Human renal transplants. II. Immunofluorescent and immunoferitin studies

Seventy-one human renal allografts treated with immunosuppressive agents and two renal isografts were biopsied 18 days to eight years after transplantation. Deposits of amorphous material were detected by electronmicroscopy on the subendothelial aspects of the glomerular capillary basement membranes of 54 (76%) of the 71 allografts. Three of the grafts with subendothelial deposits also showed focal collections of electron dense material on the epithelial surfaces of the capillary basement membranes. Mesangial deposits were common in those grafts that contained capillary basement membrane accumulations. In 49 (90%) of the 54 allografts which had subendothelial deposits, immunofluorescent examination showed IgM distributed along the glomerular capillary walls in a linear or finely granular pattern. The IgM was accompanied by complement in 35 (65%) of the grafts, by IgG in 16 (30%), and by fibrinogen in 12 (22%). The distribution of IgG and complement was similar to that for IgM, but fibrinogen was distributed in a focal mesangial pattern. Upon immunofluorescence, the three renal allografts with subepithelial deposits exhibited additional, distinctive, nodular, ‘lumpy-bumpy’ deposits of IgG, IgM and complement along the epithelial side of the glomerular capillary basement membrane. The authors suggest that the subendothelial deposits of IgM and complement found in the glomerular capillary walls of many of the allografts occurred through the reaction of circulating antibodies with antigens in the capillary basement membranes of the graft. By contrast, the large ‘lumpy-bumpy’ subepithelial deposits of IgG, IgM and complement in three of the grafts were probably caused by transmission of active glomerulonephritis from the recipient to the allograft.

Author’s address: Prof. K.A. Porter, Department of Pathology, St. Mary’s Hospital, London, W.2 (England).

Chronic renal homograft function. Correlation with histology and lymphocyte antigen matching

Renal function was studied in 29 of 34 surviving renal allograft recipients from an initial group of 64 patients, two years after transplantation. Mean clearance of inulin and PAH were, respectively, greater than and equal to half of the donors initial predicted clearances. Minimum urine osmolality during water diuresis was greater, and maximum urine osmolality during hydropenia was less than normal, an effect felt to be secondary to enhanced solute load in a single transplanted kidney. Patients with compatible donor-recipient lymphocyte antigens demonstrate statistically better function than those with one or more incompatibilities, although
there was a definite degree of overlap between the groups. In contrast, little correlation could be demonstrated between the cumulative histopathology and renal clearances. Renal function in patients with compatible donors was statistically greater than half the donors initial predicted function. Serial increases in renal clearances was documented in one patient with a compatible donor. Serial decreases were demonstrated in two patients with incompatible donors. These findings suggest that hypertrophy of the denervated, transplanted kidneys occurs when immune reaction is minimal.

Author’s address: Dr. D.A. Ogden, Department of Medicine, Veterans Administration Hospital, and University of Colorado School of Medicine, Denver, Col. (USA).

Heterophile antibodies in human transplantation

Sensitization of human recipients with transplantation antigens (leukocytes, skin or kidney allografts), resulted in the appearance of serum hemagglutinins directed against sheep, guinea pigs, and rat erythrocytes. These hemagglutinins were identified as IgG and IgM antibodies. There appearance was not related to ABO erythrocyte group incompatibility between donors and recipients, and the antibodies were not of the Forssmen or Paul-Bunne type. The antibody responses appeared to be primarily directed against antigen(s) present on rat erythrocytes, but shared to a varying extent by other species. The peak antibody titers occurred in association with allograft rejection. In this regard, they may be considered to be of interest as a possible early warning system for the diagnosis and management of rejection crisis in clinical organ transplantation.

Author’s address: Dr. F.T. Rapaport, Department of Surgery and Institute of Reconstructive Plastic Surgery, New York University Medical Center, New York, N.Y. (USA).

Transplantation antibodies in human recipients of renal homografts

Sequential serum samples obtained from eight patients who had survived rejection of one or two renal homografts were studied for the presence of transplantation antibodies by the mixed agglutination tests with cell cultures. Evidence that transplantation antibodies are removed from the recipient circulation by the functioning graft was as follows: (1) the antibodies that were detected in the sera of the patients were found only during the terminal stage of rejection or after removal of the graft but never during the normal function of the graft; (2) the antibodies could be eluted from the rejected grafts. Three of four grafts placed in recipients who had antibodies before the transplantation, underwent hyperacute rejection with massive infiltration by polymorphonuclear leukocytes. The authors interpret this data to be consistent with the hypothesis that transplantation antibodies are constantly bound to the antigens of the functioning graft and therefore, removed from the circulation. This would explain why antibodies cannot be detected in the recipient serum as long as the functioning graft remains in situ. The finding of transplantation antibodies in recipient serum during an advanced rejection process can be explained by implicating severe impairment of the graft circulation and prevention of sufficient contact between the antibodies and the antigens of the graft.

