Acta Medica et Biologica
Vol. 40, (Suppl.) 61-78, 1992

Intrarenal Reflex, Reflex Nephropathy, and Related Disorders

Hidekazu SHIGEMATSU

Department of Pathology, Shinshu University School of Medicine, 3-1-1 Asahimachi, Matsumoto 390, Japan

Summary. **Reflux nephropathy is a part of renal disorders induced by intrarenal reflux. In intrarenal reflux of sterile urine,the extratublar efflux of Tamm-Horsfall protein initiates initially inflammation of foreign body type and later, sometimes, lymphomonocytic interstitial nephritis possibly under cellular immunity. In the reflux of infected urine, the initial purulent inflammation in tuburointerstitial tissue (acute pyelonephritis) could then change into lymphomonocytic inflammation (chronic pyelonephritis) or sometimes granulomatous macrophagic inflammation (xanthogranulomatous pyelonephritis) also under cellular immunity. Thus reflux nephropathy could be recognized as rapidly progressive and destructive pyelonephritis induced by infected and/or sterile urine under vesicoureteral reflux.**

INTRODUCTION

In organs with the function of secretion and/or excretion, parenchymal disorders can be elicited by the obstruction of, or reflux via, the excretory pathway. Purulent inflammation will develop if infection supervenes, and immune-mediated inflammation can also occur if the host is sensitized by reflux and/or infection.

The kidney is situated in a part of a long secretory and excretory route that starts from the glomerulus and runs through the tubules, pelvis, ureter, and urinary bladder to end at the urethra, and renal parenchymal disorders can develop as a result of various lesions affecting the more distal parts of this pathway. This article reviews recent concepts regarding intrarenal reflux with reference to reflux nephropathy and its associated disorders.

Vesicoureteric Reflux and Reflux Nephropathy

Vesicoureteric reflux (VUR) generally results from anatomical disorders of the vesicoureteric junction.[1,2] In the normal bladder the distal portion of the intravesical ureter runs between the bladder muscle layer, forming a mucosal flap. During mictrition, the elevated intravesical pressure compresses this flap against the bladder wall and thereby occludes the ureteric orifice. In contrast, individuals with a congenitally short intravesical ureter have no such mucosal flap because the ureter enters the bladder at approximately a right angle, with the result that backflow of urine occurs during micturition.[2]

VUR is also observed in association with other abnormalities, such as duplex kindey, neurogenic bladder, ectopia vesicae, and bladder outflow obstruction.[1] It is found in 0.5-30% of children in Japan and mostly occurs in the 0-1 age group.[3]

VUR often resolves naturally during growth, and in fact more than 50% of such patients are cured naturally according to Smellie.[1]

Reflux is variable in severity, etiology and prognosis. In some children, VUR is associated with renal scarring due to atrophic pyelonephritis. It is now recognized that the Ask-Upmark kidney, which was once believed to represent anomalous segmental hypoplasia, actually results from VUR with scarring at an early age. Renal scarring is induced by the "back pressure" or backflow of urine in association with pyelonephritis, and whether reflux alone can precipitate progressive renal scarring is a question that remains unanswered. Since reflux is found in 30-50% of children with urinary tract infections and is by far the most common abnormality in this group,[4] lower urinary tract infection is apparently one of the factors that accelerates renal parenchymal scarring. Segmental scarring due to pyelonephritis has been considered to result from the reflux of infected urine and associated calyceal deformity.

"Reflux nephropathy" has been advocated as a concept by Bailey,[5] who emphasized the role of reflux itself in producing renal lesions as chronic, atrophic, and pyelonephritic scarring in patients with

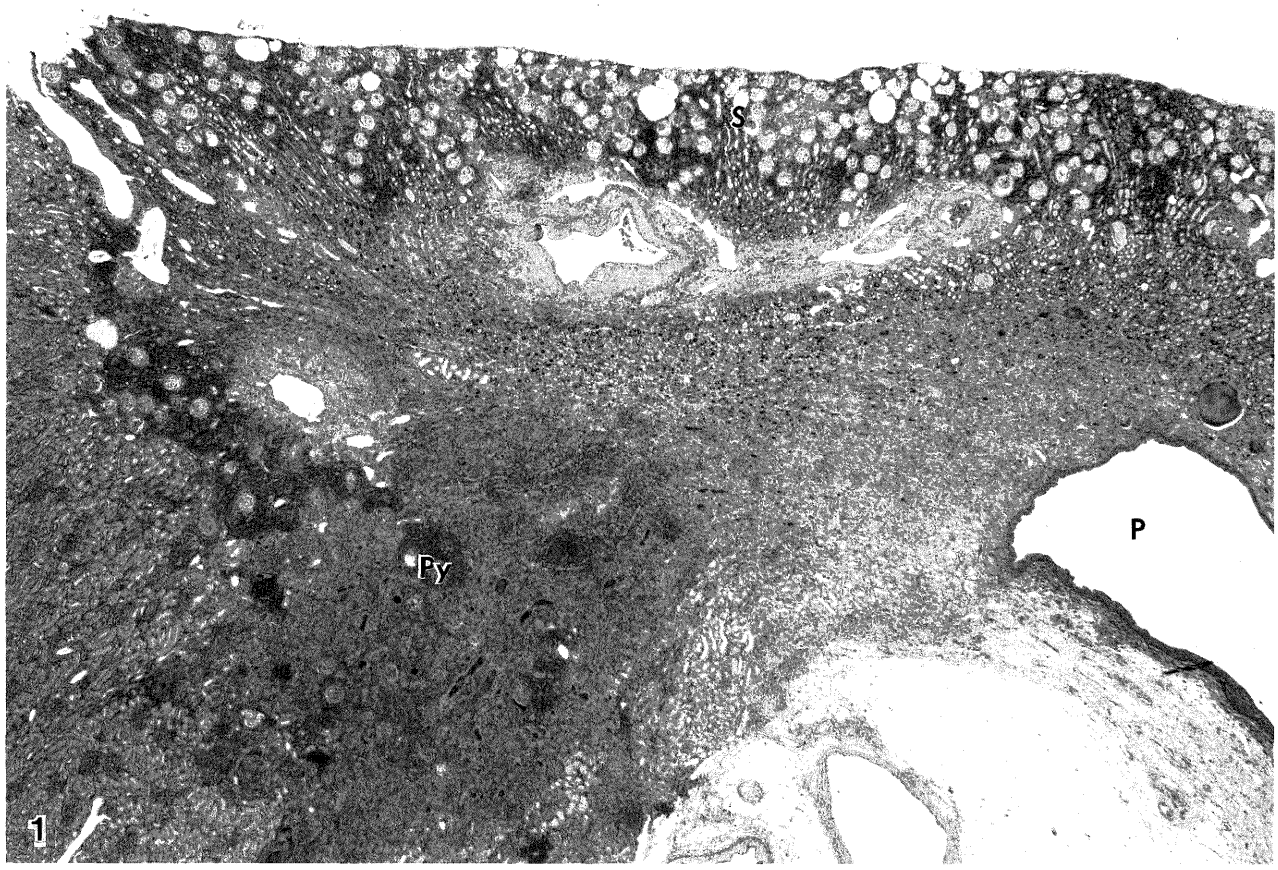


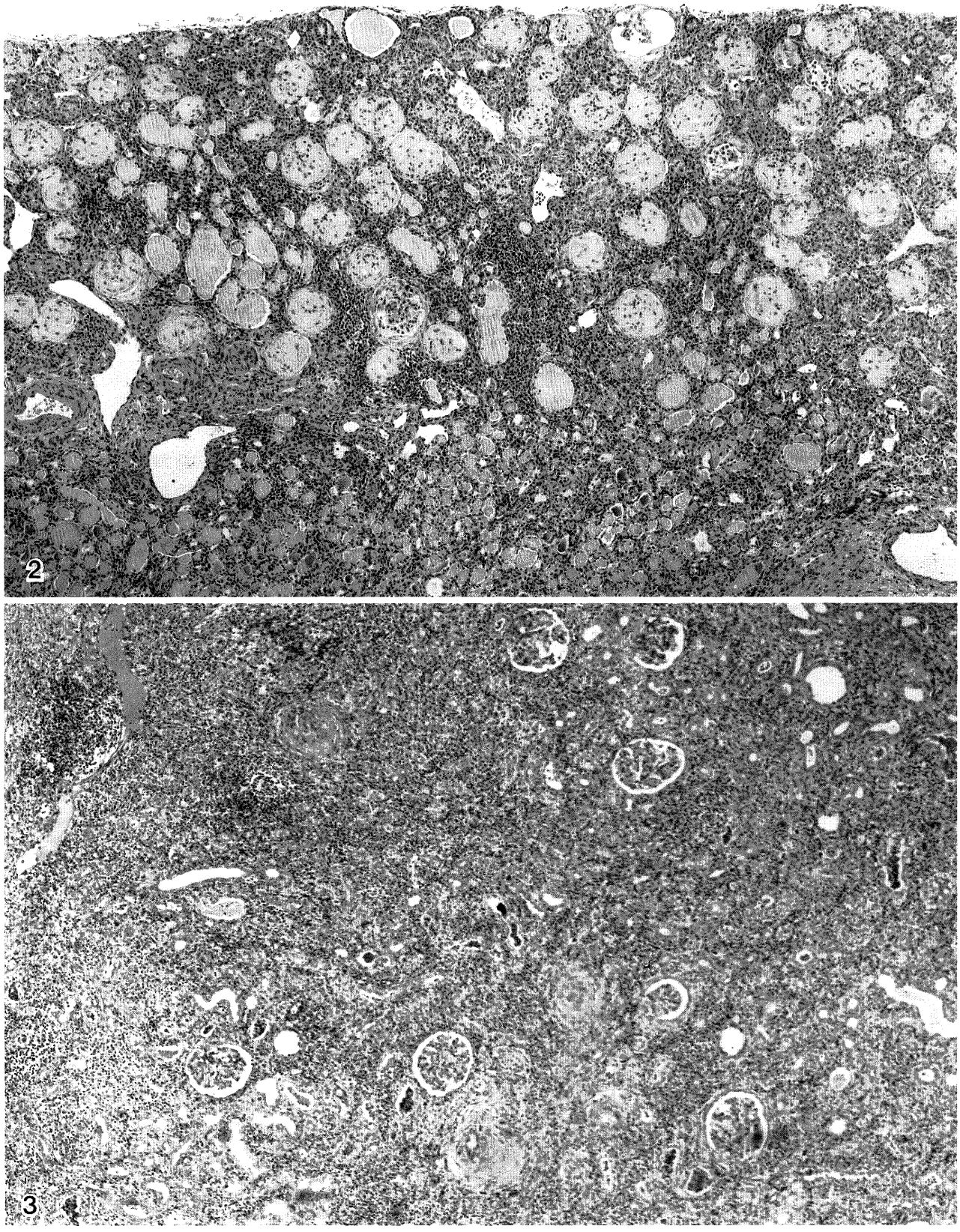
Fig. 1. Atrophic pyelonephritis with acute purulent lesions in a patient with duplex ureter and UVR. An atrophic scarred area(s) is seen in the cortex and active purulent pyelonephritis (Py) is noted at a deeper level in Bartin's column. The dilated pelvis (P) and a flattened papilla are also seen. (K50620)

