

The first three patients listed in Table 1 (S.F., L.C. and W.K.) were receiving methicillin in doses of 6 to 24 gm per day; the fourth (A.J.) was given penicillin, 20,000,000 units per day, in addition to methicillin, 4 to 6 gm per day, and the last three (O.O., M.L. and F.H.) received penicillin 12,000,000 to 60,000,000 units per day. The underlying infection for which the antibiotic was being given was staphylococcal sepsis in two patients receiving methicillin, and osteomyelitis in the third. A.J., who was given both penicillin and methicillin, was being treated for presumed bacterial endocarditis without the isolation of an organism. The three patients who received penicillin were being treated for bacterial endocarditis, caused by *Streptococcus viridans* in O.O. and F.H. and by neisseria in M.L.

In each patient the fever associated with the underlying infection had subsided within a few days of the start of treatment, only to recur after a variable period, which ranged from eight to 44 days. In four cases the fever was preceded or followed shortly by a morbilliform rash, and in all seven eosinophilia occurred being marked in six. Urinary abnormalities and azotemia appeared eight to 36 days after the institution of antibiotic therapy, following the recurrence of fever by a few days in six of the seven patients, and preceding the fever by almost three weeks in the seventh (S.F.). Hematuria occurred in all patients, minimal to moderate proteinuria in all, and pyuria in five of the seven. Blood urea nitrogen increased in all patients, the maximum level in individual patients ranging from 50 to 130 mg per 100 ml. The duration of urinary abnormalities was as short as four days and as long as 39 days, whereas the period of renal insufficiency was usually somewhat longer. Impairment of urinary concentrating ability and metabolic acidosis occurred in six patients. In four patients, acidosis persisted beyond the time that the blood urea nitrogen and urinary abnormalities had returned to normal.

Recovery, as judged by clearing of urinary abnormalities and return of blood urea nitrogen to normal levels, ensued in six of the seven patients. The interval between the appearance of urinary abnormalities and the discontinuation of penicillin or methicillin varied between three and 32 days, and recovery then followed within five weeks. However, in S.F. (Fig. 1) the urinary abnormalities subsided while methicillin was still being given, although the blood urea nitrogen did not return to normal until eight days after the drug was discontinued. In the single patient who died (M.L.) fever developed on the twenty-first, eosinophilia on the twenty-third, and rash on the thirtieth day of penicillin therapy, followed by seizures, coma, urinary, abnormalities and progressive renal insufficiency, with death occurring on the forty-second day. Penicillin was continued throughout this period. Urinary output was less than 300 ml on the last three days of life; this was the only case in which significant oliguria was observed.

Renal biopsies were obtained in S.F. and L.C., who manifested nephropathy to methicillin, and in O.O., who received penicillin. In addition, post-mortem material was available for study in M.L., who had been given penicillin. The lesions were characterized by irregular interstitial accumulation of leukocytes and by tubular damage (Fig. 2 and 3).

The infiltrate contained large numbers of mononuclear cells and eosinophils. Most of the mononuclear cells appeared to be large or small lymphocytes, although a few typical macrophages were present. In most areas mononuclear cells predominated, and in a few places eosinophils were absent. Few neutrophils were seen, and they were generally in direct association with necrotic tubules. No plasma cells were found. Tubular damage and interstitial edema were observed in association with the leukocyte accumulation; the damage was manifested by changes ranging from slight distortion of cells to destruction of a portion or the entire cross-section of the tubule. Many of the damaged tubules contained amorphous or fibrillar eosinophilic casts as well as desquamated epithelial cells and neutrophils. In most cases the affected segment of tubule could not be identified, but all levels appeared to be involved. Necrosis was conspicuous in two of the four cases. Regenerating tubular epithelium was also found in areas. The lesions were irregularly distributed; in the case studied at autopsy, they were seen to be predominantly in the cortex, although a few were present in the medulla. Most of the glomeruli appeared normal, but in one patient (L.C.), a few showed equivocal increase in neutrophils. The blood vessels appeared normal. In M.L., who was studied at autopsy, arteritis was found in the kidneys or in other organs.