Solute excretion in man during changing urine flow, occurring spontaneously and induced by vasopressin injection


(1) In 23 clearance periods with urine flows stable during phosphate infusions in 4 subjects, the mean creatinine to inulin clearance ratio was 1.03 (± SD, 0.08; probability that ratio is unity, 0.1 > p > 0.05).

During 30 instances of spontaneous increases or decreases in urine flow in a variety of experimental circumstances—with and without phosphate infusion, with and without cortisone or hydrocortisone injection, in the morning and afternoon—there were no significant differences between changes in creatinine and inulin concentrations relative to those in the preceding urine samples.

In 2 experiments on each of 3 subjects maintained on a constant water load of 20 ml/kg body weight, changes in osmolal, endogenous creatinine, urea, non-urea solute (osmolal-urea), sodium, potassium, and ammonium concentrations induced by vasopressin injection were compared in successive frequent urine samples during the rapid fall in urine flow: (a) During the decline in urine flow, the increments in osmolality and urea concentrations (and U/P ratios) relative to those in the preceding diuretic periods were smaller than those in creatinine and nonurea solute concentrations (and U/P ratios); urea to creatinine clearance ratios fell transiently to values smaller than those previously reported at similar but steady urine flows, with minimal values attained before maximal creatinine and nonurea solute concentrations (or U/P ratios), (b) Ammonium excretion relative to that of creatinine or nonurea solute also fell, (c) There were no consistent differences between the changes in nonurea solute and creatinine concentrations.

After maximal antidiuresis, the relative changes in urinary concentrations were not consistently different for any solute.

The quantitative and temporal pattern of the changes in urea and ammonium concentrations during the developing antidiuresis is consistent with accumulation in a tubular sink or peritubular pool, probably contributing to the generation of medullary concentration gradients.

Author’s address: S. Thomas, M.D., Department of Physiology, University of Manchester, Manchester (England).

Effects of ethacrynic acid (a new saluretic agent) on renal diluting and concentrating mechanisms. Evidence for site of action in the loop of Henle


The effects of ethacrynic acid, a new orally active diuretic agent, on the renal mechanisms of dilution and concentration were studied. 27 acute experiments were performed on 18 normal human subjects and 2 patients with diabetes insipidus. The experimental conditions included water diuresis and hydropenia with and without superimposed osmotic diuresis.

Ethacrynic acid caused primarily a natriuresis and chloruresis and had a distinct effect on both free water clearance (Ch2o) during maximal water diuresis and tubular reabsorption of solute-
free water (T¼2o) during hydropenia. In maximally hydrated normal subjects and in patients with diabetes insipidus, Ch2o
172
Summaries – Resumes
was significantly decreased as osmolar clearance increased, in contrast to mannitol diuresis. The drug also caused a moderate reduction in glomerular filtration rate and an increase in the excretion of potassium and hydrogen ions.

During hydropenia, T¼2o was markedly decreased at both low and high rates of solute excretion. Hypertonic mannitol or saline diuresis, which in themselves increased T¼2o, when superimposed on a diuresis due to ethacrynic acid, could not raise T¼2o to normal levels. Characteristically, during the peak of diuresis caused by the drug, a virtually isotonic urine was excreted at various levels of solute clearance, and this effect persisted even after the peak of saluresis.

These results differentiate ethacrynic acid qualitatively from other diuretic agents and suggest that an important locus of action is in the ascending limb of the loop of Henle where sodium chloride is reabsorbed in excess of water. This hypothesis would explain the effects of ethacrynic acid on both the renal diluting and concentrating mechanisms and also could account in large part for the type and magnitude of the solute diuresis following administration of the drug.

Authors’ address: M. Goldberg, M.D.; D. K. McCurdy, M.D.; E. L. Foltz, M. D. and L. W. Bluemle, Jr., M.D., 860 Gates Pavilion, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia 4, Pa. (USA).

Studies on conditioned water diuresis in man

The experiments described in the first paper (1) were designed to ascertain whether the human neurohypophyseal system is susceptible to the acquisition of new patterns of reactivity under the influence of controlled experience, that is, whether this neuroendocrine renal regulatory system can participate in a ‘learning’ process.

Normal human subjects maintained on standard schedules of hydration and activity, were conditioned by receiving 750 ml water loads in a stereotyped manner on 5 to 15 occasions. Subsequently, a single 30 ml swallow produced a phasic diuresis lasting 40 to 80 min in all subjects. Identical 30 ml swallows taken in control experiments before conditioning had no such effect, being followed by a pattern of decreasing urine flow rates.