VUR of a nonobstructive nature (Figs. 1-3). It has been reported that one third of girls aged 5-11 years with covert bacteriuria have VUR and that one fifth have reflux nephropathy.[6,7] Similarly, a review by White[8] showed that 52% of 105 children with symptomatic urinary tract infections had primary VUR and that 23% of their kidneys were scarred. There is an increased risk of hypertension due to both unilateral and bilateral reflux nephropathy, and also a risk of progression to chronic renal failure in the case of extensive bilateral disease. In fact, reflux nephropathy is still the commonest cause of chronic renal failure, accounting for 27% of children and 21% of adults entering renal transplant programs in Europe.[8]

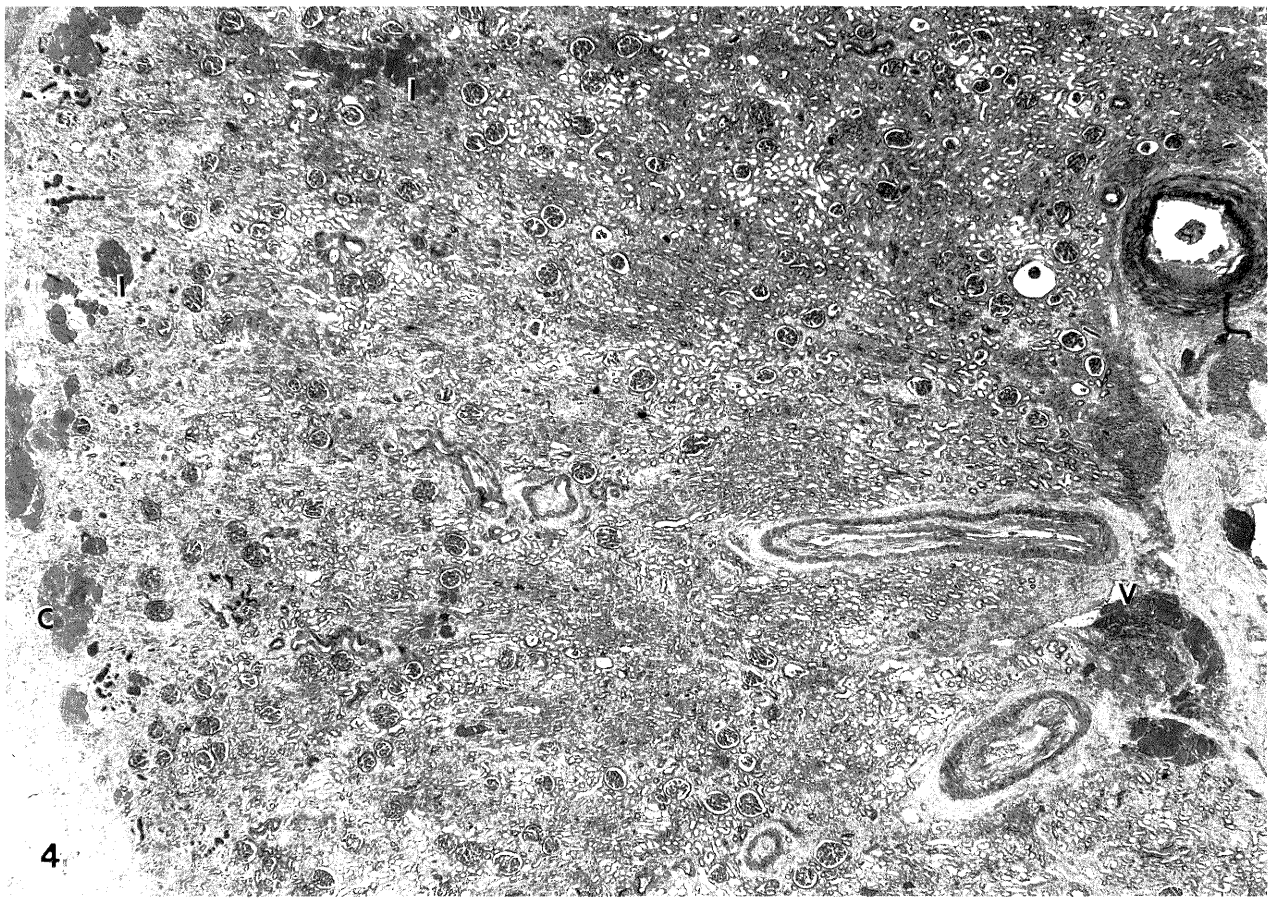
Ongoing research is now being focused on proteinuria in children with reflux nephropathy. White[8] found segmental glomerulosclerosis in 8 renal biopsies taken from 24 children with reflux nephropathy, and showed a strong positive correlation between the extent of glomerular involvement and the severity of the proteinuria. He also reported that the reflux nephropathy patients had considerably larger glomeruli and thicker arteriolar walls than normal. The percentage of glomeruli with segmental sclerosis had a significant positive correlation with glomerular size and arteriolar thickness as well as with severity of proteinuria, and had a significant inverse correlation with the glomerular filtration rate. White there-

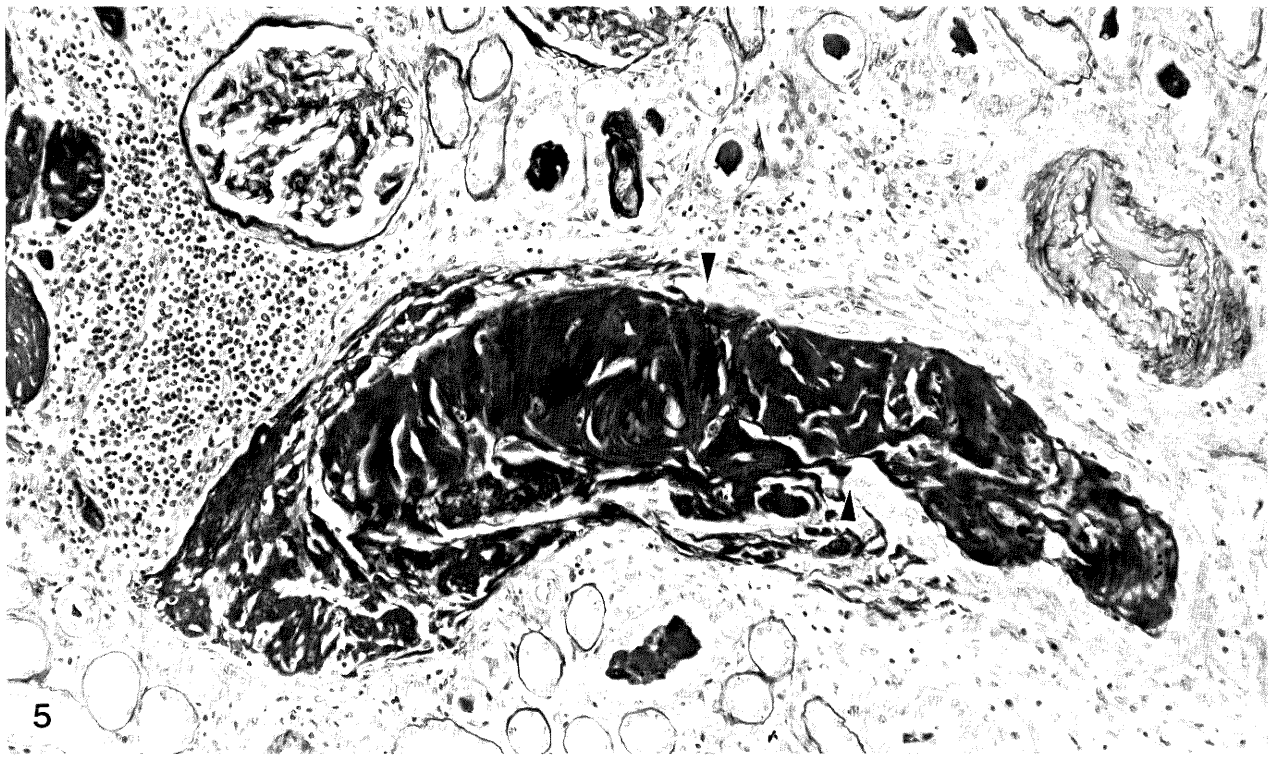
Fig. 2. Part of atrophic scarred area in Fig. 1, showing global glomerular sclerosis, interstitial fibrosis, and atrophic tubules.

Fig. 3. Part of the active pyelonephritic lesion in Fig. 1. Diffuse infiltration of mononuclear cells and dilated tubules with granular casts are seen.



Figs. 2 and **3.** Legends on the opposite page.





Figs. 4 and **5.** Legends on the opposite page.