Author’s address: Dr. G.M. Williams, Department of Surgery, Medical College of Virginia, Richmond. Va. (USA).
Extracorporeal renal transplantation in man

This report documents the successful extracorporeal transplantation of a kidney from a 9-year old child to the forearm of a 35-year old, anephric man. The kidney was perfused in a sealed chamber, especially prepared for this purpose, by blood from chronically cannulated forearm vessels utilized for regular hemodialysis treatment. Immunosuppressive drugs and heparin were administered during the procedure. Renal function was maintained satisfactorily until the 25th day, when the kidney underwent an acute vascular rejection. During this period, there were no untoward signs or symptoms which could be attributed to the procedure or the chamber itself and the patient improved, clinically. The authors suggest that extracorporeal renal transplantation may be useful as a test of viability and functional competence of cadaver kidneys prior to their transplantation into the iliac fossa. It is also suggested that this procedure may be helpful in investigation of the immune mechanisms responsible for rejection.

Author’s address: Dr. A.R. Lavender, Department of Medicine, University of Chicago, Chicago, Ill. (USA).

Combined immuno-suppression for canine renal allograft prolongation: anti-lymphocyte serum plus prednisolone or azathioprine

Canine renal allo-transplants were carried out in 72 recipient dogs receiving pre-operative horse anti-dog lymphocyte serum (ALS) and various combinations of prednisolone and azathioprine. The administration of ALS to dogs for a 6-day period prior to renal transplantation resulted in only a modest prolongation of survival compared with recipients of normal horse serum. The combination of preoperative ALS plus postoperative prednisolone, starting on the day after transplantation, failed to increase the prolongation of survival obtained with either preoperative ALS alone or postoperative prednisolone, alone. When ALS was administered preoperatively and azathioprine was begun the day after transplantation a significant increase in survival was noted, exceeding that found with either preoperative ALS, alone or postoperative azathioprine, alone. Six days of ALS treatment prior to transplantation caused a profound peripheral lymphopenia. When no postoperative drugs were given, the lymphocyte counts returned toward normal in about three weeks. The administration of either prednisolone or azathio-

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plasma prolonged the duration of the relative circulating lymphopenia, although the initial very low lymphocyte counts were not consistently maintained. The results in this paper confirm previous findings in mice which suggest that the immuno-suppression initiated by a short course of anti-lymphocyte serum can be maintained by a relatively low dose of conventional immunsuppressant drug. This combination may make it possible to avoid both the hazards of prolonged administration of foreign protein and the hazards of high doses of conventional immunsuppressant drugs.

Author’s address: Dr. R. Weil, Department of Surgery, Columbia University College of Physicians and Surgeons, New York, N. Y. (USA).

Plasma erythropoietin and renin activity after canine renal allotransplantation

Serial determinations of plasma erythropoietin and renin activities were performed in six dogs, not receiving immunsuppressive therapy, before and after renal allo-transplantation. Four of the
animals showed marked elevations in erythropoietin and renin after the transplants with maximum values for both hormones occurring on the same day. Hormone release occurred shortly after the onset of immunological rejection, as evidenced by decline in urinary solute excretion and rapid increases in plasma creatinine. One dog showed only slight post transplant elevation in hormones, and one showed no appreciable increases in either erythropoietin or renin. The latter animal had no clear evidence of an acute rejection reaction. In those animals with significant increase in plasma renin activity there was a simultaneous rise in blood pressure, while animals that did not have elevated renin activity remained normotensive. It is concluded that immunological rejection may result in renal release of both erythropoietin and renin, and that renin release may be associated with hypertension in renal transplant recipients.

Author’s address: Dr. P. H. Abbrecht, University of Michigan, Ann Arbor, Mich. (USA).

Schwartzman reaction after human renal homotransplantation

In three human recipients, five renal homografts were destroyed within a few hours after their revascularization in the new host. The kidneys, removed from 1 to 54 days later, demonstrated cortical necrosis. The major vessels were patent, however, on histologic examination, the arterioles and glomeruli were the site of fibrin deposition. There was little or no fixation of host immunoglobulins in the homograft. These findings were characteristic of a generalized Schwartzman reaction. Although the cause(s) of the Schwartzman reaction in these patients is not known, the authors speculate that they may have been conditioned by the bacterial contamination and hemolysis that often attend hemodialysis, by immunosuppression and by the transplantation, itself. In some of the patients there were preformed lymphocytotoxic antibodies and, it might be expected that certain individuals may pre-disposed. It is recommended that high-risk patients should be recognized and treated prophylactically with anticoagulants.

Author’s address: Dr. T. E. Starzl, Department of Surgery, University of Colorado School of Medicine, Denver, Col. (USA).

The role of vaso-constriction in the ischemia of renal allograft rejection

Serial studies were carried out on bilaterally nephrectomized dogs bearing renal allografts (n = 8) or autografts (n = 5). It was shown by means of direct measurement of flow, Xenon washout techniques and infusion of various drugs that the renal cortical ischemia that develops with graft rejection is associated with a marked increase in vascular sensitivity to vasodilator drugs not found in the autografts. In the late stage of rejection, the vessels which were still patent remained extremely sensitive to vasodilator action but the peak flow that could be produced was considerably reduced. The latter observation suggested that a non vaso motor component supercedes in the ischemia of late allograft rejection, when histological evidence of vascular destruction and obliteration becomes evident. These studies are consistent with hypothesis that ischemia plays an important role in the pathogenesis of allograft rejection, and suggests that a reversible, functional component due to increased vascular tone occurs first.

