In a few patients, epithelioid cell granulomas with giant cells were observed [59–61]. The existence of a humoral immune reaction is also suggested by the finding on renal biopsy of linear IgG and occasionally of C3 deposits along the tubular basement membrane. This has been reported, however, only in a few instances of methicillin-, penicillin-, or phenytoin-induced AIN [52, 53, 59, 62]. In these patients, circulating anti-TBM antibodies were also demonstrated [52, 59, 62]. It should be pointed out, however, that these abnormalities are exceptional: indeed, immunoglobulins were absent in the renal biopsy of the six patients with methicillin-induced AIN reported by Galpin [18]. In a few patients with methicillin-induced AIN and in one patient with cotrimoxazole-induced AIN, increased serum concentrations of IgE were observed [25, 63]. In a single patient with phenobarbitol-induced AIN, plasmocytes filled with IgE were observed in the interstitium [64]. Usually, however, all of these parameters are normal. Further evidence for an antibody-mediated immune reaction can be found in a positive Coombs reaction in a few instances of ampicillin-, rifampin-, or glafenin-induced AIN [8, 65, 66]. Lymphoblastic stimulation or inhibition of leukocyte migration has been occasionally reported in AIN due to methicillin, rifampin, glafenin, phenytoin, and phenindione [13, 61, 62, 67, 68]. But, as mentioned earlier, the tests are often negative. In summary, these data suggest that the same drugs may evoke AIN through a variety of immune mechanisms, either humoral or cellular as well as produce toxic, dose-dependent renal lesions.

The following hypothetical scheme might integrate the different pathogenic mechanisms defined experimentally with the various immunologic disturbances observed in clinical AIN. Interstitial accumulation of the drug may result either from a direct toxic effect of the drug on tubular cells with subsequent diffusion through a ruptured tubular basement membrane, or from its concentration within peritubular capillaries, or from its combination with the tubular membrane acting as a hapten. Once in the interstitium, the drug challenges immunity and induces either humoral immunization or cellular, delayed hypersensitivity immunization.

Table 1. Prevalence of drug-induced acute interstitial nephritis[a]

Frequent	Rare
Methicillin	Oxacillin
Penicillin	Nafcillin
Ampicillin	Carbenicillin
Rifampin	Cephalothin
Glafenin	Tetracycline
Sulfonamides	Thiazide
and cotrimoxazole	Furosemide
Phenindione	Phenylbutazone
Phenytoin	Aminophenazone
	PAS acid
	Gold and bismuth salts
	Azathioprine
	Allopurinol
	Phenobarbital
	Cephalexin

[a] Data taken from Refs. 8 and 59.

Humoral reaction is either systemic, manifested in the formation of circulating antibodies directed against the drug or against the tubular membrane, or local with infiltration of monocytes, lymphocytes, and plasmocytes. These latter cells are able to synthesize immunoglobulins locally and form immune complexes in situ. Delayed hypersensitivity will bring about the invasion of the interstitium with macrophage-stimulating lymphocytes. Within this framework, it is conceivable that the same drug elicits the same tubular lesions through different immune mechanisms, the type of response being determined by the genetically determined immune responsiveness of the patient, the degree of stimulation of immunity, and the characteristics as well as the quantity of the offending agent.

Whatever the mechanisms involved, it is quite clear that it is extremely important, both in patients with acute renal failure and in those with chronic renal insufficiency who have an unexpected decline in function, to look for evidence of activation of the immune system and to suspect a deleterious role for any drug recently taken by the patient. Detection of increased amounts of eosinophils in the urine may be helpful. If there is any doubt, renal biopsy should be performed. Immunologic tests for the detection of anti-TBM, IgE, Coombs reaction, inhibition of lymphocyte migration, or lymphoblastic transformation are useful to support the hypothesis of drug-induced interstitial nephritis. This critical attitude allowed Lyons et al [48] to modify the apparently inevitable degradation of renal function observed in some patients with glomerulonephritis simply by interrupting the administration of diuretics.

