ever, conclusive evidence is lacking, and probably could not be obtained without a suitable experimental model, which is not available at present.

If one provisionally accepts the interpretation that the renal lesions result from hypersensitivity, it remains to be determined what the underlying pathogenic mechanisms are, and why this reaction occurs in only a small percentage of the many patients receiving these drugs. Two general possibilities can be considered: in patients receiving large amounts of methicillin or penicillin, derivatives such as penicilloyl hapten may normally couple with structural renal proteins, and the damaging immune reaction may depend primarily upon an unusual immune response; or, alternatively, it may be considered that the patients in whom nephropathy develops, in contrast to the vast majority of persons, are uniquely capable of forming these hapten-kidney conjugates from the penicillins. The first explanation seems more likely, since penicillins are known to be chemically reactive with a wide variety of proteins. However, the data do not permit a definite decision. We have no immunofluorescent observations of renal tissue from patients given large amounts of methicillin or penicillin in whom interstitial nephritis has not developed. Such observations would provide information concerning this problem.

The question of the type of immunologic mechanism responsible for the damage remains. Despite the presence of gamma globulin (presumably specific antibody) and hapten in the lesions of the patient studied by immunofluorescence, several considerations indicate that the renal damage may not be initiated by antigen-antibody interaction. First of all, complement ($beta_1A$-$beta_1C$) was not detectable in association with the gamma globulin and hapten. Secondly, although gamma globulin and hapten were present in glomeruli, glomerular abnormalities were not apparent; since it is well established that glomerular damage is readily brought about by antigen-antibody complexes, (32) it seems likely that the type of complexes present in this patient were not tissue damaging (possibly because complement was not fixed). Finally, the histologic character of the lesion, with a predominantly mononuclear cell infiltrate, suggests the possibility that the damage was due to delayed hypersensitivity.* This possibility is further supported by the observation that the patient exhibited delayed sensitivity to methicillin.

Dosage of drug appears to have a role in the nephropathic reaction since the patients receiving methicillin were given a maximum dosage of 20 to 24 gm per day except for one patient (A.J.), who received only 6 gm per day. However, this patient was also receiving penicillin in a daily dosage of 20,000,000 units, and the other three in whom nephrotoxicity developed during penicillin therapy were receiving up to 20,000,000, 30,000,000 and 60,000,000 units per day. Furthermore, the shortest interval between the initiation of therapy and the appearance of urinary abnormalities was eight days, with a range between 16 and 34 days in the other six patients. Thus, it appears that high doses of drug for prolonged periods are more likely to produce nephropathy. At lower dosages of penicillin or methicillin the extraction by the kidney is almost complete, leaving little or none of these materials in the peritubular capillaries or interstitial fluid beyond the proximal tubules. At higher blood concentrations, the rate of transport by the proximal tubules increases, but extraction is incomplete, resulting in greater concentrations of drug in the blood leaving the proximal peritubular capillaries and in the interstitium. It sems likely that the increased rate of tubular transport and the increased concentrations of drug in peritubular capillaries and interstitial fluid that exist during administration of large doses have some effect on the occurrence of nephropathy. Since equivalent doses are frequently administered without any clinical evidence of renal damage, it is obvious that dosage is not the only factor responsible for nephropathy, and it is likely that the kind of immune response made to the drug is the critical feature.

The mechanism responsible for the marked azotemia that occurred in each of our patients is not clear. The absence of glomerular abnormalities and the consistent finding of interstitial inflammation and tubular damage might lead one to postulate that the reduction in glomerular filtration was due, at least in part, to increased interstitial pressure opposing filtration. Additional hemodynamic alterations other than those attributable to increased interstitial pressure, or perhaps tubular back diffusion, might also be involved. The impairment of urinary concentrating ability and the presence of striking metabolic acidosis even

*The question could be raised why a delayed sensitivity reaction did not occur in the glomeruli. Although the reason is not known, it can be stated that there is no experimental evidence that it is possible to produce a delayed reaction in glomeruli.