The conditioned diuresis was similar to standard water diuresis in composition. Analysis of urinary composition showed an addition of free water to the urine without significant alteration in electrolyte and creatinine excretion. The evidence implicating neurogenic suppression of antidiuretic hormone release from the neurohypophysis as the efferent mechanism for this diuresis is critically discussed.

A second paper (2) described a number of factors found to influence the magnitude and the timing of conditioned diuretic responses. The particular environment which had been used for conditioning as well as the customary time of day were factors necessary for elicitation of the response after conditioning. The regular conditioning procedure led to diminished magnitude of response when continued for more than 15 to 20 sessions and anticipatory conditioned responses rarely occurred under schedules of regular reinforcement with large water loads. However, when the subjects became aroused during the experiments, or when schedules of reinforcement were intermittent, anticipatory responses occurred predictably. Simple conditioned responses were similarly augmented by these factors. Urine flows as high as 7.9 ml/min for seated subjects and
12.3 ml/min for supine subjects were recorded after altered schedules of conditioning. Subjective perception of affective arousal was not necessary for augmented response magnitude to occur under the altered conditioning schedules.

The urinary composition of responses augmented by arousal or intermittent schedules of reinforcement showed marked increases in free water excretion without alteration of excretory rates for electrolytes or creatinine. The mechanism appeared to be that of a further reduction in circulating ADH levels, presumably secondary to neurogenic suppression of ADH release from the neurohypophysis.

The evidence suggests that mechanisms exist whereby the human neurohypophysis may acquire the potentiality of responding to previously neutral stimuli with decreased release of ADH. The conditioned water diuresis appears subject to augmentation or inhibition by alterations in the subject’s environment, his state of arousal and the pattern of recent experimental routine.

References


Author’s address: M. A. Hofer, M.D., Department of Psychiatry, Columbia-Presbyterian Medical Center, 722 W. 68th Street, New York, N. Y. (USA).

The renal clearance of citrate in man


Because of the paucity of data in man concerning the renal clearance of citrate, citrate and creatinine chromogen clearances were simultaneously determined in 10 normal subjects and in 8 patients with proved hyperparathyroidism prior to and after surgical correction. The hyperparathyroid patients were hypercalcicuric and had recurrent renal stones but were free of infection at the time of this study. Similar determinations were performed repeatedly in 9 patients with idiopathic renal stones without urinary tract infection and in 10 hyperparathyroid patients before specific therapy, to further evaluate the relationship between renal stones, parathyroid hormone and the clearance of citrate in man. No differences in plasma citrate levels were found between these 4 groups of patients. Citrate clearances expressed per 100 ml of GFR were similar in the normal and idiopathic stone forming group. The mean citrate clearance was slightly lower in the hyperparathyroid patient group preoperatively. Citrate clearances were low in the hypopara-thyroid patients and fell to similar significantly low levels postoperatively in the cured hyperparathyroid group. In 5 normal patients parathyroid extract administration did not alter plasma levels or citrate clearances, despite exhibition of its other typical biochemical effects. These data indicate that citrate clearance can vary independently of the plasma levels of citrate in man and suggest that endogenous parathyroid hormone exerts an effect on citrate excretion at the renal level. In addition the data suggest that stone formation in the hypercalciuric state of hyperparathyroidism and in the idiopathic stone forming group is not due to any absolute decrease in citrate excretion.

Authors’ address: J. J, Canary, M.D.; C. R. Meloni, M.D.; D. Clive, M.D. and E. Crossman, M.D. Department of Medicine, Georgetown University School of Medicine, Washington D.C. (USA).
Physiologic responses associated with steroid-induced diuresis in the nephrotic syndrome

The physiologic changes during development of steroid-induced diuresis were examined in 15 nephrotic children to determine the relationship between urinary aldosterone excretion and other responses. The earliest alterations occurred before diuresis and consisted of progressive decrements in urinary excretion of protein and aldosterone. In contrast, levels of serum albumin, determined immuno-chemically, and of serum colloid osmotic pressure were not significantly altered until diuresis had begun (Fig. 1). Plasma volume measurements, performed in a limited number of subjects, did not change consistently. The data are consistent with the interpretation that changes in aldosterone excretion during diuresis in the nephrotic syndrome are independent of serum albumin levels and, perhaps, of total circulating albumin. The findings suggest that excretion of edema fluid in this disease may be more significantly related to declining levels of aldosterone than to changes in serum albumin concentrations, serum colloid osmotic pressure, or total circulating albumin.