Author’s address: Dr. N. K. Hollenberg, Peter Bent Brigham Hospital, Boston, Mass. (USA).

Proximal tubular malfunction as a mechanism for diuresis after renal homo-transplantation
Four patients who received a renal homograft from a related donor were studied during the first 24 h after operation to determine the mechanism of a post-transplantation diuresis. The diuresis (12,591, 24,917, 3773, and 1873 ml/24 h respectively) was associated with decreased tubular resorption of sodium and glucose. Fractional excretion of filtered sodium reached values as high as 0.12 to 0.21, and fractional excretion of glucose achieved values as high as 0.10 at normal plasma glucose levels. The marked natriuresis and glycosuria subsided or improved spontaneously despite meticulous replacement of all renal and extrarenal fluid and electrolyte losses. In two subjects who excreted a hypotonic urine, free water excretion during the natriuresis rose to values as high as 12 to 20% of the glomerular filtration rate. Excreted potassium exceeded filter potassium in two subjects. The authors interpret the data to indicate that in these patients the early post-transplantation diuresis is due primarily to intrinsic defects in proximal tubular transport systems for sodium and glucose whereas the transport systems in the distal nephron are relatively intact.

Author’s address: Dr. L. W. Henderson, Hospital of the University of Pennsylvania, 36th and Spruce Street, Philadelphia, Pa. 19104 (USA).

Immunologic rejection of human cancer transplanted with a renal allograft

This report documents the inadvertent transfer with a cadaver renal allograft of an epidermoid carcinoma of the bronchus, which subsequently was rejected following cessation of immunosuppressive therapy. The case described is that of a 34-year-old man who in August, 1964, received a renal allograft from a cadaveric donor who had died of cerebral metastases from a bronchiogenic carcinoma. No other metastatic disease was known clinically or was found grossly or microscopically on postmortem examination of the donor. In January, 1966, renal function was stable in the recipient. He noted, however, at that time an enlarging mass over the lower pole of the transplant. A biopsy of this tumor and of the adjacent subcutaneous tissue revealed metastatic epidermoid carcinoma histologically indistinguishable from the original primary bronchiogenic carcinoma of the donor. The initial treatment to this tumor was irradiation of the local site. No reduction in size of the tumor was noted to follow this therapy. Immunosuppressive drugs were stopped on February 24, 1966, in the hope that the patient might retain the transplant and reject the tumor. Instead, rapid rejection of the transplant occurred. Adenopathy developed beyond the field of irradiation while therapy was in progress, and on March 22, 1966, a biopsy proved that metastatic tumor was present in the femoral lymph nodes. Because the renal allograft became acutely swollen and tender and a fever developed, on March 29, the rejected transplant was removed together with some of the involved lymph nodes. Not all the cancer could be removed. During the next month while treated with regular intermittent hemo-dialysis, the patient remained afebrile, and the residual painful swelling in the right lower quadrant and a grossly enlarged lymph node slowly regressed in size. Six months after removal of the transplant in August, 1966, a complete groin section revealed no gross or microscopic cancer. On October 15, in preparation for a second renal allograft, treatment with azathioprine and prednisone were started again. No tumor developed over the four-week observation period. On November 18, a kidney from the patient’s mother was transplanted into the patient’s left
groin. The patient has done well and returned to full daily activity and remained free of cancer more than ten months after transplantation despite the re-institution of immunosuppressive therapy. This case demonstrates clear cut evidence of immunologic rejection of human cancer.

Author’s address: Dr. R.E. Wilson, Department of Surgery, Peter Bent Brigham Hospital, Boston, Mass. 02115 (USA).

Effect of anti-lymphocyte serum on responses of human peripheral-blood lymphocytes to specific and nonspecific stimulants in vitro

This report concerns the ability of human peripheral-blood lymphocytes treated in vitro with anti-lymphocyte serum (ALS) in the absence of complement to respond to subsequent specific and non-specific stimuli. Antilymphocyte sera against human splenic and tonsillar cells were raised in goats. These sera, when tested in vitro with human peripheral blood lymphocytes had cytotoxic and agglutinating properties and could stimulate DNA synthesis and transformation of lymphocytes. Fractionation of the antisera showed that the mitogenic activity was almost exclusively in the IgG fraction. Normal goat sera treated lymphocytes gave a good response to PPD, DNA, synthesis reaching a peak four to six days after addition of antigen. In contrast, ALS treated cells showed no response to PPD at this time. Restimulation with PHA showed the ALS treated cells could nonetheless still proliferate and in fact responded sooner and to a greater extent than control cells treated with normal goat serum. Partial to complete suppression of the PPD response was obtained on two further occasions, but in a subsequent experiment, paradoxically, DNA synthesis was considerably enhanced. These differences were showed to depend on the concentration of ALS used. In addition, preliminary findings suggested that the mixed lymphocyte reaction may also be suppressed by high doses of ALS. The authors point out that these responses may provide a basis for the in vitro assessment of immunosuppressive activity of any given ALS.

Author’s address: Dr. I.M. Roitt, Middlesex Hospital Medical School, London, W.I (England).

