[CANCER RESEARCH 28, 1449-1451, July 1968]

The Immunologic Capability of Uremic Patients

John P. Merrill

Department of Medicine, Peter Bent Brigham Hospital, and Harvard Medical School, Boston, Massachusetts

SUMMARY

It seems that although a patient with chronic uremia is usually capable of producing circulating antibodies in a normal fashion, those immunologic functions which appear to be most closely related to delayed type hypersensitivity, i.e., rejection of a renal or a skin allograft, appear to be impaired. This impairment is corrected following the "cure" of uremia by successful kidney transplantation. Studies on the effects of correction of chemical uremia by dialysis alone (without renal allografting) upon skin graft rejection and lymphocyte transfer tests would be of value in ascertaining the difference between correction of the purely chemical defect and that of the complete uremic syndrome.

Infection is a serious problem in patients with both acute and chronic renal failure. In patients with acute renal failure, even when maintained by adequate hemodialysis, infection is a major cause of death. In these individuals failure of wound healing is unquestionably a contributory factor. In patients with chronic renal failure infection appears to be less of a problem except around the site of the silastic arteriovenous fistula which is utilized for intermittent hemodialysis with the artificial kidney. It is of interest, however, that in such individuals infection of the urinary tract, even in the face of marked oliguria, is virtually nonexistent, and recent studies have shown that even patients with moderate chronic renal failure, significant bacilluria is rare. Dietary protein restriction commonly used in the treatment of renal failure has been thought to be a contributory cause of susceptibility to infection. Possibly the anemia evident in all patients with renal failure of any duration may also contribute. However, no clear definition of the predisposing factor has yet been made. It is of interest that in patients with acute renal failure in whom infection is certainly the major problem, no specific reason for this susceptibility has been found other than the presence of trauma and surgical wounds which so frequently accompany the initial cause of acute renal failure. Phagocytosis and antibody production are apparently normal in such individuals (1).

Our own interest in the immunologic capability of patients with chronic renal failure began with our studies of human renal allografting (5). Previous studies of renal allografts in dogs had shown that functional survival of the transplant seldom exceeded 1 week. However, in 4 of the 9 human recipients reported in our early study survival ranged from 5 to 25 weeks, and the histology of the kidney grafts at autopsy was quite different from that of the rejecting dog kidneys. During our studies, however, a case was reported by Michon *et al.* (8) in which a kidney was transplanted into a previously healthy young man whose sole kidney had been removed following trauma. The kidney donor was his mother. The kidney functioned well for about 3 weeks and then function ceased abruptly. The graft showed the same morphologic pattern of rejection seen in the dog. Since all of our patients were chronically uremic, many maintained by dialysis on the artificial kidney, the suggestion was made that the delayed rejection or prolonged acceptance therefore might well represent an impaired immune response. Dammin *et al.* (4) in our group then undertook a study of the survival of skin allografts in uremic patients. In 7 patients with chronic renal failure, skin grafts were placed from multiple healthy donors and were biopsied at intervals from 32 to 115 days. In each of the recipients, the survival of at least 1 of the skin allografts was graded fair to good. Five were listed as good, 1 as excellent, 3 as poor, 2 as fair, and 1 could not be interpreted because of infection. Further studies carried out on the immunologic potential of these recipients showed that all had normal isoagglutinin titers. In addition, 3 patients were given an injection of B blood group specific substance, and 2 of the 3 showed responses comparable to those observed in normal individuals. Six of the 7 patients gave negative reactions to Schick tests, while tuberculin tests were positive in 2 of the 7 patients. The sera of 12 patients with chronic uremia were examined by paper electrophoresis for protein patterns. No depression considered to be significant was observed in the antibody-containing fractions. Gamma-globulin determined quantitatively by the agar diffusion method with horse antihuman gamma-globulin serum showed levels within the normal range for this method. Others have confirmed a prolonged survival of human skin allografts in chronic uremic patients (9, 11).