Author’s address: W. J. Oliver, M.D., Department of Pediatrics and Communicable Diseases, The University of Michigan Medical Center, Ann Arbor, Mich. (USA).

Glomerular lesions in the nephrotic syndrome and their relation to cortisone therapy
Lesions resembling diabetic nodular glomerulosclerosis have been noted in children with lipoid nephrosis treated with cortisone. These changes were present in fifteen of twenty-six of the reviewed cases of nephrosis with cortisone therapy. They were found to a lesser degree in cases of nephrotic syndrome without steroid treatment, but were absent in cases due to renal abnormality without glomerular changes. No comparable lesions were seen in children treated with cortisone for reasons other than renal disease. No correlations with duration of therapy, cholesterol level, hypertension, or glycosuria have been noted.

This nodular lesion is analogous with a cortisone-induced lesion in rabbits. The lesion also resembles diabetic glomerulosclerosis, but is more frequently proximal in the tuft and more pronounced in the juxtamedullary glomeruli.

Discrete hyaline ‘drops’ were noted at the base of the glomerular tuft adjacent to the afferent arteriole or in Bowman’s capsule. This lesion was seen both in treated nephrosis and in children treated with steroids for reasons other than renal disease.

Authors’ address: E. H. Oppenheimer, M.D. and J. R. Esterly, M.D., The Johns Hopkins University School of Medicine, Baltimore, Md. (USA).

Normocholesterolemic nephrotic syndrome of systemic lupus erythematosus


Although hypercholesterolemia is so often associated with the nephrotic syndrome that it has been included in most definitions of this complex state, when nephrosis is associated with systemic lupus erythematosus the serum cholesterol level may be normal.

Among 18 patients with systemic lupus erythematosus and the nephrotic syndrome, 5 had the normocholesterolemic variant. Serum cholesterol levels were normal at the height of nephrosis, when serum albumin was at its nadir; in the cases in which complete low density lipoproteins were analyzed, these values also were normal.

Patients with systemic lupus erythematosus and normocholesterolemic nephrotic syndrome (mean cholesterol level, 176 mg/100 ml) were compared with patients having systemic lupus erythematosus and hypercholesterolemic nephrotic syndrome (mean cholesterol level, 435 mg/100 ml). Those in the normocholesterolemic group were older, and had a slightly higher incidence of azotemia. The average serum albumin level was identical in the two groups, and the incidence of hypertension was similar. The prognosis in those with normocholesterolemic nephrotic syndrome was more grave than in those with hypercholesterolemic nephrotic syndrome; most patients in the former group died within 4 months, whereas more than half of the patients with hypercholesterolemic nephrotic syndrome were alive after one year. Renal failure was the major cause of death in both groups.

The average serum cholesterol in lupus nephrosis, including the hypercholesterolemic variant, was lower than in the nephrotic syndrome due to other causes. Thus the serum cholesterol level may be of diagnostic value in the occasional patient in whom the nephrotic syndrome is the sole manifestation of systemic lupus erythematosus.

176

Summaries – Resumes

Since normocholesterolemic nephrotic syndrome fits all criteria consistent with the nephrotic syndrome, it is suggested that the term ‘pseudonephrotic syndrome’ be dropped and that the variant be referred to as ‘normocholesterolemic nephrotic syndrome’.

Author’s address: M. A. Shearn, M.D., Kaiser Foundation Hospital, 280 W. MacArthur Blvd., Oakland 11, Calif. (USA).
An electron microscopic study of tubular lesions in human kidney biopsy specimens
A survey of the fine structural changes seen in the renal tubular epithelium in 122 specimens
from individuals with various types of acute and chronic renal disease has been presented.
Acutely injured cells were marked by a diminution or loss of microvilli, an increase in
cytoplasmic transport vesicles, mitochondrial swelling, and by the presence of cytoplasmic lipid
droplets. Altered reabsorption of protein and lipid, encountered especially in nephrosis, was
manifested by the accumulation of protein-like material and lipid, respectively or jointly, within
the cytoplasmic transport vesicles in the proximal convoluted tubules. Accumulation of lipid in
macrophages in the interstitial tissue was also observed in nephrosis.
In chronic, severe renal disease atrophic tubules were found to have either collapsed or dilated
lumens. The atrophic cells exhibited reduction in the total amount of cytoplasm and organelles;
microvilli were reduced in size and number. These changes were accompanied by thickening of
the basement membrane, cytoplasmic lipid droplets and an increased amount of peritubular
fibrous tissue. Various degrees of detachment and desquamation of the tubular epithelial cells
were noted in the loops of Henle and distal convoluted tubules. Migration of leukocytes through
the tubular epithelium between adjacent cells occurred in some severely injured tubules.
Early stages of cast formation were evidenced by fine granular debris and degenerating
fragments of cellular organelles, leukocytes and epithelial cells filling tubule lumens. In later
stages, dilated tubules were lined by atrophic cells and casts were composed almost entirely of
granular or amorphous material.
Authors’ address: J. B. Flume, M.D.; C. T. Ashworth, M.D. and J.A. James, M.D., Department
of Pathology, The University of Texas, Southwestern Medical School, Dallas, Tex. (USA).