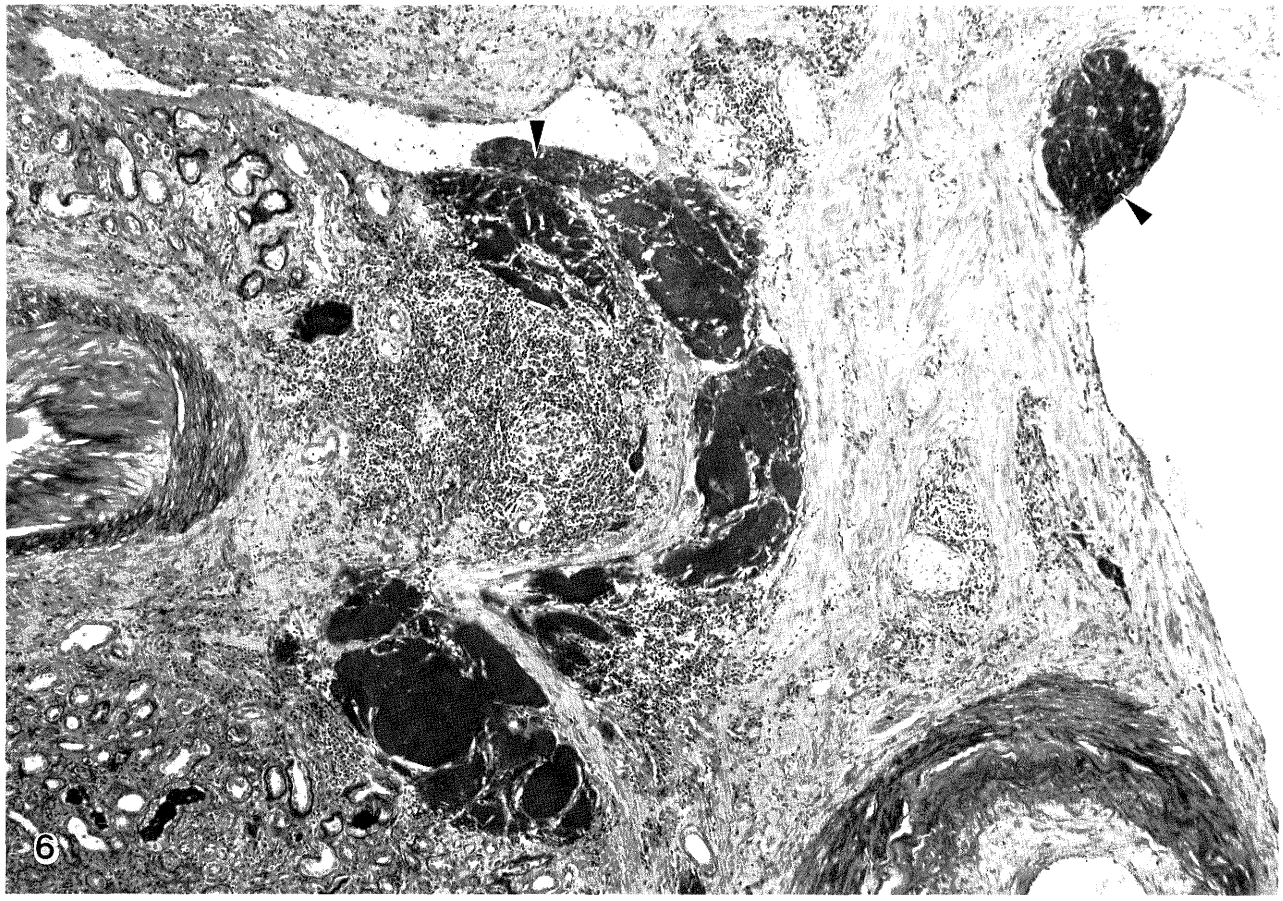


Fig. 6. Interstitial deposition of Tamm-Horsfall protein and its polyp-like protrusion into venules (arrowheads). PAS stain. (89-1780)

fore suggested that vascular changes and glomerular hypertrophy precede the development of focal segmental glomerulosclerosis in these patients.

In the case of adult reflux nephropathy, Zucchelli and Gaggi[9,10] have stated that there is often a history of recurrent urinary tract infection during childhood or pregnancy. The disease may have a largely asymptomatic course, with the late onset of proteinuria, hypertension, and/or renal failure, especially in male patients. Unilateral and segmental chronic pyelonephritis usually has a benign course, particularly in the absence of infection and hypertension. However, in patients with bilateral reflux nephropathy the destruction of a large number of nephrons induces functional and structural changes in the remaining nephron population that lead to the development of focal segmental glomerulosclerosis. Once a certain degree of renal scarring has occurred, the progressive loss of the remaining renal function appears to become inevitable, even if the original precipitating disease process is removed. Thus, the elimination of bacteriuria and reflux seems to be unable to modify the progression of these patients towards end-stage renal failure. Focal segmental glomerulosclerosis associated with heavy proteinuria has been reported in patients with unilateral reflux nephropathy from many parts of the world including Japan,[11,14] and seems to be the result of exhaustion of the capacity of the remaining nephrons

Fig. 4. Extratubular efflux of a periodic acid-Schiff-positive material, Tamm-Horsfall protein (THP), which is seen in the interstitium (I), the subcapsular lymphatic space (C), and in a vein (V). Mild cellular infiltration is observed in the interstitium. PAS stain. (89-1780)

Fig. 5. Extratubular effux of Tamm-Horsfall protein through a ruptured tubule into the interstitium. Arrowheads indicate the remnants of the disrupted tubular epithelium. PAS stain. (35073)

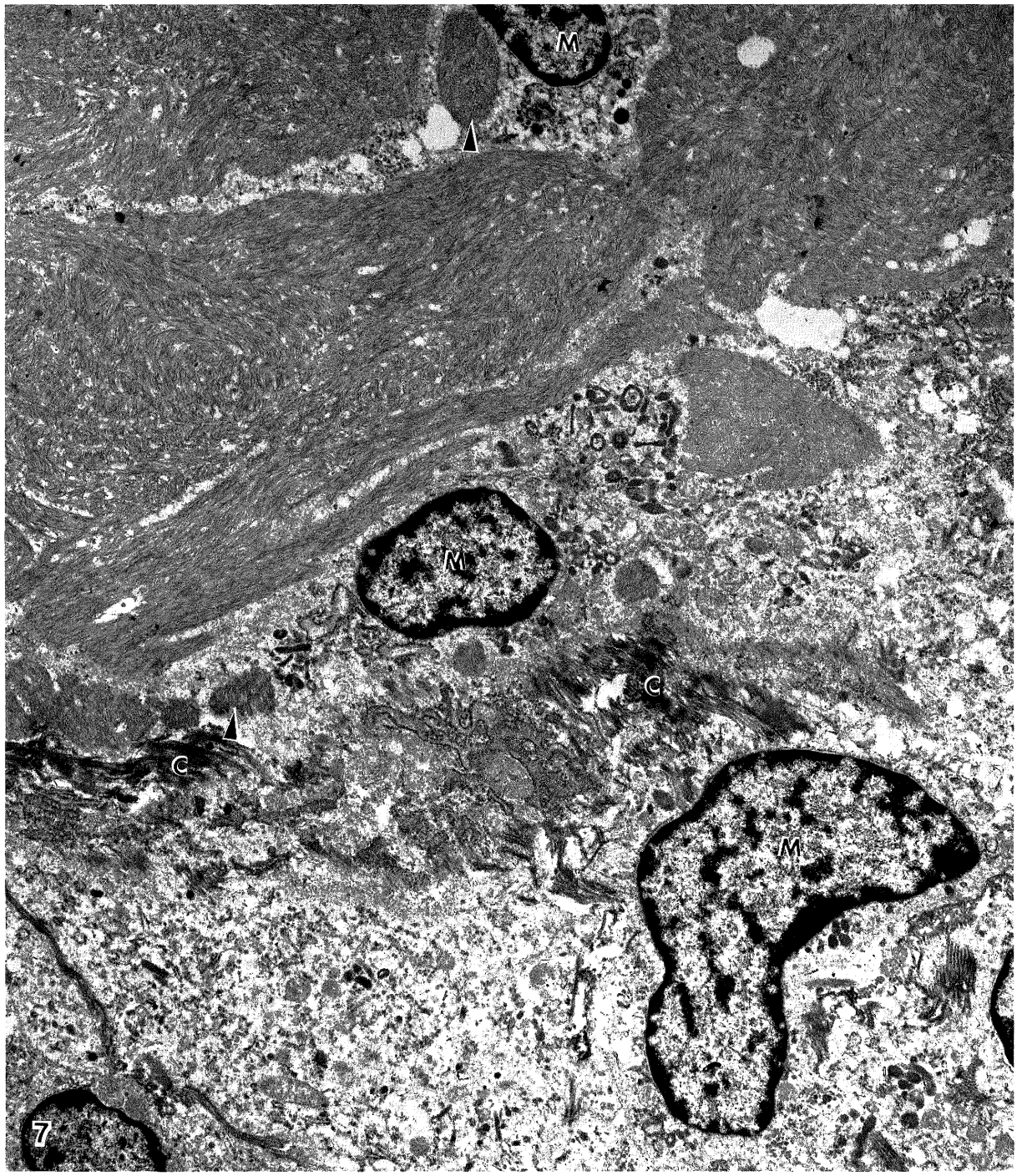


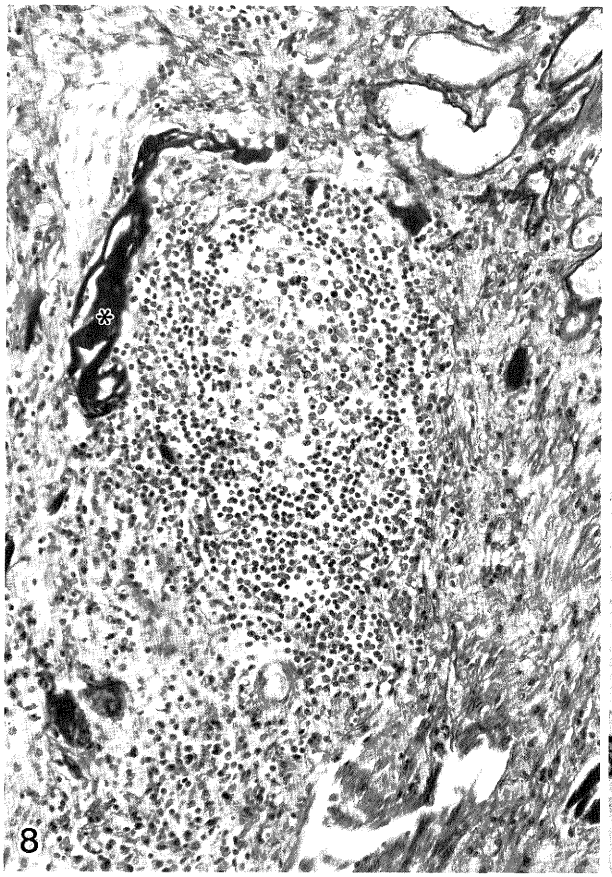
Fig. 7. Electron micrograph showing the in situ degradation of Tamm-Horsfall protein. Fibrillary material of 80–100 Å width is engulfed by macrophages (M) as shown by the arrowheads. Interstitial collagen (C) is also seen. ×5,700.

