The right abducens nerve palsy gradually improved. Six weeks after discharge lateral movement of the right eye was apparently full but the diplopia persisted and he complained of blurring in the left eye. Prednisolone was then given, but a week later vision in the right eye became blurred. The left carotid and the left radial pulses were absent and the right carotid pulse was weak. A short, soft systolic bruit was audible over the right carotid artery. Visual impairment was believed to be due to retinal ischaemia. Three months after discharge the patient still had headache and intermittent blurring of vision. The left auriculotemporal arterial pulsation was absent. Nicotinic acid added to the treatment gave no benefit. Four months after discharge he developed another crop of papulonecrotic eruptions over the back, buttocks, arms, legs, and face. The headache was intense and there was polyarthralgia involving the wrists, ankles, and knees. These symptoms persisted for over a month despite prednisolone in doses of up to 60 mg/day. Prednisolone was stopped and cyclophosphamide by mouth 150 mg/day gradually reducing to 100 mg/day was given instead. The headache became less frequent and less severe.

Aortography nine months later showed the state of the extracranial cerebral vessels to be unchanged.

Comment

The unilateral abducens palsy in this case might be attributed to a reduced blood supply to the nucleus of the nerve in the pons. The lack of any other evidence of brain-stem lesion, however, was against that explanation. Isolated oculomotor palsy associated with various causes of arteriopathy such as diabetes mellitus and syphilis is well known, but, unlike those disorders, the lesions in Takayasu's (1908) disease are confined to the large arteries.

The onset and course of the abducens palsy in our patient were similar to those of a palsy due to infarction of the nerve trunk resulting from occlusion of the vasa nervorum, and the view that this could have been the nature of the lesion in our case is supported by the presence of widespread cutaneous microangiitis, manifested as papulonecrotic, tuberculide-like eruptions. Alternatively, the nerve may have been directly affected by a granulomatous process as in cranial neuritis, or polyneuritis cranialis—a condition that seems to be highly prevalent in some countries in the Far East, including Thailand (Steele and Vasuvat, 1970).

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Kidney Transplantation in Fabry's Disease

F. R. BÜHLER, G. THIEL, U. C. DUBACH, F. ENDERLIN, F. GLOOR, H. THÖLEN

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Renal transplantation is of particular interest in congenital metabolic disorders. In this group, graft viability may be affected by the underlying disease, or the normal transplant may have a beneficial effect on the metabolic defect. Our observations in a patient with Fabry's disease who developed renal failure and received a renal allograft in 1967 provide further information about the value of renal transplantation in this inborn error of metabolism.

Case Report

Proteinuria detected on routine urine analysis prompted the examination of a 33-year-old man of Italian origin. Pertinent findings included slight burning discomfort of his hands and feet, purple-black telangiectasia, hypohidrosis and hyperkeratosis of the skin of the lower abdomen, scrotum, and buttocks. These lesions had been present since childhood and increased in size and number since that time; biopsy confirmed the angiokeratosis. Slit lamp examination of the eyes showed opacities of cornea and lens. A 24-hour urine specimen contained 1·5 g of protein and the urinary sediment showed birefringent foam cells. Creatinine clearance was 60 ml/min.

Four years later the patient presented with a blood pressure of 220/110 mm Hg, pitting oedema, and a creatinine clearance of 15 ml/min. Shortly thereafter, in August 1967, haemodialysis was begun. Nephrectomy was performed two months later for intractable hypertension. Histologically extensive hyalinization of nearly all glomeruli and pronounced interstitial fibrosis were found. Fat stains showed lipid deposits in glomerular epithelial cells, mesangial cells, interstitial macrophages, and tubules, and in the walls of intrarenal blood vessels (figs. 1 and 2).

Enzyme measurements showed a total lack of ceramide trihexosidase in the acetone-dried powder of this patient's kidney, whereas simultaneously measured normal kidneys contained 4·6 nmol ceramide trihexosidase/mg protein/hr (Dubach *et al.*, 1969).

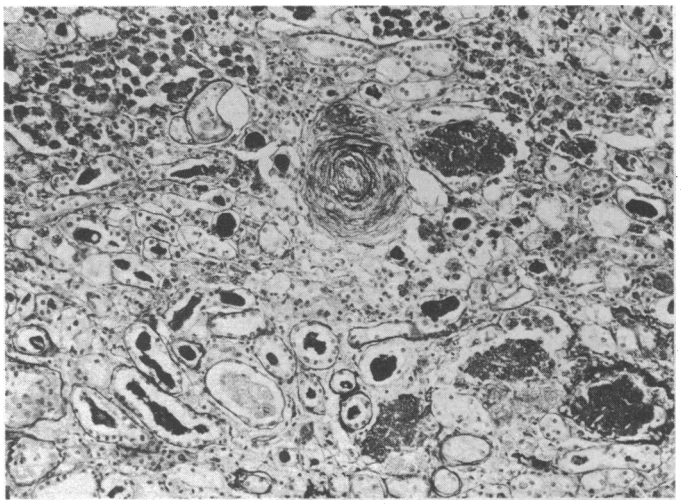

FIG. 1—Kidney section showing hyalinization of glomeruli, atrophic tubuli with protein casts and desquamated tubular foam cells, lipid deposits in arteriolar and glomerular epithelial cells, tubules, interstitial macrophages; adaptive intimal fibrosis of vascular walls. (P.A.S. X 60.)