The role of infectious agents in the genesis of AIN with mononuclear infiltration has been demonstrated, although it is less extensively documented than drug-induced AIN. The streptococcus has been implicated in the context of a hyperergic reaction that is sometimes associated with eosinophilia [43, 69, 70] and is reminiscent of AIN following scarlet fever, described more than a century ago [71]. Leptospirosis may also produce AIN. Its mechanism has been delineated in studies performed in infected dogs [72]. The leptospires are initially found in the tubular lumen, but subsequently their antigenic material is found in the interstitium, either within macrophages or as discrete granular deposits combined with antileptospire antibodies, which are secreted locally by plasmocytes. An analogous lesion has been found in a lepromatous patient [43]: the Hansen bacilla or its antigenic component has not been identified, but plasmocytes that produce IgG have been found in the interstitium. Toxoplasmosis [73], mononucleosis [74], and measles [4] have also been incriminated. No antibodies have been identified in situ but the viral antigens have been identified in the tubular cells. Virus-induced AIN is well documented in animals. In the fowl, infectious bronchitis virus is able to damage tubular cells and induce a mononuclear infiltration of the interstitium [75]. In the dog infected with canine adenovirus, the virus penetrates into tubular cells and destroys them. Focal necrotic material is then surrounded by lymphocytes, macrophages, and plasmocytes that are filled with IgG anticanine adenovirus antibodies [72]. Under those circumstances, however, anti-TBM antibodies have not been demonstrated.

The same scheme as used earlier for drugs can account for these observations: accumulation in the interstitium of bacterial or viral antigens, which arrive there either through tubular cells or by blood flow; formation in situ of antibodies secreted by plasmocytes; or arrival of delayed hypersensitivity lymphocytes, creating a general inflammatory reaction. Moreover, it has been demonstrated in a patient with leptospirosis that the infectious agent may elicit further the formation of anti-TBM antibodies, thus "amplifying" the initial renal lesion [76]. In addition to AIN generated by drugs or infectious agents, there are several reports in which it has not been possible to indict either of these agents because of the complexity of the situation [17, 77, 78].

At the end of this discussion of the causes of AIN, I should reiterate that renal biopsies of many patients with ATN do show conspicuous interstitial infiltration. This occurrence is not unusual; of the 69 patients with ATN reported by Richet [43], 15 had slight interstitial lesions and 9 had severe ones. These lesions have also been described by Kimmelstiel [79], by Zollinger [80], and more recently by Pasternack [81] in patients with ATN. The origin of the infiltration has not been clearly defined: it may represent residue of hematogenous bacterial dissemination; it may be due to drug toxicity; or, as we suggested earlier, it may be attributable to autoimmune reactions.

As already stated, the course of AIN is usually favorable as soon as the offending drug is withdrawn or the infectious agent destroyed. In a few patients, however, the response was less favorable and prednisone has been administered with some success [16, 18, 48, 54, 77, 78]. Recently, Galpin evaluated the effectiveness of steroids in methicillin-induced AIN [18]. Of the eight patients who were treated with prednisone, serum creatinine re-

turned to control values in six patients, and stable concentrations were obtained after an average of only 9 days. In contrast, in the six patients who did not receive prednisone, serum creatinine returned to control values in only 2, and stable concentrations were obtained only after 54 days. Although these data suggest that prednisone may be effective in AIN, the incidence of residual renal functional impairment in the control group was higher than that reported elsewhere in the literature. In conclusion, I should like to point out that the more frequent use of renal biopsy in acute renal failure may be very helpful. This technique discloses unsuspected glomerular or vascular disease, allows the identification of AIN as in the patient discussed today, and should make it possible to institute appropriate treatment more promptly.