The studies of Kirkpatrick *et al.* (6) are of particular interest. They reported on 28 patients with chronic renal failure, the majority of whom had chronic glomerulonephritis. The patients were candidates for renal allografting and were studied before and after this procedure. Skin tests were made with various pollens, molds, and the antigens of tricophyton and *Candida albicans*. In addition, tuberculin tests (PPD), histoplasmin, and mumps antigen were administered. The results revealed that skin reactions of the delayed hypersensitivity type were distinctly weaker in the uremic patients (22/170 positive tests) than in normal donors (73/177 positive tests). Following renal allografting each of 18 patients not on steroid therapy developed at least 1 positive test of the delayed type. The authors attributed this to the transfer of immunologically competent tissue, i.e., lymphocytes, in the renal interstitium or blood contained in the renal vasculature. In their studies

there was no correlation between the skin tests and the preoperative level of blood urea nitrogen. In fact, in those patients who developed allograft rejection and a rising blood urea nitrogen following transplantation, positive skin tests occurred in some who had been previously negative. The authors did not believe that malnutrition was correlated with the suppressed immunologic potential, since positive tests developed in individuals soon enough after transplantation so that malnutrition could not have been corrected. In spite of this, however, the authors concluded that the suppression of immunologic potential was connected with the marked protein wasting of chronic renal failure and not with the inability of the skin of patients with uremia to react. It should be emphasized that the defect demonstrated here was in the development of delayed hypersensitivity reactions. These same authors (13) extended their studies and enlarged their series to 68 patients with renal failure receiving renal allografts. One hundred thirty-eight of 295 tests in normal individuals showed positive delayed cutaneous hypersensitivity while only 36 of 295 uremics did so. The skin reaction to histamine was normal, however. They noted a relative lymphopenia and remarked on the presence of atrophy and cystic changes in the thymus of chronically uremic patients, alterations not seen in young adults autopsied after accidental death. Their studies also suggest that uremic patients who did not respond with delayed cutaneous hypersensitivity reactions tended to have delayed rejection of renal allografts and vice versa. It was also found that the antibody response to both typhoid O and H antigen was decreased in uremic patients. However, in both the studies of Dammin *et al.* (4) and Stoloff (12), the production of circulating antibody by uremics apparently was normal. Stoloff *et al.* studied 14 Schick negative patients with chronic renal failure and uremia whose response to diphtheria toxoid was in all ways comparable to that of normals.

Krow and Vazquez (7) found that passive cutaneous anaphylaxis and passive Arthus reactions were markedly suppressed in guinea pigs made uremic by either bilateral ureteral ligation or by the injection of mercuric bichloride. Their conclusions were that impairment of the peripheral components of immunologic reactivity existed and that the suppressed skin reaction in animals with uremia might be due to lack of effective interaction of antigen and antibody at the sites, failure of release of chemical mediators, or both. These studies of course are not germane to the delayed type of skin reaction.

Recently interest has focused on the impairment of the immunologic potential of the lymphocyte in patients with chronic renal failure. Smiddy and his colleagues (10, 11) noted that skin graft survival was prolonged in rabbits with acute renal failure. In their studies skin grafts were placed upon the ear and the weight of the regional lymph nodes draining the skin graft was compared with that of non-uremic animals. They found considerable delay in increase of weight of the regional lymph nodes in the uremic animal when compared to controls. Although, as the authors themselves pointed out, this might perhaps be related to the adrenal cortical response to the stress of surgery used to produce acute renal failure, an inadequate response of the regional lymph nodes in the uremic animals was suggested. Further evidence along these lines is provided by the study of Bridges *et al.* (2) who pointed out that in 3 of 7 uremic patients studied with the normal lymphocyte transfer reaction (NLT), lymphocytes from the uremic donors failed to produce a reaction when injected intradermally into normal recipients. In 4 of these individuals the response was variable. There was no relation between failure of lymphocytes to produce a reaction and the amount of lymphocytes injected (somewhat less than in the normal controls), and there was no relation to the level of blood urea nitrogen. In the NLT test, the injection of peripheral blood lymphocytes intradermally into a normal recipient produces induration and erythema after a 24- to 36-hour period. The reaction is presumed to be due to immunologically competent lymphocytes reacting against tissues of an antigenically disparate host. In our own studies (3) the evidence is even clearer that the immunologic capability of lymphocytes in patients with uremia is impaired. We were fortunate to be able to conduct these studies under ideal circumstances, using lymphocytes from two sets of identical twins, one of whom was normal and the other chronically uremic. "Uremic" lymphocytes, in amounts comparable to those taken from the normal donor twins, injected into the same recipients constantly gave a weaker reaction. Following successful allografting of one of the uremic twins, the test was repeated and the NLT reaction from the normal donor and from the now normal allograft recipient were comparable, suggesting that the immunologic capability of the lymphocyte had been restored by the acquisition of normal renal function.