Carotid sinus pulse pressure, a determinant of plasma antidiuretic hormone concentration

Experimental manipulation of carotid arterial pulse pressures were utilized in anesthetized, vagotomized dogs (under conditions in which carotid sinus chemo-receptor activity was unaffected) and plasma bioassay ADH measurements were made. When the carotid sinus perfusion pressure was changed from pulsatile to essentially non-pulsatile, mean systemic arterial pressure increased 56% and plasma ADH levels increased 89%. It was concluded that a reduction in carotid sinus baroreceptor activity (induced by changes in carotid arterial pulse pressure) results in decreased inhibition of the release of ADH from the neurohypophysis resulting in elevated plasma ADH levels.

Author’s address: Prof. Leonard Share, Department of Physiology, Western Reserve University, Cleveland, Ohio (USA).

Clinical reaction and serologic changes after the administration of hetero-logous antilymphocyte globulin to human recipients of renal homograft

Clinical reactions and serologic changes after intramuscular administration of horse anti-human lymphocyte globulin (ALG) were studied in 53 human recipients of human renal homografts.
The ALG was used as an adjuvant immunosuppressive drug. In the usual case, 47 injections were given over a four-month period.

All patients had pain, tenderness, erythema, and swelling at the injection sites. Benign systemic side effects included fever in all cases, hives in eight cases, rash in five, pruritis in five, arthralgia in three, and periorbital edema in one. Anaphylactic reactions occurred in eleven cases. These were easily treated, and there was complete recovery in every instance within 90 min. In eight of these cases, the ALG administration was discontinued. Subsequent injections were given in the other three.

Four of eleven patients tested have positive skin tests to ALG before therapy. Antibodies against sheep red blood cells developed during therapy in 39 of 40 patients; ten reached titers as high as 1:128 to 1:512. Precipitin antibodies as measured by an electroimmunodiffusion technique developed in 36 of 40 patients. All three immunologic tests were of value in predicting the probability of an anaphylactic reaction, but the discrimination was imperfect. Immuno-electrophoretic studies of sera from 13 patients showed antibody to horse Beta globulins in all cases, to alpha globulin in nine cases, and to gamma globulins in only one. The authors conclude that the latter finding indicates that a safer ALG could be made by removing the trace quantities of alpha and beta globulins from the immunologically more active gamma globulin.

Author’s address: Dr. Thomas Starzl, Veterans Administration Hospital, 1055 Clermont Street, Denver, Col. 80220 (USA).

Effect of renal homotransplantation on the metabolism of the light chain of immunoglobulins

The free light (L) polypeptide chains of human immunoglobulins were measured in the serum and the urine of 14 uremic patients before bilateral nephrectomy, during an anephric period, and after 16 renal homotransplantation procedures. Markedly elevated serum and urine concentrations were found in all azotemic patients, and serum levels, in general, rose further after bilateral nephrectomy. After successful homotransplantation, serum levels became less than 0.02 mg/ml as L chain diuresis occurred. Immediate failure of graft function was characterized by continued elevation of serum and urine concentrations of L chains in a pattern similar to the prenephrectomy stage. In the period from 7-25 days post-transplantation, two groups of patients could be distinguished: those with elevated serum and urine L chain concentration and those who returned serum and urine L chain concentrations to normal or near normal. The first group was found to have a significantly higher prevalence of irreversible renal homograft rejection subsequently when compared to the second group. Homograft rejection was associated with a rise in the urine L chain concentration which subsided with successful treatment of the rejection episode. Measurement of L chains would appear to provide an additional parameter of renal function, and as such, to potentially serve as a prognostic and diagnostic guide in the course of renal homotransplantation.

Author’s address: Dr. W.V. Epstein, University of California, San Francisco Medical Center, San Francisco, Cal. 94122 (USA.)

Histological diagnosis of rejection of renal homografts in man

This report documents the author’s four-year experience with the use of renal biopsy to confirm the diagnosis of homograft rejection. Percutaneous renal biopsy was carried out at the time of suspected homograft rejection in 36 instances. An
additional ten surgical biopsy specimens were also studied. Severe acute rejection was present in 11 patients, 6 of whom died. In all but one instance, severe acute lesions were found in patients in whom the first rejection occurred within two weeks of grafting. Most patients with severe acute rejection failed to show any response to treatment. The few who did respond to treatment showed features of rejection again when the steroid dose was reduced. In six patients the biopsies were interpreted as showing mild changes of rejection. These patients responded to treatment with increased steroids and immunosuppressive drugs, and as a group, had satisfactorily stable renal function. Four biopsy specimens taken at four days, six days, two weeks, and six weeks after transplant were normal. These patients had clinical features which suggested rejection; because the biopsy specimen was normal, three were operated upon and found to have infection related to problems with the ureteric anastomosis. In the remaining patient, renal function recovered after successful treatment of septicemia. The primary histologic lesion in acute rejection showed thrombi in the afferent arterioles and glomerular capillaries and closely resembled those seen in thrombotic thrombocytopenic purpura. Obliterative lesions in interlobular arteries were similar to those of malignant hypertension and seemed to result from organization of mural thrombi. The author has found renal biopsy to be a valuable guide in the clinical management of patients with cadaveric renal homografts.