Further observations on the renal production of acid in uremia
In a previous study, it appeared that the lesser excretion of ‘net proton’ by uremic patients, when
compared with non-nephritic controls on the same diet and the same load of phosphoric acid,
might have been due to their excessive excretion of K+ (a consequence of the development of
more excessive tissue acidity). Since there was no significant difference between the 2 groups in
the renal reclamation of Na+ it seemed that the potassium effect might be attributed to more
competition (K+ versus H+) in the exchange for Na+ by the uremic kidneys; as an alternative the
effect could be explained by assuming the excretion of K+ as KHCO3 in the
Summaries – Resumes
177
distal tubule–with resulting neutralization of part of the liberated acid. In the present study
uremic patients and normal controls have been studied during a period of several days on a
controlled acid-producing diet, but without acid loading. Our results show no significant
difference between the 2 groups in excretion of either K+ or net proton. Replacement of plasma
HCO3 by H2PO4 + SCXi” seemed to offer the best explanation for the acidosis. A few
observations were also made on the influence of a small dose of KC2H3O2 which was
administered to each subject during the course of his study–no augmentation in the reclamation
of Na+ was noticed.
Authors’ address: A. P. Briggs, M.D.; T. Findley, M.D. and W.S. Harms, M.D., Department of
Biochemistry, Medica College of Georgia, Augusta, Ga. (USA).

Nephrotic syndrome associated with penicillamine therapy of Wilson’s disease

A case of the nephrotic syndrome and focal glomerulonephritis demonstrated by renal biopsy is described in a forty-one year old woman with Wilson’s disease of four years’ duration who was treated with DL-penicillamine for eight months. Th[e renal disease and other manifestations of hypersensitivity were associated with penicillamine therapy. This case affords good evidence to support the concept that the nephrotic syndrome and focal glomerulonephritis may be caused by hypersensitive mechanisms. The clinical manifestations of the renal disease responded to withdrawal of the drug and administration of prednisone in high dosage.

Authors’ address: Dr. Donald A. Adams, Ralph Goldman, Morton H. Maxwell and Harrison Latta, Departments of Medicine and Pathology, University of California School of Medicine, Los Angeles, Calif, (USA).

The use of potentially nephrotoxic antibiotics in the treatment of gram-negative infections in uremic patients


In uremic patients infection with gram-negative organisms, chiefly Escherichia coli, Aerobacter aerogenes, B. proteus, or Pseudomonas aeruginosa causes a serious and often fatal complication (1). Potentially useful antibiotics such as kanamycin, polymyxin B, or colistin, have been shown to be nephrotoxic when given in full dosage (2). However, recent evidence (3) has provided a theoretical basis for the use of these effective antibiotics on a reduced dosage program in patients with preexistent renal disease.

The present communication reports on the therapy of 12 uremic patients who were infected with gram-negative organisms that were sensitive only to kanamycin, polymyxin B, or colistin. To avoid time lapse, antibiotic therapy was initiated immediately after blood cultures were drawn. Kanamycin, polymyxin B or colistin were administered according to the following programs: oliguric patients received a loading dose of 1 g of kanamycin or 100 to 150 mg of polymyxin B, or colistin (in divided doses) by the intramuscular route, followed by injections of one-half the loading dose at intervals of 2 to 4 days. Patients recovering from the oliguric phase of acute tubular necrosis, or uremic patients whose glomerular filtration rate was estimated to be greater than 10 ml/min, received the same loading dose, and subsequent doses of one-half of the loading dose at intervals of 1 to 2 days.

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Fig. The clinical course of a 48-year-old white female who developed acute renal failure after a transfusion of mismatched blood. Kanamycin and polymyxin B were given during the early diuretic phase for treatment of an E. coli bacteremia and urinary tract infection with this organism and A. aerogenes and Ps. aeruginosa.