Questions and Answers

DR. N. LAMEIRE *(Instructor in Medicine, Renal Service, Akademisch Ziekenhuis, University of Ghent)*: We discussed the first patient presented today earlier in Ghent, and our tentative diagnosis was salmonella food poisoning with dehydration and possible ATN. That diagnosis was based on the history of ingestion of the spoiled pate, the splenomegaly, the absence of lymphocytosis, and the pulse rate of only 100 beats/min despite a temperature of 40° C. Of course, now that the two other cases from the same laboratory have been presented, our original hypothesis must be dropped. Nonetheless, I would return to your comments on the urinary findings used to distinguish between ATN and AIN. The first urine tests revealed a low concentration of sodium and a high concentration of urea. During the first several days following admission, she received no saline and she was vomiting. That suggests to me that she had prerenal acute renal failure, which later evolved to ATN simply because of dehydration.

DR. C. VAN YPERSELE: On admission renal failure was already present as evidenced by a serum creatinine concentration of 1.9 mg/dl, but there were no clinical signs of dehydration and the patient was not yet oliguric. Therefore, I do not think that the patient initially had prerenal acute renal failure. As to the subsequent progression of renal failure, I have rarely seen prerenal failure from dehydration evolve to ATN without associated severe signs of hypovolemia, which this patient never had.

DR. P. MICHIELSEN *(Professor of Medicine, Head, Renal Service, University of Leuven Medical School, Akademische Ziekenhuis, St-Rafaël, Leuven)*: With respect to Dr. Lameire's diagnosis in this patient, you dismissed the hypothesis that she had ATN secondary to dehydration. I believe we should recall that this patient took aspirin in addition to cotrimoxazole prior to admission, and that she received 1 g of acetylsalicylic acid intravenously just before the episode of dehydration. The recent work of Henrich suggests that prostaglandins seem to balance the vasoconstrictive action of angiotension and renal nerves during hypovolemic or hemorrhagic hypotension [82]. It could be argued that the degree of dehydration seen in this patient, which would not have evoked ATN, did so here because of the earlier treatment with acetylsalicylic acid.

DR. C. VAN YPERSELE: That is an interesting idea, but I believe that hypothesis must remain speculative until sufficient data have been collected. Furthermore, this hypothesis does not fit with the interstitial infiltrate found on biopsy.

DR. P. MICHIELSEN: There is a study by Torres in which indomethacin has been shown to aggravate glycerol-induced ATN in rabbits [83]. At one time, we gave indomethacin to patients following transplantation, but we had to discontinue this practice because of the high incidence of ATN in this group [84]. Thus, these observations support my hypothesis.

DR. C. VAN YPERSELE: I think it is an alternative possibility. As Dr. Lameire already pointed out, the similar findings in the two other patients also argue against that explanation.

DR. J. P. GODON *(Agrégé, University of Liege)*: To follow up the comments of Dr. Michielsen, we observed a case of aspirin-induced AIN several years ago in a woman who had absorbed 9 g of aspirin.

DR. P. MICHIELSEN: The clinical evolution of the two other patients was much more benign. They had an acute febrile evolution followed by rapid recovery of renal function. They did not have the protracted anuria characteristic of the first patient's course. She also had an i.v. urographic procedure before the biopsy; do you know when that took place?

DR. C. VAN YPERSELE: Yes, the i.v. urography was performed in preparation for the biopsy, which was done 2 hours after urography; the patient had already been anuric for several days.

DR. P. MICHIELSEN: Are there any data that allow us to eliminate the iodine given on urography as the cause of some of the interstitial infiltration? The earliest report I know from the literature indicates that definite ATN lesions can appear 1 day after the procedure [85].

DR. J. T. HARRINGTON: While I don't have any systematic data regarding this issue, we have performed many biopsies using fluoroscopy and I don't believe we have seen an unanticipated degree of interstitial infiltration or edema.

DR. N. LAMEIRE: Performing i.v. urography in a dehydrated, anuric patient is certainly not without danger, and for this reason we never use this procedure preparatory to renal biopsy. Instead, we use echography prior to biopsy, which gives a very good visualization of the kidney even in a patient with anuria.

DR. C. VAN YPERSELE: I should point out that the patient was not dehydrated at the time of the urographic procedure. Dehydration had been corrected earlier.

DR. P. MICHIELSEN: Another question, if I may. Which kidney did you biopsy?