Author’s address: Dr. Priscilla Kincaid-Smith, Melbourne Hospital, Victoria (Australia).

Extracorporeal perfusion of canine kidneys for periods of 24-72 h were studied. The functional viability of the perfused kidneys was proved by reimplanting them and simultaneously removing the contralateral kidneys. The isolated perfusion circuit consisted of a pulsatile pump adjusted for rate and stroke volume with a membrane oxygenator. A mixture of air and carbon dioxide was used on the gas side of the membrane oxygenator. The temperature was maintained in the range of 8-12°C by means of a refrigerator circuit and a heat exchanger incorporated into the circuit. The perfusate was pooled canine plasma derived from blood collected in acid-citrate-dextrose solution. To each liter of plasma was added 4 mEq of magnesium sulfate, 250 mg of dextrose, 80 units of insulin, 200,000 units of penicillin and 100 mg of hydrocortisone. The perfusate was prefILTERED and was passed through a 0.22 µ millipore filter immediately before use. When 24-h or 72-h perfusion was completed, the dog was reanesthetized and the contralateral kidney was removed. The perfused kidneys was reimplanted. Five of six dogs who underwent 24-h perfusion had only a transient rise in blood urea nitrogen and this returned to normal levels by the 11th or 12th postoperative day. There were no deaths in the group perfused for 72 h (6 dogs). All dogs had a temporary rise in blood urea nitrogen which was somewhat higher than in the 24-h preservation group. Five of the six dogs had normal BUNs by the 5th week. In one animal the BUN was slightly elevated at six weeks. The authors feel that this latter experiment may have been complicated by severe pyelonephritis at the time of initial nephrectomy. Histological examination of the material obtained by open biopsy in the 24- and 72-h animals showed normal renal architecture. The results indicate that the method employed for renal preservation is dependable and inflicts only slight
and reversible cell damage on the kidney. Although lengthier periods of kidney preservation are being studied, 24-72 h seems adequate for preparing human recipients for transplantation and for pretransplant studies of the donor kidney.

Author’s address: Dr. Folkert O. Belzer, Department of Surgery, University of California, Medical Center, San Francisco, Calif. 94122 (USA).

Phagocytosis by polymorphonuclear leukocytes from patients with renal failure

Twelve uremic patients with chronic renal failure from a variety of causes were studied. The morphology and function of their polymorphonuclear leukocytes were compared with those of cells from 17 hospital inpatients with normal renal function. The morphology of the polymorphs were examined by phase contrast microscopy; the phagocytic activity was estimated from the proportion of living cells that were seen to contain test particles. Serum dependent and independent phagocytosis was also examined. The sensitivity of the polymorph preparations to bacterial endotoxin was determined by the concentration of lipopolysaccharide (Salmonella abortus- equi) that would cause a 50% depression of phagocytic activity as compared with controls. Serum-independent phagocytosis was found to be depressed only slightly in the polymorphs from uremic patients, but neither serum dependent phagocytosis nor the capacity of uremic serum to promote phagocytosis (as assessed by complement content) was affected. No difference in effect on phagocytosis was found between ultrafiltrates of serum from uremic patients and from patients not in renal failure. Susceptibility to endotoxin was greater in polymorphs from uremic patients than in cells from control patients, and this, the author feels, is the most significant finding of this investigation. He speculates that this difference in sensitivity to a toxic bacterial product may account for the greater than average susceptibility to acute infection in uremia.

Author’s address: Dr. T.D. Brogan, Welsh National School of Medicine, The Royal Infirmary, Cardiff (England).

Use of a balanced low-protein diet in chronic renal failure

Thirty-four patients with chronic renal insufficiency were instructed to subsist on a 20 g balanced low-protein diet during a 21-month study period. There was a 22% incidence of inability to follow this regimen. Patients who adhered to the diet and had adequate renal function, as judged by urea nitrogen clearance of greater than 1.5 ml/min, experienced improvement in uremic symptoms. Complications of this regimen included hyperkalemia and edema. The duration of remission from uremic symptoms averaged 5.3 months per patient and varied from 2.1 months in the group with a poor result to 8.3 months in the group with a good-excellent result. The duration of response appeared to be dependent on several independent variables which determined the rate of progression of renal disease. These were the severity of edema, the severity of hypertension, the presence of uncontrollable active pyelonephritis, and the presence of active glomerulonephritis. Return of uremic symptoms generally occurred when urea nitrogen clearance decreased below 1.5-1.0 ml/min or when urine volume decreased below 1 1/24 h. The authors conclude that the duration of remission from uremic symptoms depends on prevention of deterioration in renal function and cooperation of the patients in adhering to this special diet.
The killing effect of normal human serum and complement on a susceptible strain of E. coli was studied in the presence of a variety of physico-chemical modifications within the ranges expected in the normal kidney. These physico-chemical changes included the manipulation of sodium chloride concentrations from 24.8 to 404.8 mM per liter; potassium chloride concentrations between 111.3 to 252.5 mM per liter; glucose concentrations ranging from 55.6 to 555.6 mM per liter; urea concentrations ranging from 250.0 to 1000.0 mM per liter; and creatinine between 2.5 to 30.0 mM per liter. Sucrose-induced changes in osmolality ranged from 288.0 to 1020.0 mOsM per liter and pH changes ranged between pH 4.5 to 8.5.