University of Basel, 4000 Basel, Switzerland
F. R. BÜHLER, M.D., Resident, Division for Organ Transplantation, Department of Medicine and Surgery (Present address: Department of Medicine, College of Physicians and Surgeons, Columbia University, New York 10032)
G. THIEL, M.D., Medical Director of Division of Organ Transplantation
U. C. DUBACH, M.D., Director of Outpatient Clinic, Department of Medicine
F. ENDERLIN, M.D., Surgical Director of Division of Organ Transplantation
H. THÖLEN, M.D., Medical Director, Division of Nephrology, Department of Medicine

Academy of Medicine, St. Gallen, Switzerland
F. GLOOR, M.D., Director of Department of Pathology

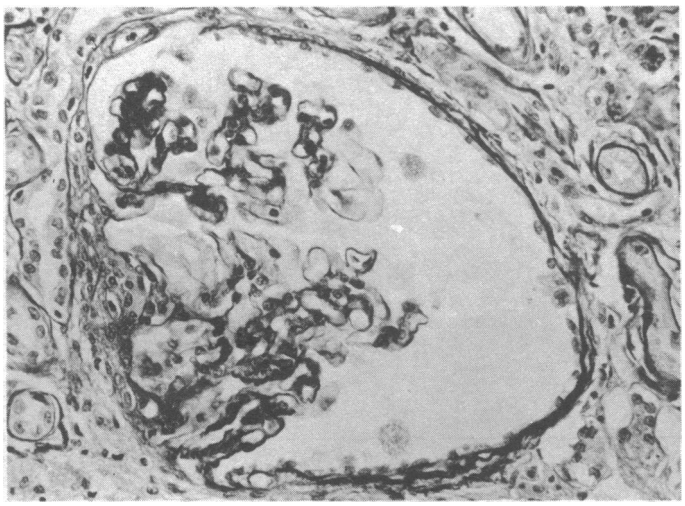

FIG. 2—Glomerulus with shrunken mesangial pole, fibrosis, and lipid laden endothelial cells—that is, foam cells. (P.A.S. X 135.)

In November 1967 a cadaver kidney transplant was performed with an uncomplicated early postoperative course. Immunosuppressive therapy included azathioprine 125 mg/day and prednisone 100 mg/day which was gradually reduced to 15 to 20 mg/day. Renal function remained stable with a creatinine clearance of 60 ml/min. Frequent urine analysis failed to show proteinuria or birefringent substances throughout the remainder of the patient's life. Five months after transplantation a reversible acute rejection occurred and eight months after transplantation, because of subacute rejection, immunosuppressive therapy was again increased to maintain the creatinine clearance at 30 to 40 ml/min. Fourteen months after transplantation progression of chronic rejection could not be prevented despite the use of 40 mg prednisone/day together with 75 to 125 mg/day of azathioprine. Azathioprine toxicity was complicated by a *Candida albicans* pharyngitis and by a suppurative pneumonitis with *Nocardia asteroides*. The patient died 17 months after transplantation during an episode of septic shock. No transfusions were necessary in the entire postoperative period.

Necropsy showed widespread lipid deposits in skin, spleen, lymph nodes, periportal areas of the liver, ganglion cells of submucosal and myenteric plexus of the intestinal tract, alveolar epithelial cells, in myocardial fibres, and in media of arteries. Sections of the wall of the radial arteriovenous fistula used for haemodialysis also contained the lipid deposits. The microscopical changes in serial graft biopsy specimens obtained at two weeks, as well as four, five, and 14 months after transplantation, were compatible with various degrees of immunologic rejection. However, no ceramide deposits were found in any of the biopsy or necropsy sections of the transplanted kidney. The accompanying ureter and renal artery and vein were similarly free of ceramide deposits.

Comment

Renal transplantation in Fabry's disease represents a new approach in the management of this congenital metabolic disorder where renal failure in general is life-limiting. This disorder has been shown to involve a lack of a specific beta-galactose hydrolase, an enzyme necessary to cleave the terminal galactose of the trihexosyl ceramide. This enzyme is missing in plasma and tissues (Brady *et al.*, 1967), and increased amounts of the substrate ceramide are present in plasma (Vance *et al.*, 1969), kidney (Sweely and Klionsky, 1963), and urinary sediment (Philippart *et al.*, 1969). The patient reported here showed the characteristic clinical and biochemical features of Fabry's disease and, to our knowledge, represents the first instance of renal transplantation performed in this disorder (in 1967).

During the 17 months after transplantation there was no evidence of progression of the disease, and, in contrast to the disseminated nature of the storage disease elsewhere, no ceramide deposits could be found in the transplanted kidney. Although the absence of deposits in the graft is a provocative finding, this observation must be interpreted with caution since manifestations of trihexosidase deficiency may become evident only after a period of many years. It is legitimate to ask whether, had our patients survived the *Nocardia* sepsis, the renal manifestations of Fabry's disease might indeed have developed in the allograft after a number of years. Whatever the answer to this question, the experience in this patient suggests that the renal involvement, if indeed it occurs at all, is a slowly developing process, and that Fabry's disease per se is not a contraindication to renal transplantation.

In addition to restoring normal excretory function, renal transplantation in Fabry's disease may confer an additional benefit by enhancing ceramide elimination either through excretion or degradation. Moreover, the allograft might manufacture the lacking enzyme resulting in a rise of plasma enzyme activity and clearance of total body ceramide, thus correcting the metabolic defect (Desnick *et al.*, 1972; Philippart *et al.*, 1972). Recently this view has been challenged by the suggestion that the reduced plasma ceramide concentration may reflect a decrease in the rate of ceramide formation rather than an increase in ceramide catabolism by the graft (Clarke *et al.*, 1972). Whatever biochemical mechanisms prove to be involved, the total absence of lipid deposits in the renal allograft as documented in our patient suggests that renal transplantation in Fabry's disease may have therapeutic effects beyond those simply attributable to the correction of the uraemic state.

Requests for reprints should be addressed to: Dr. G. Thiel, Medical Director for Organ Transplantation, University of Basel, 4000 Basel, Switzerland.

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