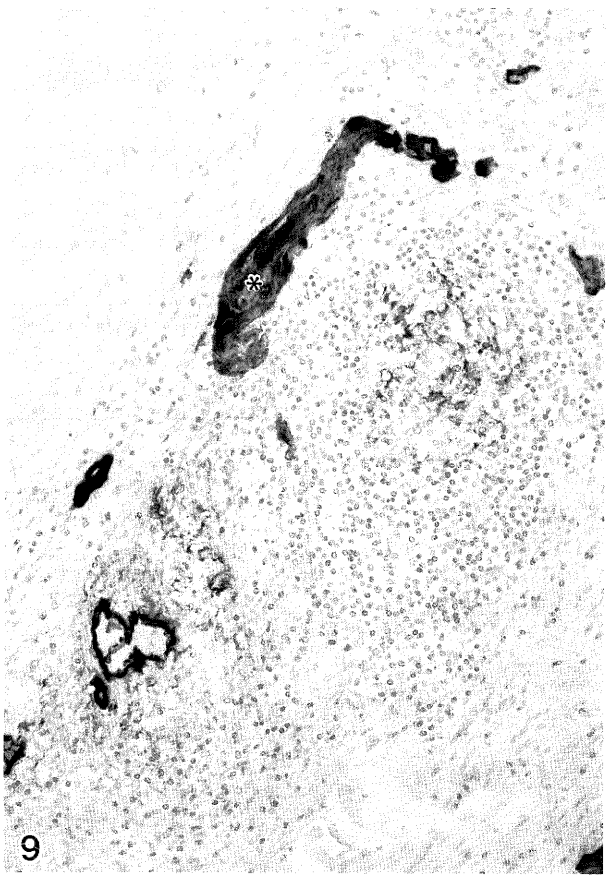
Fig. 8. A reactive lymphoid follicle developing due to Tamm-Horsfall protein deposition (*). PAS stain. (88-3116)

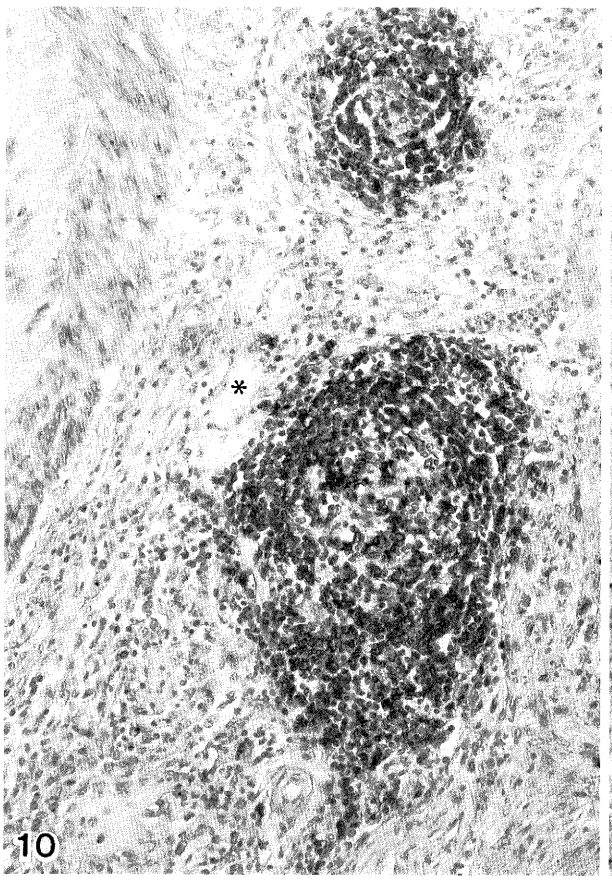
Fig. 9. Step section of Fig. 8 stained with anti-THP by the PAP method. Fibrillary positive material is seen in the germinal center.

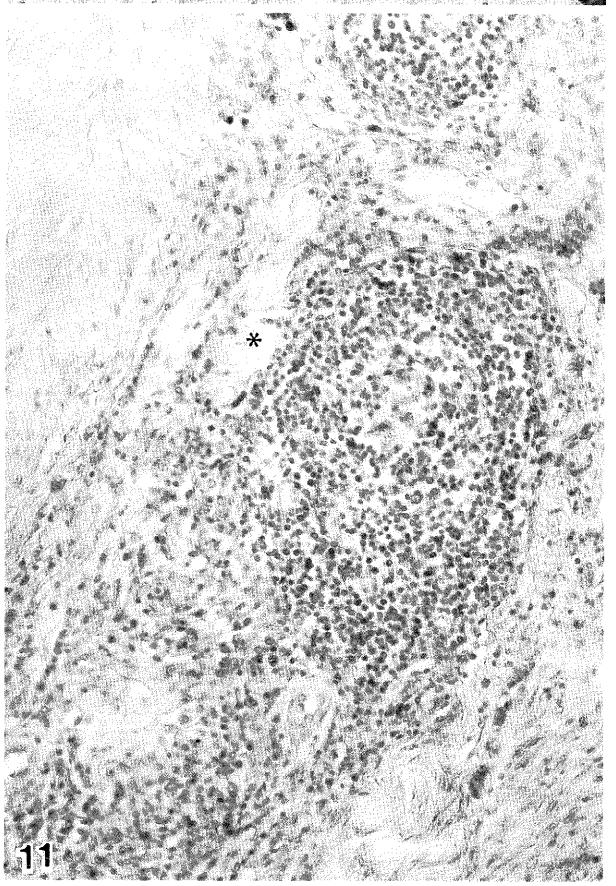
Fig. 10. Step section of Fig. 8 stained with anti-L25 (a B lymphocyte marker).

Fig. 11. Step section of Fig. 8 stained with anti-UCTL-1 (a T lymphocyte marker). A few lymphocytes are positive.









Figs. 8–11. Legends on the opposite page.

to compensate for renal damage by hypertrophy and hyperfiltration.[12,14]

Extratubular Efflux and Interestitial Nephritis

Progressive renal damage resulting in atrophic nephritis is an event that has been demonstrated well by radiology in patients with VUR,[15,16] but the backflow of urine is also observed in various other situations.[17,18] Urinary substances such as uromucoid (Tamm-Horsfall protein) are positive for the periodic acid-Schiff reaction (PAS) due to their mucopolysaccharide content.[19,21] Using the extratubular efflux of PAS-positive material as a histological indicator of the intrarenal reflux of urine, we have analyzed the relationship between such intrarenal reflux and various lesions of the kidneys.[17,18] This PAS-positive material mainly leaks out from the distal tubules, where the intratubular stagnation of PAS-positive urinary casts is evident (Figs. 4 and 5). The tubular basement membrane is disrupted and epithelial cells show degeneration in association with such leakage. Efflux of PAS-positive materials is seen in various disease, such as hydronephrosis (63.0%), renal calculi (46.6%), VUR with hydronephrosis (100%), and other conditions (cystic kindney, trauma, etc.) (44.4%).[17]

An anti-Tamm-Horsfall protein (THP) antibody[18] and the peroxidase anti-peroxidase (PAP) method have disclosed the localization of cytoplasmic reaction products in the epithelial cells of the macula densa, the distal cortical tubules, and the distal medullary tubules. In contrast, the proximal tubules and collecting ducts are negative for staining by this anti-THP antibody. A decrease of THP production is correlated with an increase in the severity of hydronephrosis. THP is also positive in the cylinders of the distal tubular lumens, and remains weakly positive even in severe hydronephrosis where no production of THP is found in the epithelial cells.

Material that stains like THP is not only observed in the interstitium but also in the lymphatics (Fig. 4) around interstitial vessels, as well as the subcapsular lymphatics and/or those of the urinary pelvis. The same material is also seen in venules and veins where it causes polyp-like protrusion into the vascular lumen (Fig. 6). This extratubular THP preserves its antigenicity even in severely inflamed areas of the kindey. Its accumulation due to extratubular efflux is more frequent in kindneys with progressive papillary deformity (hydronephrosis). In severe hydronephrosis, however, such efflux is scanty in the areas with thyroidation of the tubules (i.e., their development of a thyroid follicle-like appearance). This extratubular THP is apparently degraded in situ in a manner identical to the processing of foreign materials and sometimes causes a foreign body granulomatous reacion (Fig. 7). Mononuclear cell infiltrates may also be seen in intimate contact with this effluxed material (Figs. 8-11). In inflamed areas, no significant immunoglobulin deposition is observed in connection with the effluxed THP, although some plasma cells positive for each class of immunoglobulin may be seen. There is a significant but apparently random accumulation of T and B lymphocytes around the effluxed material. The B lymphocytes may actually form follicular structures in some of the inflammatory lesions (Fig. 10). Interstitial inflammation with mononuclear cell infiltrates becomes more widespread as the grade of hydronephrosis becomes more severe. However, in severely hydronephrotic kidneys inflammation is not so evident in the areas of thyroidation.

THP is also found in some of the Bowman's spaces, where it apparently reaches by flowing back through the proximal tubules. This is observed in nearly 50% of the patients with a well preserved papillary structure. However, the glomeruli positive for THP always remain under 60% in a kindney section.[19] The THP material is seen to twine around the glomerular capillary tufts, but there is neither proliferation, sclerosis, nor adhesions to the Bowman's capsule. Mild proliferation of parietal epithelial cells is seen on rare occasions without any associated alterations of the glomerular tufts. No significant deposition of immunoglobulines G, A or M is found in the affected glomeruli. Global glomerular sclerosis apparently increases with progressive hydronephrosis. However, in severe hydronephrosis there are no glomeruli detected in 50% of the cases.[8] In contrast, focal glomerular sclerosis is seen in only a few patients (9%), and causes scattered lesions that are found mostly in the interstitium and in the areas with global glomerular sclerosis. No reflux of THP into Bowman's space is observed in such glomeruli.

The intrarenal backflow of urine has been detected histologically by several investigators.[22,24] Berrie found that proteinaceous urinary glycoproteins were extruded from ruptured tubules and extended to form polypi in the arcuate and interlobular veins in 16% of 300 hydronephrosis patients, in contrast to 1.4% of 5,000 consecutive necropsies.[22] Thus, the backflow of urinary substances into the renal parenchyma appears to be rather common in the presence of a high ureteric pressure (including VUR), and the pathogenesis of intrarenal reflux deserves to be elucidated. Studies with an anti-THP antibody have shown two

routes for the backflow of THP into the renal parenchyma, i.e., extratubular efflux into the interstitium and reflux into Bowman's space.[18] The fate of these refluxed substances appears to be in situ degradation and excretion through the lymphatics and/or veins. In the former situation, interstitial inflammation resembling a foreign body reaction may be observed, but mononuclear cell infiltrates are also associated with extratubular efflux. The fact that the antigenicity of THP is preserved in such lesions and that the inflow of THP into lymphatics and veins occurs in intrarenal reflux suggests that the reflux of such urinary components could cause an allergic reaction in the kidneys.[18] Accumulation of T and B lymphocytes is observed in inflammatory lesions without immunoglobulin deposits, suggesting a role for cellular immunity in the development of THP-related interstitial nephritis.

An experimental model of interstitial nephritis induced by THP has been reported in the rabbit; there was focal mononuclear cell infiltrate without immunoglobulin deposition in the distal nephron segments despite elevation of the serum levels of IgG directed against THP. In this model, the peripheral lymphocytes from the affected rabbits are cytotoxic and undergo in vitro blast transformation in the presence of homologous urine or THP.[25] A similar type of interstitial nephritis related to cellular immunity has also been reported in guinea pigs sensitized with homologous THP,[26] and the possibility of sensitization to THP has even been suggested in humans.[27,28] Further investigations are needed, however, to determine whether such sensitization is actually present in patients with intrarenal reflux.