The results obtained indicated to the authors that increased concentrations in sodium and potassium chloride, urea and osmolality as well as changes in pH away from neutrality, interfered with the bactericidal activity of serum against E. coli in the presence of complement. The specific action by which these induced changes in milieu interfered with serum bactericidal activity was not established.

In seven patients with severe hypertension, a natriuresis and diuresis occurred independent of any measured changes in creatinine or paraaminohippurate clearance; seven patients with normal blood pressure or mild hypertension responded to angiotensin by bilateral reductions in sodium excretion, urine flow, glomerular filtration rates, and renal plasma flows.

In four patients with unilateral renal arterial disease, no differential effect of angiotensin was noted, that is, both the contralateral and diseased kidney responded in similar fashion.

Circadian patterns of urinary electrolyte excretion in central nervous system disease were investigated in 8 normal subjects, and in conscious patients with (1) hypothalamic disease (10 patients) without significant endocrinopathy; (2) extrahypothalamic central nervous system disease (6 patients), and (3) pituitary disease (5 patients). All subjects received a diet of known electrolyte composition on which they were maintained for three days prior to study. Normal circadian patterns of urinary electrolyte excretion were observed in all cases of extrahypothalamic central nervous system disease. Abnormal patterns (consisting of phase reversal) were found in 5 of 10 patients with hypothalamic disease. Abnormalities were most marked in the case of potassium excretion. Urinary sodium and chloride excretion patterns tended to concur with those of
potassium excretion but were less consistent. There was no correlation between the abnormalities observed in the circadian pattern of plasma 17-hydroxycorticosteroid levels in patients with hypothalamic disease [Krieger, D. T. and Krieger, H. P., Circadian variation of the plasma 17-hydroxycorticosteroids in central nervous system disease, J. Clin. endocrin. 26: 929 (1966)] and abnormalities in the circadian pattern of urinary electrolyte excretion noted in such patients. The patients with pituitary disease all tended to show flattening of the circadian pattern of urinary electrolyte excretion. The alteration observed in this group was independent of the extent of endocrinopathy present. These findings support the contention that delimited central nervous system disease is associated with abnormal circadian patterns of urinary electrolyte excretion. They offer no explanation as to the mechanism by which CNS regulation of circadian patterns of urinary electrolyte excretion is effected.

Author’s address: Dorothy T. Krieger, Assistant Professor of Medicine, The Mount Sinai School of Medicine, New York, N. Y. (USA).

The Alport syndrome (hereditary nephritis with deafness)
A case record of a 15 year old boy with nephritis and bilateral perception deafness is reported. Investigation of 102 family members revealed the probable existence of an Alport-syndrome in 21 of them. Shortly before his death the reported patient suffered from serious hemoptysis such as occurs in Goodpastures syndrome. Post mortem examination of the lungs showed a picture of hemorrhagic alveolitis that is regarded as typical for this syndrome.

In the patient as well as in his mother hyperlipaemia and hyperbeta-lipo-proteinemia were found, in the absence of a definite nephrotic syndrome. The question is raised whether some etiological significance should be attributed to this elevation of the lipoid fractions in analogy with the role of phospho- and glyco-lipids in Fabry’s disease (Angiokerotoma corporis diffusum).

In the renal biopsy as well as on post mortem examination, the authors found indeed ‘foam cells’, localised not only interstitially but also subintimally in the renal arterioles and glomeruli. The latter localisation is considered to be typical for Fabry’s disease. The finding of star-shaped osmophilic granules in all cell types of the kidney on electron microscopic investigation further supported the suggestion that there might be a pathogenetic relationship between Alport’s and Fabry’s disease.

Author’s address: Dr. J. B. M. J. Trimbos, St. Franciscus Gasthuis, Schiekade 80, Rotterdam (The Netherlands).

‘Disappearance’ of cystinuria in a patient treated with prolonged low methionine diet
A unique patient, in whom the use of a rigorously controlled low methionine diet for 10 years has been associated with the disappearance of his cystinuria, is reported. Ornithine, lysine and arginine continue to appear in the urine in large amounts and renal function remains excellent. Oral loading with methionine promptly resulted in reappearance of large amounts of cystine. Possible explanation for improvement of cystinuria while on a prolonged low methionine diet have been offered. This case confirms the effectiveness of a low methionine diet in selected adult patients and demonstrates that it is a safe long-term therapy for adults.
Letal kidney contraction in a case of glycogen storage disease (type of Gierke) / Tödliche Schrumpfniere bei Glykogenspeicherkrankheit Typ von Gierke


Clinico-pathological description of a uremic case of glycogen storage disease in a 16 year old girl with contracted kidneys and retarded growth. Furthermore the girl showed an increased tendency to hemorrhage, which was explained by a functional lesion of the platelets. The kidney contraction was of the tubular-interstitial type with heavy thickening of the tubular basement membranes. This lesion seems to be the consequence of an increased permeability of the tubular epithelium damaged by extremely severe glycogen storage. Similar cases of kidney damage in glycogen storage disease could not be found in the literature.