DR. C. VAN YPERSELE: The right kidney was biopsied.

DR. P. MICHIELSEN: I am somewhat puzzled by the occurrence of intense pain on the right side in this patient.

DR. C. VAN YPERSELE: As I mentioned earlier, Hamburger, who has enormous experience in this area, reports that diffuse lumbar pain in ATN may be a bit more characteristic on the right side for reasons that are not clear [86].

DR. N. LAMEIRE: If you suspect that the acute episodes of the three patients presented today have a similar etiology, you may have a slight clue to a possible cause in the rise in the antibody titer against Coxsackie virus in the second patient. As you know, Coxsackie virus has been associated with the lesions of glomerulonephritis, not interstitial nephritis [87]. May I have your comments on this possibility?

DR. C. VAN YPERSELE: First, our virologist believes that the small changes in the antibody titer against Coxsackie virus noted in our patient should not be viewed too rigorously. As I pointed out, I think AIN is a very heterogeneous condition in which most of the mechanisms that have been implicated in the development of the several types of glomerulonephritis are also involved. I quoted a report of AIN following measles, and measles has also been implicated in the development of glomerulonephritis. Thus, I don't think there is an incompatibility—as a matter of fact, it makes things more interesting.

DR. J. T. HARRINGTON: You mentioned earlier Richet's indications for kidney biopsy and stated that one was "prolonged" oliguria. What would you consider to be prolonged oliguria—2 weeks, 3 weeks?

DR. C. VAN YPERSELE: In our department we are slightly more conservative than Richet. I would consider oliguria that lasts beyond 1 month to be a prolonged episode.

DR. J. T. HARRINGTON: Earlier, you commented on the difficulty in distinguishing between ATN and AIN in the absence of a kidney biopsy. This is a specific example of a more general problem, that of making two different diagnoses affecting the same organ system. We had similar difficulties with that problem in the patients we described who had diuretic-induced interstitial nephritis [48]. All were patients who had known chronic glomerular disease and in whom renal failure slowly progressed over a matter of months. The major clue that superimposed disease was causing the renal failure was the persistence of normal kidney size. That was the primary reason for repeating the kidney biopsies. Only later, when we carefully perused the clinical records systematically, did we realize that mild intermittent eosinophilia and fleeting skin rashes had often occurred.

DR. G. RORIVE *(Established Investigator, Fonds National de la Recherche Scientifique, Head, Renal Hypertension Unit, Hôpital de Bavière, University of Liege)*: I am somewhat surprised by the delay between the first symptom and renal failure. In my experience, the evolution of AIN is more rapid.

DR. C. VAN YPERSELE: The delay between drug ingestion and the onset of renal failure is highly variable—a few hours in the case of patients who have probably been presensitized, several weeks in other patients.

DR. G. RORIVE: I agree that the delay between drug absorption and the first symptoms varies considerably among patients. Once the clinical signs are present, however, the disease has an acute course, and the reduction in renal function is maximal within a few hours or days. The evolution of this patient was somewhat slower.

DR. C. VAN YPERSELE: The course of AIN is by no means always as acute as you suggest; in diuretic-induced AIN, for instance, the evolution observed by Dr. Harrington in his patients [48] extended over a period of several months.

DR. G. RORIVE: In five cases of glafenin-induced AIN, I was struck by the rapidity of the evolution, which lasted 3 or 4 days. One patient complained of lumbar pain and three had anuria; urine volume returned to normal rapidly and renal function became normal within 4 to 5 days.

DR. C. VAN YPERSELE: Your observations are in agreement with those of many others who have at-

tributed these signs to an overdose of the drug, thus characterizing the effect as toxic, which is only part of the picture. The possible existence, documented in a few cases, of preformed antibodies should not be ignored in evaluating the clinical evolution of AIN. Once the concentration of glafenin is sufficient in the kidney, an interstitial reaction ensues.

DR. G. RORIVE: I should like to know if you can classify the drugs involved in AIN according to the type of immune reaction elicited by each agent.