Pyelonephritis

This abnormality can result from the reflux of the infected urine into the renal pelvis and calyces during micturition.[2] However, bacteria are not neccessarily carried into the renal parenchyma by this ureteropelvic reflux, since the simple papillae of the central calyces are convex and do not readily admit refluxing urine. In contrast, the concave compound papillae of the upper and lower poles allow the easier access of bacteria to the collecting tubules, and such reflux is apparently the initial step in the development of pyelonephritis.[2,28,29]

Also, if a high intraureteric and intrapelvic pressure is prolonged as in obstructive uropathy, even the simple papillae are eventually rendered vulnerable to retrograde entry of urine. The vast majority of cases of acute pyelonephritis stem from ascending infection by Escherichia coli originating from the gastrointestinal tract.[2,30] The infected kidneys develop small subcapsular and parenchymal abscesses, and most infections involve only one or two papillary systems. The cortex may be extensively damaged by purulent inflammation, but the glomeruli and vessels show resistance to some degree. The papillae may also undergo destruction and necrotizing papillitis is associated with severe reflux or obstruction.

In chronic pyelonephritis, the role of bacterial infection is less certain than in the acute disease. However, infected urine is thought to generally play a role, and the chronic tubulointerstitial damage is invariably assosiated with either obstructive uropathy and/or VUR. In patients with mechanical obstruction, the parenchymal changes are due to a combination of obstruction and infection; the calyces and the pelvis are dilated and the parenchyma is usually uniformly thin (Fig. 12). In cases associated with VUR, the calyces at the poles of the kindney are prerefentially expanded and discrete, coarse scars produce depressions on the renal surface (Figs. 1 and 2). Early in the course of the disease, mixed lymphocytic and polymorphonuclear cell infiltration is seen around the dilated pelvis and in the parenchyma (Fig. 14). The formation of lymphoid follicles may even be observed in some cases (Fig. 13). In the advanced stage,the scarred regions are composed of atrophic dilated tubules surrounded by interstitial fibrosis. The glomeruli usually show global sclerosis with periglomerular fibrosis. Thyroidation can be seen as a result of the presence of severely atrophic tubules containing diffuse eosinophilic hyaline casts.

The immune response to infecting bacteria involves both the local antibody response in the urinary tract[31,32] and a generalized circulating antibody response, and both may play a role in the development and/or prevention of chronic pyelonephritis,[33]

Experiments have also suggested an autoimmune mechanism for pyelonephritis, where autoantibodies are directed against kidney specific antigens or against a hepatic antigen. Furthermore, antibodies have been demonstrated which were directed against an antigen of *E. coli* that was identical with a renal antigen.[31] In addition, a study has shown that by the transfer of interstitial mononuclear cells from rats with enterococcal pyelonephritis, tubular atrophy and papillary changes can be created in normal rats. suggesting a role for cellular immunity in the development of pyelonephritis.[35]

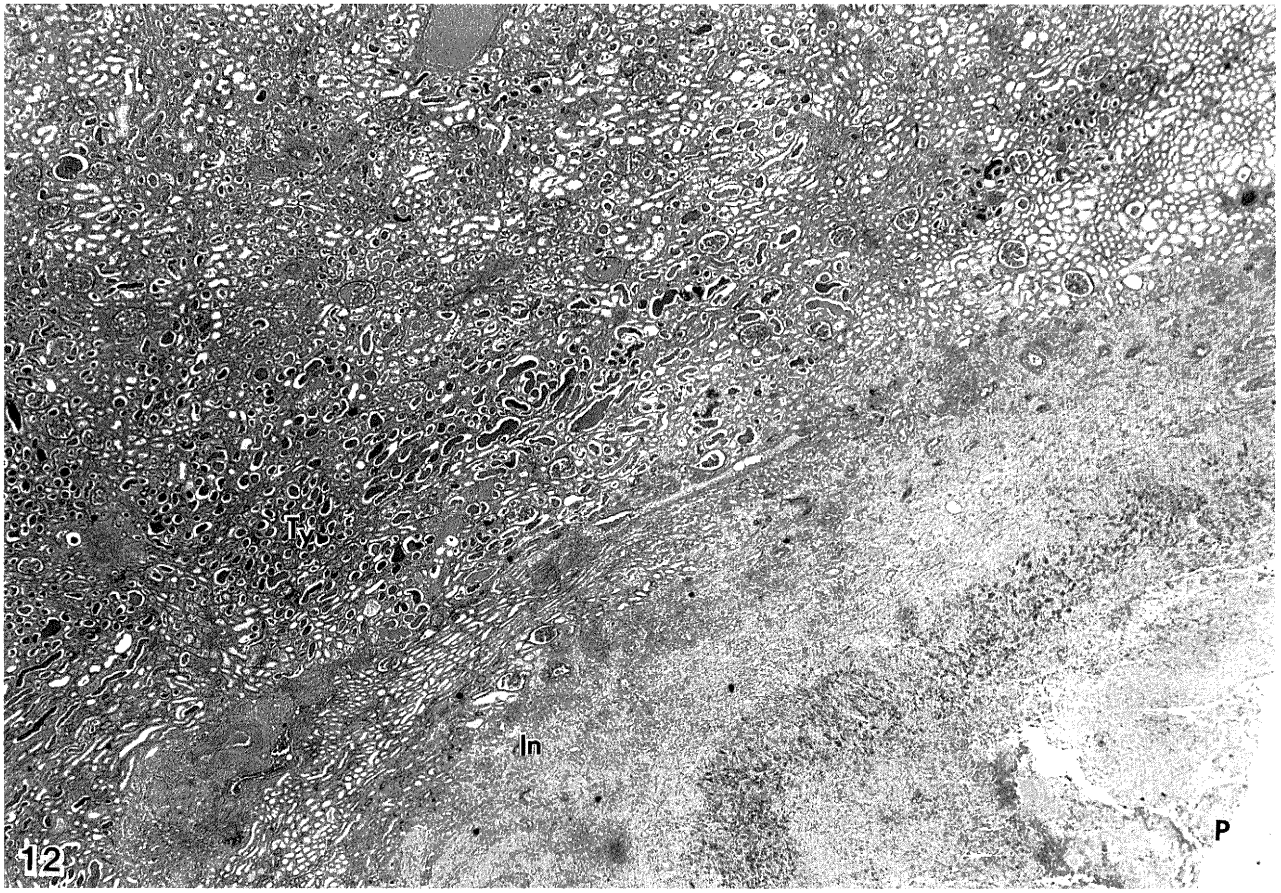


Fig. 12. Chronic pyelonephritis. Deformed papilla and dilated pelvis (P) in the right lower region. Thyroidation of the tubules (Ty) is seen near the zone of interstitial inflammation and fibrosis (In). (K-49987)

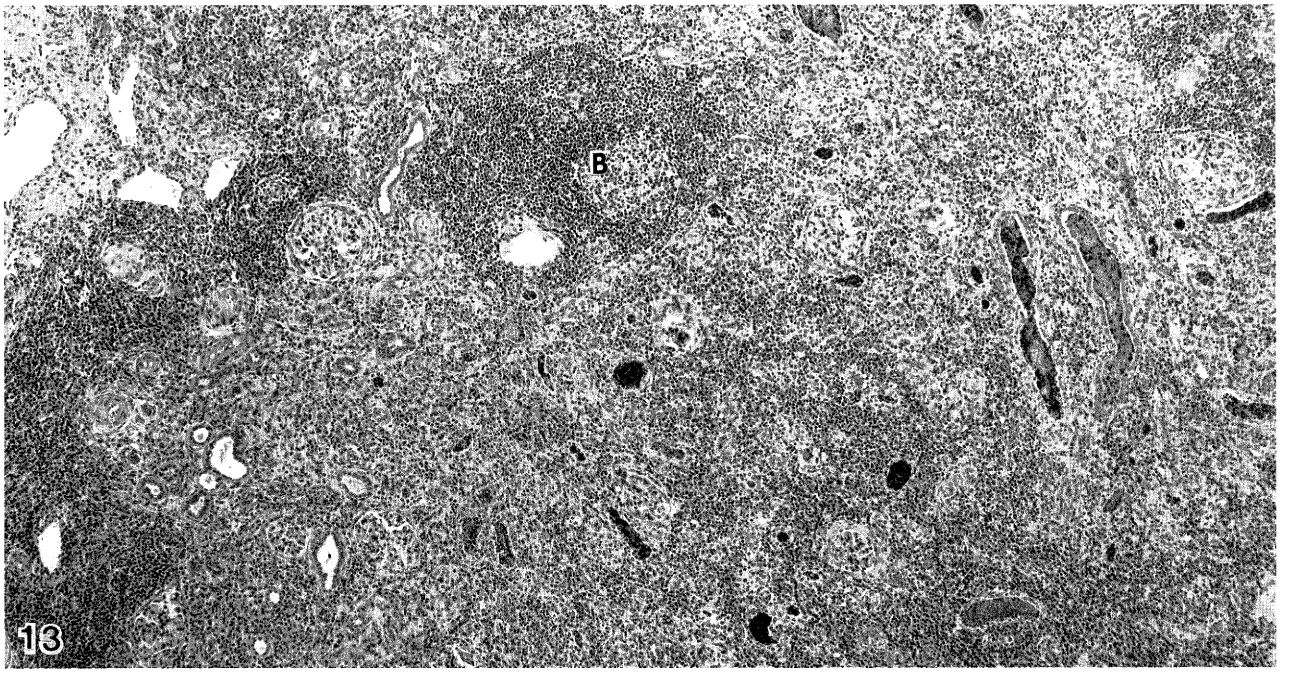
Xanthogranulomatous Pyelonephritis

Xanthogranulomatous pyelonephritis is a chronic disease process accounting for less than 1% of pathologically proven cases of pyelonephritis.[36] It affects mainly women aged 50-60 years, and is characterized by slow progression and a clinical presentation suggestive of a renal mass. It also occurs sometimes in children, and the clinical and pathological features described in recent series have been similar to those seen in adults.[37,38] The pathogenesis of this disease is not clear-cut, although its association with renal abscess has been reported.[39] A review of several of cases recorded in the antibiotic era indicates that the lesion is more often unilateral, and is associated with renal calculi (usually staghorn calculi), obstructive uropathy, and previous urinary tract procedures.[40,41] Consequently, xanthogranulomatous pyelonephritis involves the kindney diffusely in association with pelvic and calyceal dilatation.