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Micrococcaceae from the urinary tract in pregnancy


Gram-positive, catalase positive cocci (Micrococcaceae) were obtained from the bladder by suprapubic aspiration of urine in antenatal and postnatal patients. These bacteria were compared with similar organisms isolated from midstream specimens of urine when the suprapubic specimen was sterile.

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Using the classification of Baird-Parker (1963), 14 (70%) of 20 organisms isolated from the bladder were micrococci and 6 (30%) were staphylococci. In contrast 17 (85%) of 20 similar organisms containing midstream urine specimens were staphylococci and only 3 (15%) were micrococci.

Some factor in the urinary tract acts selectively in favour of micrococci. As with other urinary tract pathogens, infections due to Micrococcaceae may resolve spontaneously, persist asymptotically or result in acute pyelonephritis. Reports of ‘coagulase negative staphylococci’ in midstream specimens of urine cannot be dismissed as contamination.

Reference


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Use of a solid reagent in the triphenyl tetrazolium chloride test for bacteriuria


The triphenyl tetrazolium chloride (T.T.C.) test is a chemical test for significant bacteriuria. In the original procedure, an alkaline solution of T.T.C. is added to 2 ml of urine which is incubated at 37°C for 4 h; a red precipitate then indicates more than 100,000 bacteria per ml urine. In this paper the authors have compared the original test with a modified one employing a solid T.T.C. reagent prepared in disposable marked tubes by British Drug Houses (B.D.H. bacteriuria reagent). In the modified test urine is added to the mark on the tubes which are then incubated and examined as in the original test.
Quantitative bacterial counts and both T.T.C. tests were performed on 462 specimens of urine. 119 contained more than 100,000 organisms per ml. 101 (85%) of these gave a positive result with the modified test and 95 (80%) with the standard test. 297 specimens contained less than 10,000 organisms per ml of which 27 (9%) gave a positive result with the modified test and 24 (8%) with the standard test.

As no laboratory facilities are required to perform the modified test, it is suggested that it may be of particular value in general practice. Some possible reasons for the different results obtained by different users of the T.T.C. test are discussed.

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Sixty children with urolithiasis. Proteus infection of the urinary tract as a cause of urinary calculi, frequently seen in infants


During a period of six and a half years, 60 children with urinary calculi were admitted at the Juliana Hospital for Children, The Hague.

One group of 29 children, mainly infants, were infected by urea-splitting bacteria, 28 B. Proteus and 1 Staphylococcus albus. In 16 of these children urinary calculi resulted from natural infection of a normal urinary tract. In 7 the Proteus infection was a natural complication of a congenital anomaly of the urinary pathways. In 6 children it was an iatrogenic complication of the surgical treatment of an urologic malformation (5 extrophy vesicae, 1 sphinctersclerosis). Many of the patients had multiple calculi in kidney, ureter and bladder, 9 children had staghorn stones in the pyelia. On analysis of the concrements struvite (Mg₃(NH₄)PO₄·6 aq.), often in combination with apatite (Ca₁₀(PO₄)₆(OH)₂) was found. Especially in the patients with normal urinary tracts, surgical treatment combined with intensive and long-term antibacterial therapy has proved to be effective.

The other group of 31 children, mostly aged 5 years or older, showed single concrements of calcium oxalate in pyelum or ureter. This type of stone is the same as found in adults with ‘idiopathic urolithiasis’. These children rarely had a urinary infection, but if they had one, the isolated bacteria turned out to be non-ureolytic (mainly E. coli). In some patients stasis of urine, caused by an urodynamic disorder, resulted in secondary stone formation. Metabolic disorders causing urolithiasis were not seen by the authors in this period.

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Oligo-anuric acute glomerulonephritis. Evolution and prognosis of the surviving patients


Twelve patients are presented with acute glomerulonephritis and anuria or severe oliguria–less than 250 ml/24 h. All were treated for uremia by extracorporeal dialysis. Four patients had a history of previous angina while three developed glomerulonephritis during or after scarlet fever. Five patients died during the acute episode and two within three years.

Five patients survive. Two are completely asymptomatic with normal urine analysis, one after six months and the other after five years. The last two patients have minimal uremia, one is hypertensive, but both are leading normal lives five and six years after their initial episode. The remaining patient, followed for two years, is clinically normal but presents a slight proteinuria. Histological examination by biopsy or at autopsy, demonstrated that an acute glomerulonephritis can exist with the characteristics of the typical post-strepto-coccic lesions and be accompanied
by reversible anuria if the patient is maintained by hemodialysis. Patients without clinical signs
and with normal urine analysis can present glomerular alterations still progressive three years
after the initial episode. An added or previous pyelonephritis will, a long time after the initial
episode, complicate the histologic demonstration of the acute glomerulonephritis responsible for
the clinical picture.

An anuric patient with acute glomerulonephritis should be dialysed at least until a biopsy shows
the type of the glomerular lesion. Even when the lesions are of the type considered irreversible,
new biopsies should be carried out in order to assure the universality of the lesion before
suspending treatment with hemodialysis.