All but one of the 12 patients survived both infection and therapy. In seven patients, renal function returned to normal after acute renal failure. In another, progressive necrotizing papillitis was arrested. In three patients renal functional impairment remained stationary. The one individual who died had inexorable renal failure despite cure of infection.

Since the original study was published, 5 of 6 additional patients with acute renal failure and gram-negative infection have been treated successfully.

References

Reversal of early graft rejection after renal heterotransplantation in man

The transplantation group at Tulane University in New Orleans has undertaken an exploration of clinical heterotransplantation, using kidneys from non-human primates. This investigation was prompted, in part, by a shortage of suitable human donor organs. Furthermore, this group doubted that the pessimism surrounding heterotransplantation, derived largely from skin grafting studies among widely disparate species, was applicable to the problem of renal heterografting among primates, including man. It was their basic conjecture that kidneys from non-human primates closely related to man might respond similarly to human organs.

In their early case, a 43-year-old man in terminal uremia received a renal transplant from a chimpanzee. The grafted kidneys began functioning immediately but four days later threatened rejection occurred. This was reversed following increased doses of immunosuppressive drugs and radiotherapy. A milder episode of threatened rejection occurring in the fourth week was also reversed. Tests demonstrated function of both transplanted kidneys without evidence of function of the patient’s own kidneys. As the patient entered his sixth posttransplantation week he was ambulatory, eating an unrestricted diet, had normal urinary volume and content, and normal blood urea nitrogen and serum creatinine levels. Two months following the heterotransplantation, the patient died with pneumonia. The transplanted kidneys showed no evidence of rejection.

In subsequent cases also infection has proved to be a serious problem. One patient, however, lived nine months after renal heterotransplantation.

Authors’ address: K. Reemtsma, M.D.; B. H. McCracken, M.D.; J. U. Schlegel, M.D.; M. A. Pearl, M.D.; C W. De Witt, M.D. and O. Creech, Jr., M.D., Department of Surgery, Tulane University School of Medicine, 1430 Tulane Avenue, New Orleans, La. (USA).

180

Summaries – Resumes
Infraglomerular epithelial reflux. An early lesion of acute renal failure

Infraglomerular epithelial reflux consists of the detachment and upward displacement of epithelium of the uppermost part of the proximal convoluted tubule. The displaced pyknotic cells occupy part of the urinary space of Bowman’s capsule where they form spectacular aggregations (Fig. 1). Reflux was found in unselected kidney sections of 15 of 109 consecutive human autopsies. In six of the seven adequately documented cases there was clinical evidence of terminal renal ischaemia or oliguria. It is concluded that the lesion represents an early manifestation of acute renal failure.

Earlier studies on rats (Waugh, D. and Beschel, H. Infraglomerular epithelial reflux in the evolution of serotonin nephropathy in rats. Amer. J. Path. 39: 547-560 [1961]) have indicated that the reflux lesion is a transient phenomenon probably of no more than six hours duration. This short duration is attributed to the flushing of the upper nephron by the re-establishment of glomerular filtration. The failure of earlier studies of renal failure to note the lesion can be
explained by the fact that reflux has probably disappeared by the time renal failure has become clinically obvious.


Fig. 1 (Case 15). Infraglomerular epithelial reflux in a 49 year old diabetic who died in cardiac failure with terminal hypotension. Refluxed tubule epithelium with pyknotic nuclei occupies the left third of Bowman’s space and is continuous with partly detached epithelium of the adjacent proximal tubule. Hemalum, phloxin, and saffran stain; × 244.

Authors’ address: D. Waugh, M.D.; W. Schlieter, M.D. and A.W. James, M.D., Department of Pathology, Dalhousie University, Halifax, Nova Scotia (Canada).

181

Macroglobulinemic nephropathy. Acute renal failure in macroglobulinemia of Waldenstrom

The close relationship between myeloma and Waldenstrom’s macroglobulinemia has been demonstrated on biochemical, clinical and anatomic grounds. This has also been reflected in certain similarities of the renal manifestations in both diseases (1). In contrast to myeloma, however, macroglobulinemia is usually not a cause of major renal complications.

The present study involves the first recorded instance of fatal, acute renal failure in Waldenstrom’s disease. This complication followed a state of severe dehydration and resulted in a rapidly progressive uremia and death. The anatomic lesions associated with the acute renal failure consisted of deposition of dense, eosinophilic substances in the glomerular capillaries (Fig. 1). Occasional giant cells
were also noted in the periphery of glomeruli. The histochemical studies were applied to gain an understanding of the composition of these intracapillary deposits. The reactions were negative for fibrin and other thrombus elements, lipids, R.N.A. or D.N.A. substances and amyloid. The deposits were non-argyrophilic and did not stain with alcian blue or basic dyes. They showed an intense periodic acid-Schiff reaction. The staining of the electrophoretic strip also revealed an identical reaction in the abnormal globulin boundary. These studies suggested that the intracapillary deposits were composed essentially of the abnormal proteins detected on filter paper electrophoresis of serum.