Proteus mirabilis, *E. coli*, and other enteric gram-negative rods have been the common pathogens isolated from patients with this disease,[36,42] suggesting a role for ascending urinary tract infection. Infection by Staphylococcus aureus and even methicillin—resistant Staphylococcus aureus has also been reported.[43]

Xanthogranulomatous pyelonephritis has been produced experimentally in rats by permanent ligation of the ureter and a single intravenous injection of an *E. coli* suspension.[44,45]

The extent of renal involvement by the disease process has been macroscopically graded as follows[42]: slight (focal changes in the pericalyceal renal tissue), moderate (diffuse pericalyceal changes, but limited to the renal medulla, Figs. 15 and 16), and severe (changes involving the whole kidney, Figs. 17 and 18). It is also not rare for the granulomatous tissue to spread outside the kidney and extend retroperitoneally into other organs.



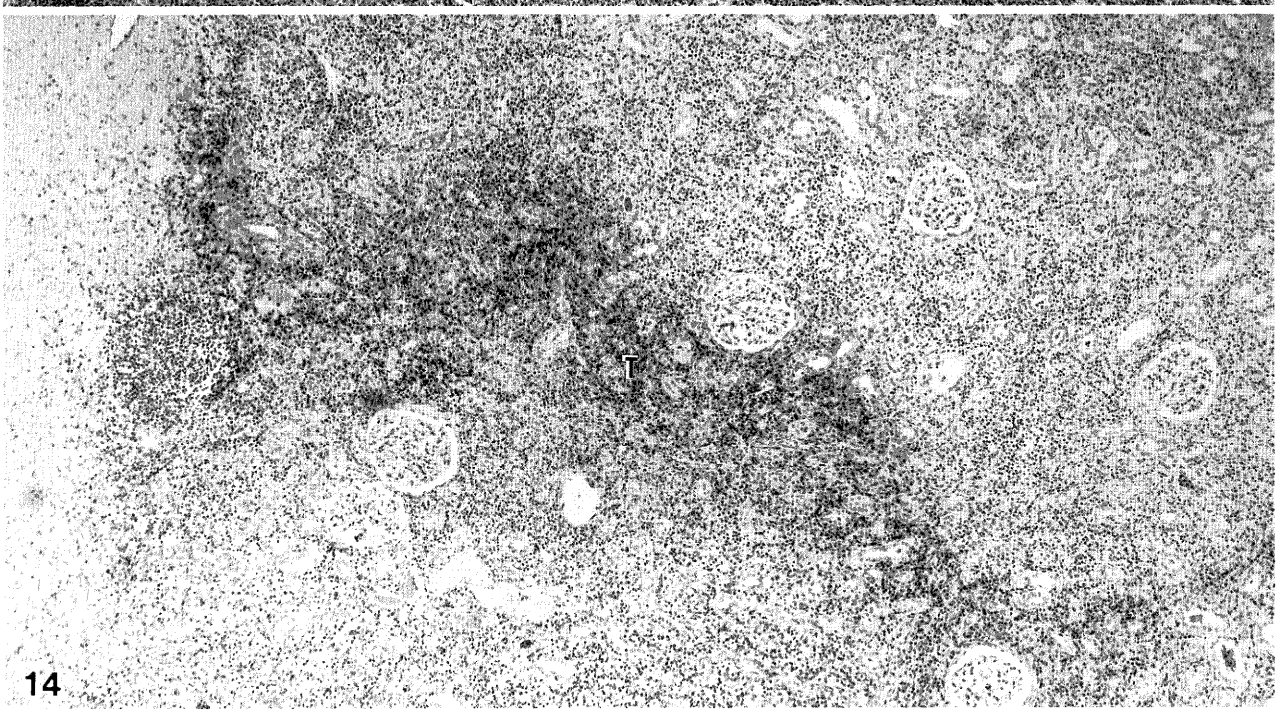


Fig. 13. Lymphocytic reaction with a germinal center (B) is seen in chronic pyelonephritis. (K-52500)

Fig. 14. Accumulation of UCHL-1-positive lymphocytes (T) is observed in the same patient. (K-52500)

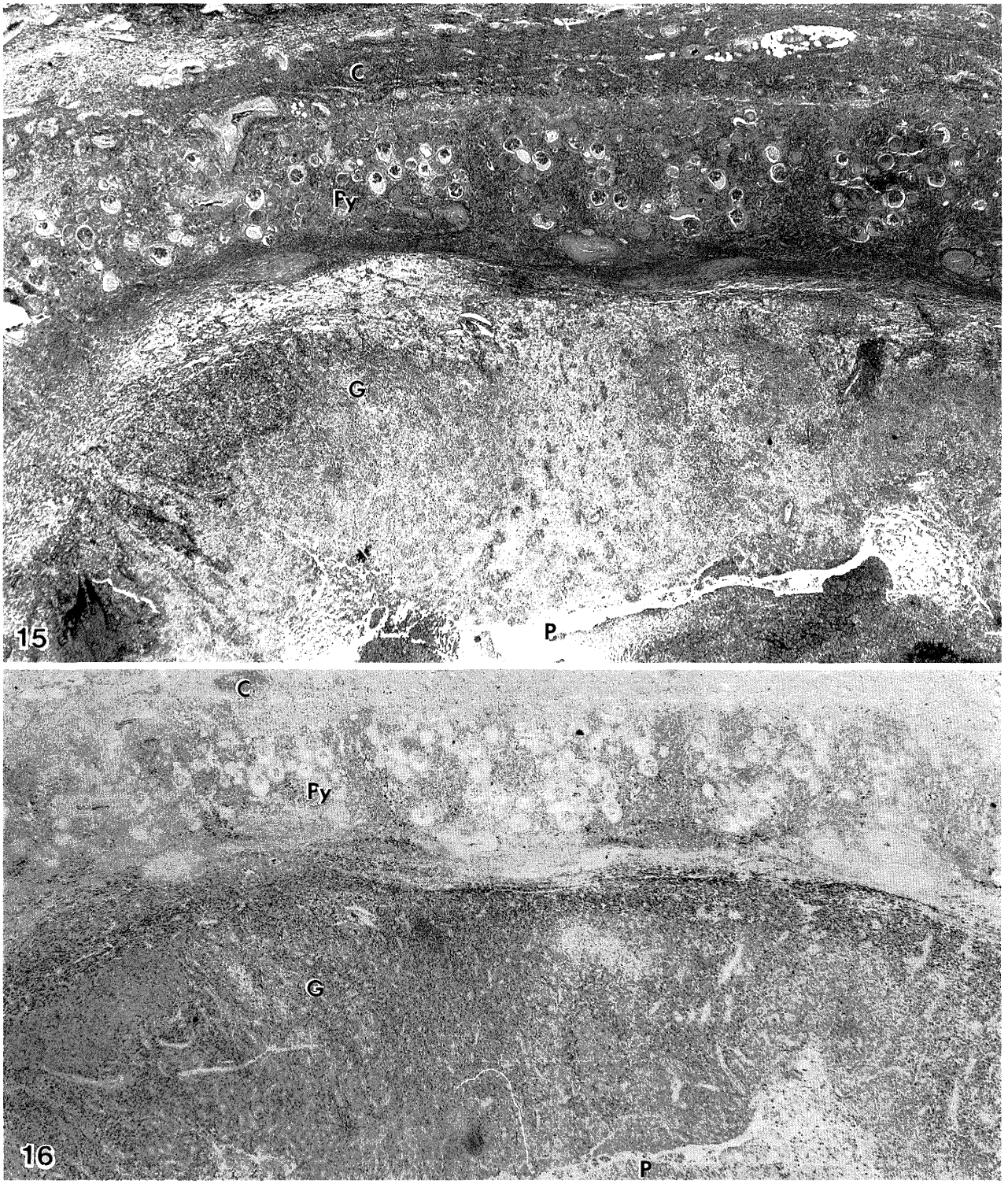


Fig. 15. Xanthogranulomatous pyelonephritis. A granulomatous inflammatory lesion (G) is located in the deformed pelvis (P) beneath the inflamed region of chronic pyelonephritis (Py). Capsule (C) (13970)

Fig. 16. Step section of Fig. 15 stained with anti-CD68 (a marker of macrophages) by the PAP method. Abundant macrophages have accumulated in the granulomatous lesion.

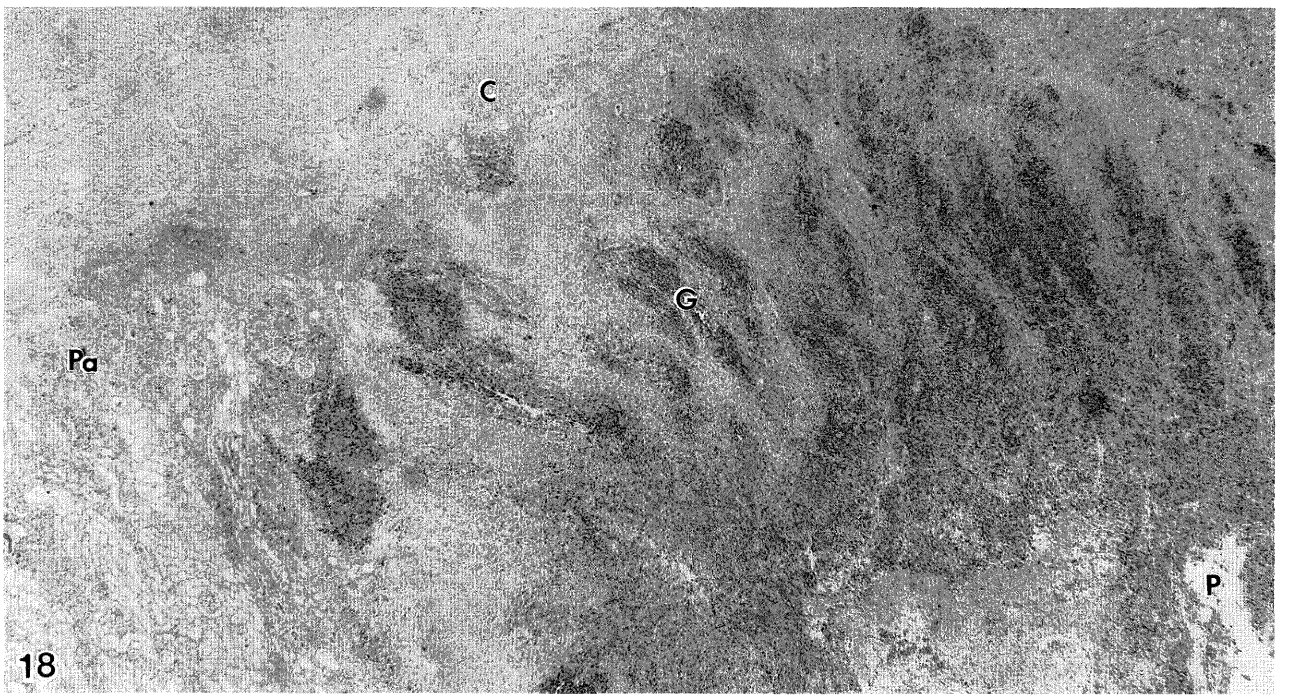


Fig. 17. Xanthogranulomatous pyelonephritis has extended to the renal capsule (C) and the granulomatous lesion (G) is replacing the renal parenchyma. Residual renal cortex (Pa) is seen at the left of the figure. (13746)

Fig. 18. Step section of Fig. 17 stained with anti-CD68 antibody. Abundant accumulation of macrophages is seen in the granulomatous lesion.