REFERENCES

1. Balch, H. H. The Effect of Severe Battle Injury and of Post-Traumatic Renal Failure on Resistance to Infection. Ann. Surg., *142:* 145–163, 1955.
2. Bridges, J. M., Nelson, S. D., and McGeown, M. G. Evaluation of Lymphocyte Transfer Test in Normal and Uraemic Subjects. Lancet, *1:* 581–584, 1964.
3. Carpenter, C. B., Glassock, R. J., Gleason, R., Corson, J. M., and Merrill, J. P. The Application of the Normal Lymphocyte Transfer Reaction to Histocompatibility Testing in Man. J. Clin. Invest., *45:* 1452–1466, 1966.
4. Dammin, G. J., Couch, N. P., and Murray, J. E. Prolonged Survival of Skin Homografts in Uremic Patients. Ann. N. Y. Acad. Sci., *64:* 967–976, 1957.
5. Hume, D. M., Merrill, J. P., Miller, B. S., and Thorn, G. W. Experiences with Renal Homotransplantation in the Human. Report of Nine Cases. J. Clin. Invest., *34:* 327–382, 1955.
6. Kirkpatrick, C. H., Wilson, W. E. C., and Talmage, D. W. Immunologic Studies in Human Organ Transplantation. I. Observation and Characterization of Suppressed Cutaneous Reactivity in Uremia. J. Exptl. Med., *119:* 727–742, 1964.
7. Kroe, D. J., and Vazquez, J. J. Hypersensitivity Reactions in Experimental Uremia. Am. J. Pathol., *50:* 401–419, 1967.
8. Michon, L., Hamburger, J., Oeconomos, N., Delinotte, P., Richet, G., Vaysse, J., and Antoine, B. C. Healthy Individual Receiving an Allograft from a Healthy Donor. Presse Med. *61:* 1419–1423, 1953.

9. Morrison, A. B., Maness, K., and Tawes, R. Skin Homograft Survival in Chronic Renal Insufficiency. Arch. Pathol., *75:* 139–143, 1963.
10. Smiddy, F. G., Burwell, R. G., and Parsons, F. M. The Effect of Acute Uraemia upon the Survival of Skin Homografts. The Influence of Uraemia upon Certain Aspects of Lymph-Node Reactivity. Brit. J. Surg., *48:* 328–333, 1960.
11. Smiddy, F. G., Burwell, R. G., and Parsons, F. M. The Influence of Uraemia on the Survival of Skin Homografts. Nature, *190:* 732–734, 1961.
12. Stoloff, I. L., Stout, R., Myerson, R. M., and Havens, W. P., Jr. Production of Antibody in Patients with Uremia. New Engl. J. Med., *259:* 320–323, 1958.
13. Wilson, W. E. C., Kirkpatrick, C. H., and Talmage, D. W. Suppression of Immunologic Responses in Uremia. Ann. Internal Med., *62:* 1–14, 1965.

The Immunologic Capability of Uremic Patients

John P. Merrill

Cancer Res 1968;28:1449-1451.