It is known that the high degrees of plasma viscosity in Waldenstrom’s disease may impede the capillary circulation. The dehydration affects a higher concentration of plasma proteins, and thus a more viscous plasma. In the glomerular capillaries filtration takes place and the paraproteins are even more concentrated.

182

Summaries – Resumes
The plasma viscosity is further increased and the glomerular circulation further compromised. It is suggested that the effects of severe dehydration in Waldenstrom’s disease may lead to deposition of paraproteins in the glomerular capillaries and result in acute failure of kidneys which have already been affected by macro-globulinemia.

Reference

Addendum
Since the publication of this article, two additional cases of macroglobulinemia with similar renal lesions have been observed by the authors.

Authors’ addresses: I. Argani, M.D., Fordham Hospital, Bronx, New York, N.Y. (USA) and G. F. Kipkie, M.D., Queen’s University, Kingston, Ont. (Canada).


(1) A brief survey is given of the side effects, especially polyneuritis, occurring after Furadantin therapy in urinary-tract infections. With the two patients described in the present paper, a total of 33 cases of Furadantin-induced polyneuritis are on record. The Eaton Laboratories, Norwich,
N.Y., know of 14 additional cases reported to them by personal communications. Pharmacia, Denmark, and the author are similarly aware of a few other unpublished cases. The polyneuritis is attributable to a toxic or, possibly, allergic effect of the drug, with degeneration of the myelin sheaths developing after long-continued treatment, and especially in patients with impaired renal function, in whom the injury may be of rapid onset. The manifestations consist of slight distal sensory disturbances which gradually increase in severity, abolished reflexes and loss of motor units followed by pronounced muscular wasting and ending in a completely disabling condition. (2) Two cases of typical polyneuritis after Furadantin therapy are described. A man, aged 76, with cystitis arisen after prostatectomy but with normal renal function, received a total dose of 363 g Furadantin during a period of 3 ½ years. After the lapse of 2½ years typical severe symmetrical polyneuritis with paralysis of the radial, ulnar, median and peroneal nerves developed. Typical hypoesthesia was present, and pronounced muscular wasting in the distal parts of the limbs developed. Electromyographic studies showed delayed conduction in the muscles of the forearms and nearly abolished conduction in the muscles of the lower legs. A muscle-biopsy specimen showed degenerative changes as in neurogenic affection. Treatment with vitamin-B preparations and electrostimulation therapy (‘Myotensor’) for 9 months resulted in some improvement in the condition, especially as far as the hands were concerned, but the gait remained greatly impaired. The condition must be regarded as grossly disabling. In a woman, aged 55, with pyelonephritis (‘tablet kidneys’) and greatly impaired renal function, moderately severe polyneuritis developed after four short periods with Furadantin therapy (total dose 11.2 g). Treatment with vitamin-B preparations and electrostimulation (‘Myotensor’) for several months resulted in considerable improvement in the condition. The author warns against prolonged Furadantin therapy. Caution should be exercised in administering the drug to patients with impaired renal function; in the presence of severe renal insufficiency Furadantin should not be attempted at all. Dosage schedules used by Norwegian and Swedish investigators are mentioned; these are somewhat lower than that stated by the licensee (Pharmacia, Denmark) and seem to be less hazardous. In view of the very common use of Furadantin in the treatment of urinary-tract infections and the relatively small number of published cases of polyneuritis after this therapy, it must be assumed that the above-mentioned rules have largely been adhered to. However, in our experience, it is likely that some mild to moderately severe cases have passed unnoticed. Author’s address: E. Roelsen, M.D., Department of Internal Medicine, The Central Hospital, Silkeborg (Denmark). Use of the rapid sequence intravenous pyelogram in the diagnosis of reno-vascular hypertension By Maxwell, M.H.; Gonick, H.C.; Wiita, R. and Kaufman, J.J.: New Engl. J. Med. 270: 213-220 (1964). A new technic of rapid-sequence intravenous pyelography is described and evaluated as a screening procedure for the diagnosis of renovascular hypertension. In 121 patients with and without diastolic hypertension but free of renal-artery disease it was established that the ‘appearance time’ of injected contrast medium is equal in both kidneys and generally occurs 2 or 3 minutes after injection. Abnormalities in the rapid-sequence pyelogram