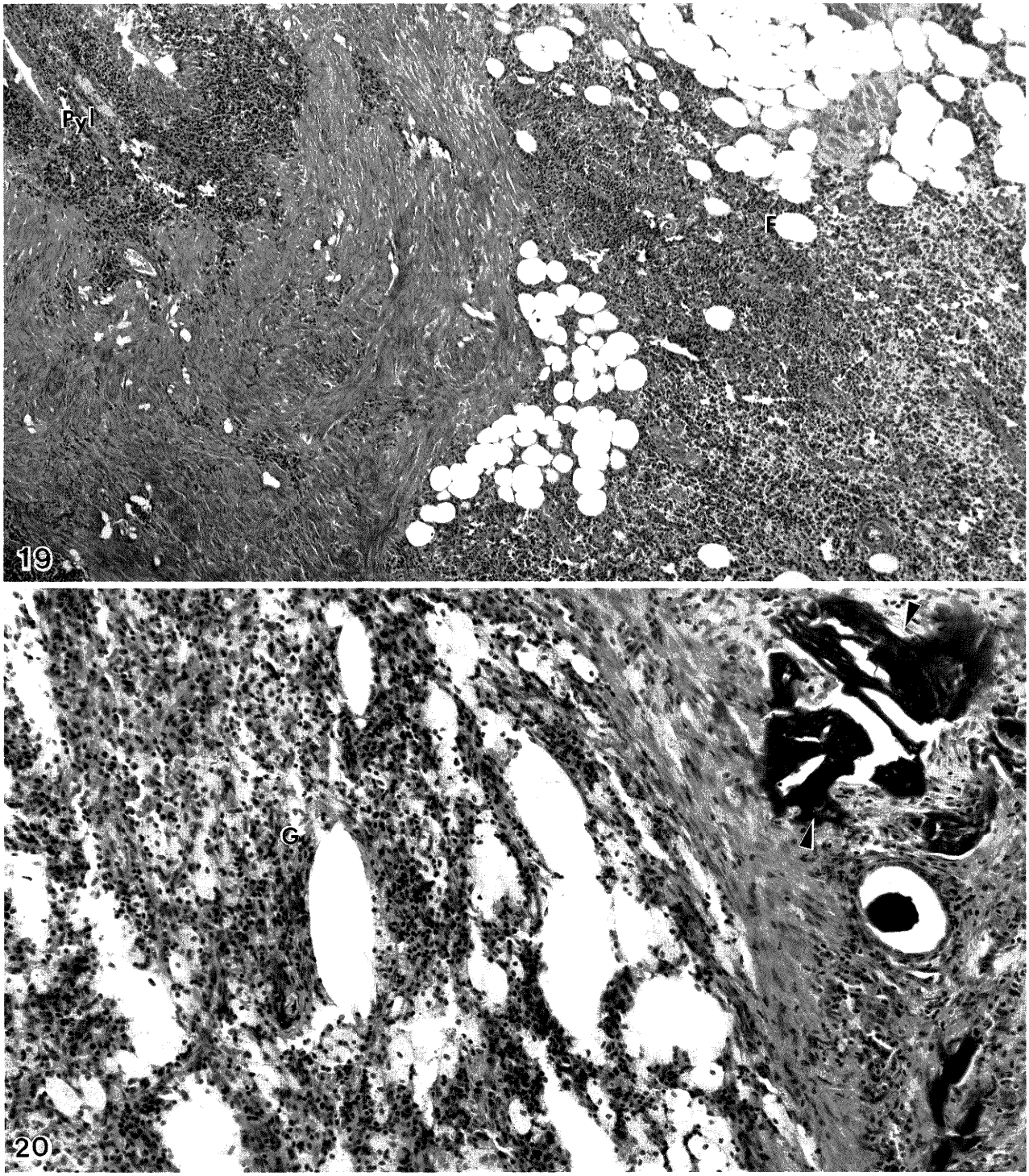
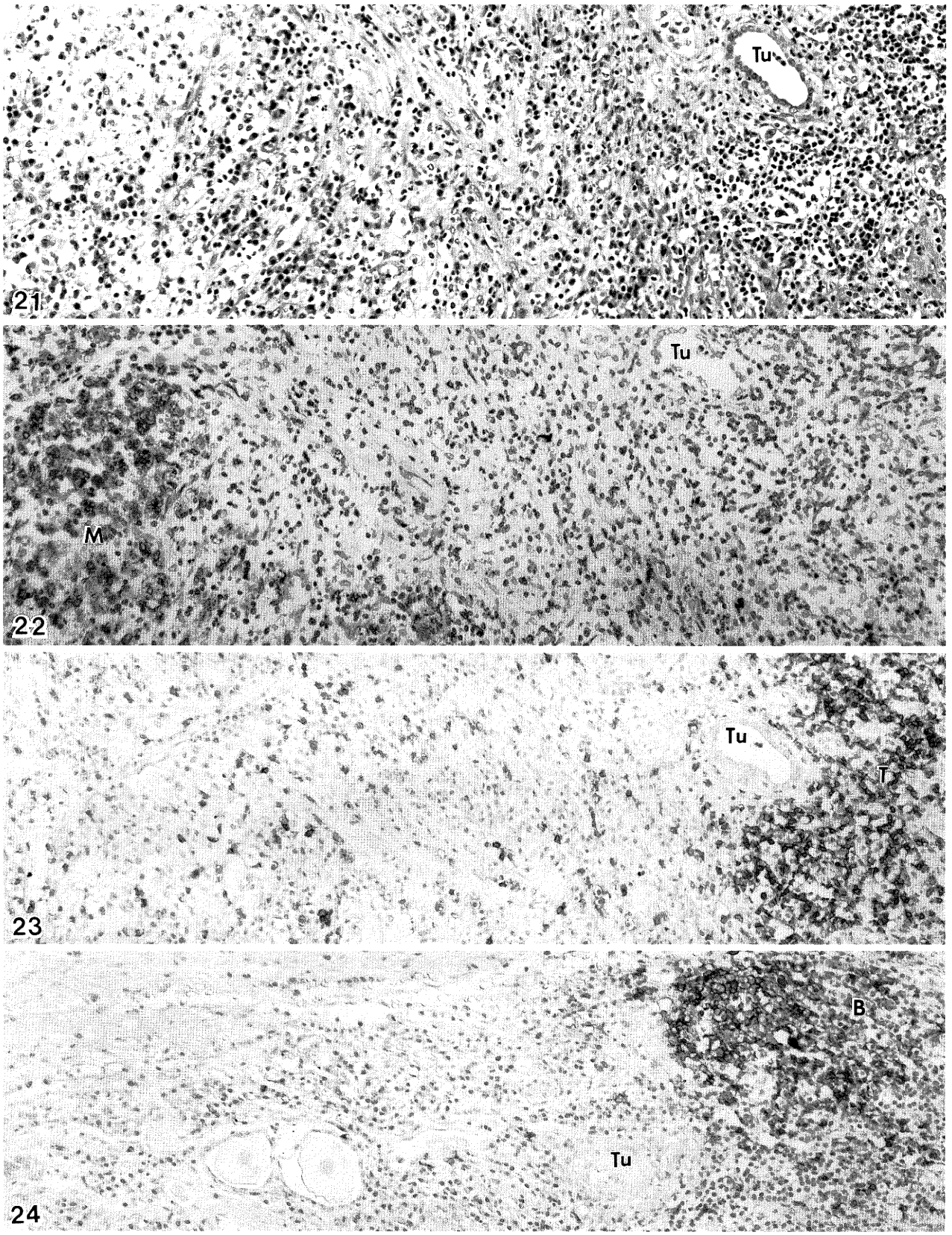


Fig. 19. The pelvic fatty tissue (F) is involved in inflammation and a mononuclear cell infiltration is present, suggesting the possible initial lesion of xanthogranulomatous pyelonephritis. Pyelitis(Pyl). (82-3526)

Fig. 20. Xanthogranulomatous pyelonephritis with foam cell accumulation (G) is seen next to a zone of extratubular efflux (arrowheads). PAS stain. (23635)



Figs. 21–24. Mononuclear cells in xanthogranulomatous pyelonephritis. Step sections stained with HE (Fig. 21), anti-CD68 (Fig. 22 M), anti-UCTL-1 (Fig. 23 T), and anti-L25 (Fig. 24 B). A residual tubule embedded in the granulomatous lesion (Fig. 24, Tu). (13746)

Histological examination reveals several stages to the inflammatory reaction.[42] Stage I shows maximal necrosis and granulocytic infiltration, including loosely arranged xanthoma cells. In stage II, the xanthoma cells are organaized in more solid formations along the capillaries with sporadic necrosis. Xanthoma cells are seen closely packed in a well vascularized stroma in stage III, while their numbers decrease and the cells become scattered in the zone of fibrosis in stage IV.

Accumulation of foamy macrophages is occasionally observed in the pelvic fatty tissue of kidneys with extratubular efflux including hydronephrosis and nephrolithiasis (Figs. 19 and 20). Along with the infiltration of lymphocytes, inflammation of the pelvic fatty tissue with foam cell involvement could lead to xanthogranulomatous lesions (Fig. 19) The intimate connection of xanthogranulomatous lesions in renal parenchyma with inflammation in the pelvic fat implys that this disease is a peculiar type of cellular immune-mediated granulomatous inflammation involving the renal fat tissues. The granulomatous lesions not only contain foamy macrophages but also T and B lymphocytes (Figs. 21-24). Thus, the development of this disease due to abnormal cellular immunity has been proposed in some reports, while a defect in the lysosomal processing of bacteria by host macrophages has also been suggested to be responsible.[46]

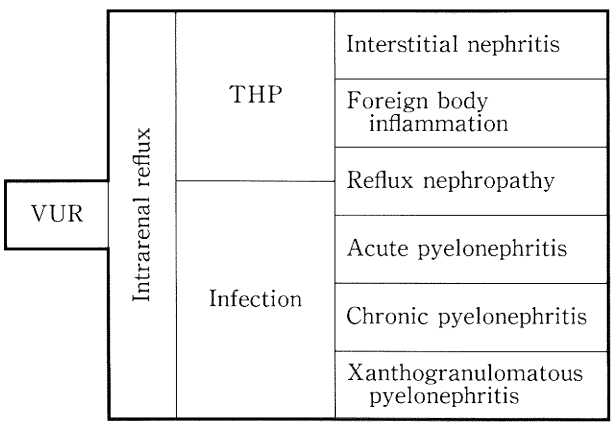


Fig. 25. Summary of reflux nephropathy and its circumferential disorders. Backflow of sterile of infected urine initiates various renal disorders from foreign body type or purulent inflammation to lymphomononuclear or macrophagic granulomatous inflammation under cellular immunity.