DR. C. VAN YPERSELE: I do not believe that such a classification can be made. As a matter of fact, there is evidence that the same drug may be nephrotoxic through different mechanisms. For instance, in methicillin-induced AIN, anti-TBM antibodies have been present in a few patients. Clearly, another mechanism must be invoked in those patients in whom no anti-TBM antibodies have been demonstrated. This latter category includes the majority of patients with methicillin-induced AIN [18]. It is also possible that one mechanism, such as the development of anti-TBM antibodies, is only a secondary response that amplifies the interstitial lesions induced by another primary reaction.

DR. J. T. HARRINGTON: Dr. McCluskey has stated that in 10 patients with drug-induced allergic interstitial nephritis they were unable to find circulating anti-TBM antibodies in any patients, yet all had similar histologic findings and clinical histories [88]. That observation would relegate anti-TBM antibodies to secondary importance.

DR. Y. PIRSON *(Physician, Renal Service, Cliniques Universitaires St-Luc, Louvain en Woluwe, Brussels):* Dr. Masson, what is the specificity of the different types of immunologic tests that have been mentioned in identifying humoral and cellular immune reactions and delayed hypersensitivity?

DR. P. MASSON *(Professor of Experimental Medicine, University of Louvain Medical School, Louvain en Woluwe, Brussels)*: It is impossible, in fact, to get an immune reaction if there is no lymphoblastic transformation. Each time an immune response occurs there is a lymphoblastic transformation. Thus, it is impossible on the basis of this test to say whether the immune response is either humoral or cellular. When the antibody is detected in the blood, then of course it is a humoral response, but on the basis of just a lymphoblastic transformation I would not dare to say that it was just a cellular one. The lymphocyte incorporation of thymidine, which is used in this test, will be due not only to T lymphocytes but also to the B lymphocytes and other cells that could be involved. So I would be very careful in interpreting it.

DR. G. RORIVE: Would you say the reverse? Would you say that if you have lymphoblastic transformation, this means that the drug could produce such an effect?

DR. P. MASSON: That means that the body is mounting an immune response against this drug, but it doesn't mean that the mechanism is necessarily involved in the pathogenesis of the disease.

DR. N. LAMEIRE: Patients with AIN often take one or more drugs. In one case we have seen, the patient took approximately 20 drugs. In such a patient, it is difficult to determine whether the reaction is drug related and which drug is responsible. Couldn't you then perform a lymphoblastic transformation test in which all 20 drugs would be tested, eliminate some of them, and conclude that one or another drug may be responsible?

DR. P. MASSON: Statistically, you increase your chances. If you have a lymphoblastic transformation with a given drug, of course you have more chance that this drug is involved. I would ask a question myself. Is AIN very often associated with other disorders? You mentioned a positive Coombs test. What I mean is, for example, is there hemolysis or thrombocytopenic purpura, or is the disorder restricted to the kidney?

DR. C. VAN YPERSELE: Hemolytic anemia has been occasionally reported, for instance in association with glafenin-induced AIN.

DR. G. RORIVE: Perhaps the most usual hematologic disorder is eosinophilia. Isn't it?

DR. C. VAN YPERSELE: Yes. If I may go back to the question which was put to Dr. Masson. You said that the lymphoblastic transformation test merely shows that some immune stimulation has occurred. Whether it reacts in the kidney or not is another matter. What is your feeling on the specificity of the leukocyte migration inhibition test?

DR. P. MASSON: Exactly the same. The specificity is certainly not better than the lymphoblastic transformation test and personally I would trust the lymphoblastic transformation more than the so-called MIF test, which is measuring the migration inhibiting factor.

DR. C. VAN YPERSELE: Why?

DR. P. MASSON: Oh, just for technical reasons; the lymphoblastic transformation test is easier to perform. Personally, I would recommend obtaining an intradermal reaction as soon as you suspect a drug; a simple scratch test or an intradermal injection of a small amount of this could be useful and perhaps be more informative than all of these sophisticated tests, which are somewhat fashionable.

I think that sometimes a skin test can give as much information as a laboratory test.

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