were noted in 39 of 42 patients with renovascular hypertension. A discrepancy in appearance
time was the most frequently seen abnormality.
The rapid-sequence pyelogram compares favorably with the radioisotope renogram and
individual kidney-function tests as a screening procedure for renovascular hypertension.
Authors’ address: M. H. Maxwell, M.D.; H. C. Gonick, M.D.; R. Wiita, M.D. and J. J. Kaufman,
M.D., University of California, Department of Medicine, School of Medicine, Los Angeles,
Calif. (USA).
Renal artery stenosis without renal ischaemia
By Lawrence, J.R.; Doig, A.; Knight, I.C.S.; MacLaren, I.F. and Donald, K.W.: Lancet /: 62-65
(1964).
In the separate kidneys of 20 hypertensive patients with renal artery stenosis measurements were
made of glomerular filtration rate, renal plasma flow and electrolyte excretion using a
modification of the method described by Stamey et al. (1961).
The results are classified into 4 main groups according to the changes in the ischaemic kidney
resulting from the relative increase in the tubular reabsorption of sodium and water: (I) absence
of a functional pattern of ischaemia; the sodium
184
Summaries – Resumes
excretion (or rejection) fraction in the kidney with the arterial lesion did not differ significantly
from that in the contralateral organ; (II) presence of a pattern suggesting mild ischaemia; in this
group the sodium excretion fraction in the kidney with the arterial lesion was reduced by 13-25%;
(III) presence of the pattern of moderate to severe ischaemia; in the kidney showing the
abnormal pattern the reductions in sodium excretion fraction ranged from 35-95% ; and (IV)
complete unilateral loss of renal function.
These patterns are shown to correlate with the degree of obliteration of the renal arterial lumen
and, to a lesser extent, with reductions in renal plasma flow. A surprising finding was the
proportion of patients (one third) in whom the functional pattern of unilateral renal ischaemia
was absent despite unequivocal radiological evidence of renal artery stenosis. In these cases the
reduction in the diameter of the lumen of the renal artery did not exceed 50%. The occurrence of
‘false’ negative results in radio-isotope renograms and divided renal function tests is also noted
in these patients.
Reference
Stamey, T.A.; Nudelman, I.J.; Good, P.H.; Schwentker, F.N. and Hendricks, F.: Functional
Authors’ address: J. R. Lawrence; A. Doig; I. C. S. Knight; I. F. MacLaren and KΛV. Donald,
Departments of Medicine and Clinical Surgery, University of Edinburgh and the Royal
Infirmary, Edinburgh (Scotland).
Functional differences between the two kidneys in normal and hypertensive man
By Hulet, W.H.
Knowledge of the functional capacity of the individual kidneys in hypertensive man is of clinical
importance since such information may be valuable in the diagnosis of curable hypertension
secondary to unilateral disease of the renal artery or its branches. The first study (1) served to
establish the range of functional difference between the two kidneys in normal subjects.
Hemodynamics, maximal tubular excretory capacity for / >-aminohippurate and sodium, solute
and water excretion of the individual kidneys were comparable in normal man. On the basis of
this study, subsequent observations in hypertensive subjects were judged abnormal when
functional differences exceeded 15%. In a series of observations on patients with essential hypertension (2), ureteral catheterization studies were conducted during basal conditions of moderate hydropenia. Differences between the two kidneys in excess of 15% were uncommon, and, with one exception, all 13 patients were considered to have equal function. The results of this study indicated that gross differences in filtration rate, plasma flow, and water and electrolyte excretion between the two kidneys are rare in uncomplicated essential hypertension, and therefore, provided a more secure basis for the use of catheterization studies in the diagnosis of hypertension of unilateral renal origin. Our recent report (3) demonstrated a pattern of functional difference found in hypertensive patients with unilateral renal artery stenosis who were successfully treated by nephrectomy. In these patients the affected kidney was characterized by a marked decrease in the excretion of total solute, sodium, potassium, and water far out of proportion to the decrease in filtration rate. In contrast to the excessive reabsorption of sodium and potassium, the excretion of ammonia was increased in the diseased kidney.