CONCLUSION

Although the intrarenal reflux of urine is evident in VUR, the similar backflow of sterile or infected urine is also observed in individuals without VUR (Fig. 25). Reflux nephropathy is thus only one of the renal disorders induced by intrarenal reflux.

Following the intrarenal reflux of sterile urine, THP initiates interstitial inflammation. The initial reactive inflammation of the foreign body type sometimes develops into a mononuclear cell interstitial nephritis possibly involving cellular immunity.

The reflux of infected urine initially produces purulent or supprative inflammation of the tubulointerstitial tissue which is characteristic of acute pyelonephritis. Chronic pyelonephritis is characterized by the accumulation of mononuclear cells in addition to atrophy of the renal parenchyma.

In some cases, xanthogranulomatous pyelonephritis develops with extensive destruction of the renal parenchyma. Participation of the cellular immune response in this disease is strongly suggested.

Thus, it seems reasonable to assume that the reflux of urine, either sterile or infected, can sensitize the host and thus induce chronic tubulointerstitial damage by activating cell-mediated immunity.

REFERENCES

1) Smellie J, Edwards D, Hunter N, Normand ICS, Prescod N: Vesico-ureteric reflux and renal scarring. *Kidney Int* 8: 65s-72s, 1975.
2) Spargo H, Taylor JR: Tubulointerstitial diseases. In: Rubin E, Farber JL (eds) Pathology. Lippincott Co, Philadelphia 1988, p 868-873.
3) Maki S, Miyata H, Yoshioka K, Yamamoto T, Akano N, Kinoshita T, Takemura T, Moriguchi N, Katoka T: Reflux nephropathy. (1) Ethiopathogenesis from the pediatric field. In: Annual Report of Study Group for "Progressive Renal Disease" 1990, p 223-231.
4) Rolleston GL, Shannon FT, Utley WLF: Follow-up of vesicoureteric reflux in the newborn. *Kidney Int* 8: 59s-64s, 1975.
5) Bailey RR: The relationship of vesico-ureteric reflux to urinary tract infection and chronic pyelonephritis-reflex nephropathy. *Clin Nephrol* 1: 132-141, 1973.
6) McLachlan MSF, Meller ST, Verrier JER: Urinary tract in schoolgirls with covert bacteriuria. *Arch Dis Child* 50: 253-258, 1975.
7) Edwards B, White RHR, Maxted H, Deverill I, White PA: Screening methods for covert bacteriuria

in schoolgirls. *Brit Med J* **2**: 463-467, 1975.
8) White RHR: Reflux nephropathy. *Jap J Pediat Nephrol* **4**: 1-7, 1991.
9) Zucchelli P, Gaggi R: Reflux nephropathy in adults. Nephron **57**: 2-9, 1991.
10) Zucchelli P, Gaggi R, Zuccala A: The natural history of the reflux nephropathy. Contr Nephrol **75**: 90-99, 1989.
11) Kincaid-Smith P: Glomerular lesions in atrophic pyelonephritis and reflux nephropathy. *Kidney Int* **8**: 81s-83s, 1975.
12) Cotran RS: Pathogenetic mechanisms in the progression of reflux nephropathy: The roles of glomerular sclerosis and extravasation of Tamm-Horsfall protein. Proc 8th Int Congr Nephrol, Athens 1981, p 374-381.
13) Kikuchi K, Koiso K, Koyama A: Studies on reflux nephropathy. Clinical investiation of renal lesions. *Jap J Nephrol* **32**: 245-251, 1990.
14) Tanizawa T, Shimada K, Tomimoto, Y, Hattori M, Wada H, Ikoma F, Inaba S, Okada T, Yanagihara T, Takada T: Reflux nephropathy and glomerular sclerosis: glomerular hypertrophy as a possible result of remnant glomerular hyperperfusion and hypertension. *Acta Medica Biol* (Niigata) **38**: 93s-106s, 1990.
15) Hodson CJ, Maling TMJ, McManamon PJ, Lewis MG: The pathogenesis of reflux nephropathy (chronic atrophic pyelonephritis). *Brit J Radiol* (Suppl) **13**: 1-26, 1975.
16) Senkjian HO, Suki WN: Vesicoureteral reflux and reflux nephropathy. *Amer J Nephrol* **2**: 245-250, 1982.
17) Shigematsu H, Murakami S, Akikusa B: Extratubular efflux and nephropathy. *Acta Pathol Jap* **34**: 715-725, 1984.
18) Shigematsu H, Murakami S: Intrarenal reflux and nephropathy. *Jap J Nephrol* **32**: 331-337, 1990.
19) Heptinstall RH, Bhagvan BS, Solez K: Urinary deposits in veins and interstitium of the kindney. Their possible role in causing renal damage. *Contr Nephrol* **16**: 70-77, 1979.
20) Wenk RE, Bhagavan BS, Rudert J: Tamm-Horsfall uromucoprotein and the pathogenesis of casts, reflux nephropathy and nephritides. In: Ioachim HL (ed) Pathobiology Annual. Ravan Press, New York 1981, 229-257.
21) Zager RA, Cotran RS, Hoyer JR: Pathologic localization of Tamm-Horsfall protein in interstitial deposits in renal disease. *Lab Invest* **38**: 53-57, 1978.
22) Barrie HJ: Herniations into the renal veins with special reference to hydronephrosis. *J Pathol Bact* **82**: 177-182, 1961.
23) Helmke K: Die Nierenveraenderungen bei Harnstauung besonders ueber die Bildung von "Lymphgefaess und Venen-zylindern" bei chronischer Harnstauung. *Archs Pathol Anat* **302**: 323-370, 1938.
24) Resnick JS, Sisson S, Vernier RL: Tamm-Horsfall protein: Abnormal localization in renal disease. *Lab Invest* **38**: 550-555, 1978.
25) Mayer AD, Kashgarian MH, Marier RR, Hodson CJ, Richard FF, Andriole VT: Tubulointerstitial nephritis and immunologic responses to Tamm-Horsfall protein in rabbits challenged with homologous urine or Tamm-Horsfall protein. *J Immunol* **128**: 2634-2642, 1982.
26) Sato K, Oguchi H, Yoshie T, Koiwai T: Tubulointerstirtial nephritis induced by Tamm-Horsfall protein sensitization in guinea pigs. *Virchows Arch B Cell Pathol* **58**: 357-363, 1990.
27) Ooi BS, Weiss WA, Kant KS, Hong CD, Pollak VE, Andriole VT: Antibody to Tamm-Horsfall protein after acute tubular necrosis. *Amer Nephrol* **1**: 48-51, 1981.
28) Bhagavan BS, Wenk RE, Dutta D: Pathways of urinary backflow in obstructive uropathy. Demonstration by pigmented gelatin injection and Tamm-Horsfall Uromucoprotein markers. *Human Pathol* **10**: 669-683, 1979.
29) Ransley PG, Risdon RA: Renal papillary morphology and intrarenal reflux in the young pig. *Pro Res* **3**: 105-109, 1975.
30) Ishikawa E: Pathology of pyelonephritis. *Tr Soc Pathol Jap* **66**: 27-58, 1977.
31) Virginia LT, Forland M, Shelokov A: Antibody-coated bacteria in urinary tract infection. *Kidney Int* **8**: 20s-22s, 1975.
32) Hanson LA, Ahlstedt S, Jodal U, Larsson P, Lidin-Janson G, Lincoln K, Lindberg U, Mattsby I, Olling S, Peterson R, Sohl A: The hostparasite relationship in urinary tract infections. *Kidney Int* **8**: 28s-34s, 1975.
33) Neter E: Estimation of escherichia coli antibodies in urinary tract infection: A review and prespective. *Kidney Int* **8**: 23s-27s, 1975.
34) Losse H, Intorp HW, Lison AE, Funke C: Evidence of an autoimmune mechanism in pyelonephritis. *Kidney Int* **8**: 44s-49s, 1975.
35) Kalmanson GM, Glassock, RJ, Harwick HJ, Guze LB: Cellular immunity in experimental pyelonephritis. *Kidney Int* **8**: 35s-43s, 1975.
36) Malek RS, Elder JS: Xanthogranulomatous pyelonephritis: a critical analysis of 26 cases and of the literature. *J Urol* **119**: 589-593, 1978.
37) Braun G, Moussali L, Balanzar JL: Xanthogranulomatous pyelonephritis in children. *J Urol* **133**: 236-249, 1985.
38) Kierce F, Carroll R, Guiney EJ: Xanthogranulomatous pyelonephritis in childhood. *Brit J Urol* **57**: 261-264, 1985.
39) Richie JP, Eichhorn JH: Case Records of the Massachusetts General Hospital. Case 38-1989 *New Eng J Med* **321**: 813-823, 1989.
40) Anhalt MA, Cawood CD, Scott R Jr: Xanthogranulomatous pyelonephritis: a comprehensive

review with report of 4 additional cases. *J Urol* **105**: 10-17, 1971.
41) Lorentzen M, Nielsen HO: Xanthogranulomatous pyelonephritis. *Scan J Urol Nephrol* **14**: 193-200, 1980.
42) Moeller JC, Kristensen IB: Xanthogranulomatous pyelonephritis. A clinicopatological study with special reference to pathogenesis. *Acta Pathol Microbiol Scand* [*A*] **88**: 89-96, 1980.
43) Treadwell TL, Craven DE, Delfin H, Stilmant MM, MaCabe WR: Xanthogranulomatous pathogenesis caused by methicillin-resistant staphylococcus aureus. *Amer J Med* **76**: 533-537, 1984.
44) Povysil C, Konickoval L: Experimental xanthogranulomatous pathogenesis. *Invest Urol* **9**: 313-318, 1972.
45) Povysil C: Ultrastructure of experimental xanthogranulomatous pathogenesis. *Virchows Arch B Cell Pathol* **20**: 155-167, 1976.
46) Antonakopoulos GN, Chapple CR, Newman J: Xanthogranulomatous pathogenesis: a reapraisal and immunohistochemical study. *Arch Pathol Lab Med* **112**: 275-281, 1988.