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Summaries – Resúmenes
The renal excretion of hydrogen ion in uric acid stone formers
Renal hydrogen ion excretion was examined in 16 patients with uric acid calculi and in 2 control
groups, the first consisting of 16 patients with calcium oxalate calculi and the second, 11 normal
subjects. It was found that, both under basal conditions as well as during acid loading with
ammonium chloride, patients with uric acid calculi tended to excrete urines of lower pH, lower
ammonium and higher titratable acid than those forming oxalate stones. Not only was there a
decrease in the absolute urine ammonium excretion of the uric acid stone formers but also the
ammonium was low in relation to urine pH. Of 532 random urines tested in the uric acid group,
before acid loading, 87.1% had a pH 5.5 or less, compared to 37.1% of 565 urines measured over
the same pH range in the oxalate group. The defect responsible for the low urine pH and
ammonia excretion in the uric acid group appeared to exert its effect primarily in the basal state
since no difference was found, between the 2 stone-forming groups, in the increases of urine
ammonia or in the decreases in urine pH during acid loading. It is suggested that the tendency of
uric acid stone formers to excrete urines of consistently low pH contributes greatly to the
pathogenesis of their stones. A rational explanation for the efficacy of alkalinization in the
management of patients with uric acid calculi is provided by these findings.

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Citrate metabolism and the mechanism of renal calcification induced by magnesium depletion
By Lifshitz, Fima; Harrison, Helen C.; Bull, Evelyn C. and Harrison, H. E.: Metabolism 16:
345-357 (1967).
The effects of magnesium deficiency in rats on serum, bone and urine citrate concentrations and
the influence of concurrent vitamin D depletion were studied. Our findings are in agreement with
the concept that a fall in serum magnesius stimulates parathyroid hormone output. Elevated
serum calcium and citric acid levels, hypocalciuria. hypophosphatemia and hyperphosphaturia
were found consistently in magnesium-deficient rats. The development of hypercalcemia and
hyperuricemia was prevented by vitamin D deficiency which is in accord with the data
indicating that full expression of parathyroid hormone activity does not occur in the absence of
vitamin D. Citrate excretion was reduced in the magnesium deficient rats. Whatever the
mechanism involved in the reduction of urinary citrate by magnesium deficiency, the sequence
of events favors the precipitation of calcium phosphate in the renal tubules in a manner
resembling that seen in acetazolamide administration (1). Kidney calcinosis was prevented by vitamin D deficiency, by reduction of phosphorus excretion or by increasing urine citrate concentrations. Magnesium deficiency is an additional example of the association of hypocitruria and nephrocalcinosis.

Reference

Book Reviews – Livres nouveaux
Nephrons and Kidneys

L’ouvrage de J. Oliver est le plus beau de sa longue et féconde carrière. A nouveau J. Oliver redresse, par une observation minutieuse, les erreurs répétées depuis des décennies. La technique utilisée et la rigueur de l’observation permettent de donner à la fois une description plus exacte des structures qui constituent le rein et de leur assemblage, en même temps qu’elles éclairent le développement embryologique de cet organe. L’esprit qui a animé la rédaction de ce magnifique ouvrage, un infolio digne de la Grande Epoque, est caractérisé par le désir, en découvrant la vérité, de donner une base à ceux qui ont à charge de comprendre le pathologique, opportunité précieuse au moment où la place occupée par les affection congénitales du rein est sans cesse croissante en Néphrologie. La physiologie bénéficiera tout autant de cette œuvre, l’interprétation des résultats obtenus par microponction dépendant de la connaissance géographique des néphrons. Le tube connecteur, unissant le tube contourné distal et le collecteur, pièce maîtresse dans l’architecture rénale, a-t-il une fonction particulière? telle est l’une des questions que pose immédiatement ce nouveau chef d’œuvre du maître incontesté de la morphologie rénale. G. Richet

Techniques histologiques

L’un des objets de la néphrologie est de tenter d’établir des correlations entre la morphologie et les fonctions. Les «Techniques histologiques» de M. Gabe sont précieuses à cet égard car elles facilitent une meilleure étude des structures cellulaires grâce à la somme de renseignements pratiques et de connaissances que contient cet ouvrage. La rigueur de la description des techniques reflète l’exceptionnelle expérience de l’auteur, proverbiale chez les histologistes. La masse de notions théoriques, logiquement classées et exposées, contribue à la classe de l’ouvrage. Enfin, un style clair, incisif et concis, ainsi qu’un vocabulaire d’une exemplaire simplicité rendent ce livre facilement accessible, même à ceux pour qui la langue française pourrait n’être pas familière. L. Morel-Maroger

Varia
Sixth Conference of the E.D.T.A.
The 6th Conference of the European Dialysis and Transplant Association (E.D. T.A.) will be held from 17th to 19th June 1969 in Berlin (German Democratic Republic) under the presidency of Prof. Dr. H. Dutz, 2nd Medical Clinic, Charité, 104 Berlin, Schumannstrasse 20/21.
The Secretariat of the Congress is: Dr. R. Natusch, 2nd Medical Clinic, Berlin Charité, 104 Berlin, Schumannstrasse 20/21.