Summaries – Resumes

185

This latter phenomenon may have been the consequence of insufficient sodium delivered to the distal nephron for ion exchange. It was suggested that the determination of ammonia and other components of hydrogen ion excretion in urine from each kidney in patients suspected to have unilateral renal artery stenosis might be a useful diagnostic measurement when combined with the information obtained from the analysis of sodium excretion and renal arteriography. The usefulness of catheterization studies in the identification of patients with surgically correctable renal lesions responsible for hypertension depends to a great extent on precise measurement of urine flow during a steady state, comparison of excretion rates to filtered load, and consideration of the influence of total solute excretion on the concentrations of various substances in the urine. Functional evaluation of the individual kidneys and renal arteriography should be considered as complementary and inseparable procedures.

References


Author’s address: Dr. W. H Hulet, Medical Service, Veterans Administration Hospital, Department of Medicine, Coral Gables, Fla. (USA).

The role of percutaneous renal biopsy in the evaluation of arterial and par-enchymal disease of the kidney in the hypertensive patient

By Roland, A.S.

More than thirteen years have now passed since the first systematic study of percutaneous renal biopsy in man by Iversen and Brun. Since then, many thousands of biopsies have been reported. The clinical indications and contraindications have gradually been established. It was initially thought that the presence of hypertension so increased the hazard of gross hematuria or perirenal hematoma following biopsy, that the procedure was contraindicated in the hypertensive patient.
However, during the past five years there has been a renewal of interest in the relation between hypertension and the kidney. This has led to a re-evaluation of the safety and usefulness of renal biopsy in the study of the hypertensive patient. It has been shown that the incidence of post-biopsy bleeding is increased in the presence of hypertension. More important, however, was the demonstration that this increased risk may be substantially reduced by pharmacologic reduction of blood pressure prior to biopsy. Percutaneous biopsy may be of value in the study of both renal parenchymal and renal vascular disease in the hypertensive patient. During the past several years, due largely to advances in vascular reconstructive surgery, there has been considerable interest in the relationship between stenotic lesions of the renal arteries and human hypertension (1). Unfortunately, surgical correction is curative.
in not more than 40-60% of patients. Presumably then, there exist renal arterial stenoses which are not hemodynamically significant and which do not produce a Goldblatt kidney. It is well known that atherosclerotic stenosis of one or both renal arteries may be found at postmortem examination in patients who were never hypertensive. We must conclude, therefore, that a reliable method is necessary, whereby it can be determined whether a given renal arterial lesion (demonstrated by arteriography) is a significant lesion, i.e., whether it is actually giving rise to hypertension. Renal biopsy may be of considerable value by the demonstration of: (1) hyperplasia or hypergranularity of the juxtaglomerular cells on the side of the lesion, with a
decrease on the contralateral side, (2) ‘ischemic’ atrophy of the proximal convoluted tubules on
the side of arterial stenosis, (3) a difference between the kidneys in the severity of
arteriosclerosis (the renal vasculature on the side of a significant stenosis is ‘protected’ from the
effects of systemic hypertension), (4) a difference in the 'kidney pulse' tracing between the two
kidneys, and (5) the status of the contralateral kidney.

There has been so much recent emphasis on renal arterial lesions that there is a tendency to
overlook the fact that parenchymal disease of the kidney is a statistically more common cause of
hypertension (2). Failure to recognize renal parenchymal disease is unlikely to occur when the
history, urinalysis or intravenous pyelogram strongly suggests the presence of underlying
pyelonephritis or glomerulonephritis. However, in a number of patients no such obvious clues
are available, and the patient is thought to have essential hypertension.

Recently, a group of 70 hypertensive patients was studied at a university hospital to rule out
underlying primary renal disease and other possible causes of hypertension. Percutaneous renal
biopsies were performed in this selected group. Thirty-nine percent were found to have
unsuspected chronic pyelonephritis or glomerulonephritis (Figs. 1 and 2). Of those patients under
30 years of age (20), 65% had unsuspected primary renal disease, which may have played an
etiologic role in the development of hypertension.

Only 23% of patients with histologically diagnosed pyelonephritis had bacterial confirmation of their diagnosis (positive pre- or postbiopsy urine or biopsy needle cultures). Pyuria was also an unreliable indication of pyelonephritis, being present in only one-half of these patients.

It was concluded that percutaneous renal biopsy was the most reliable, currently available
technique for identifying patients with clinically silent primary renal disease and separating this
group from those with essential hypertension.

In summary, percutaneous renal biopsy may be performed safely in the hypertensive patient,
providing blood pressure is first reduced to near normal levels. It is of considerable value in the
study of suspected renal arterial disease and in the identification of patients with unsuspected
renal parenchymal disease. Renal biopsy would appear to be a valuable procedure in the study of
selected hypertensive patients.

Fig. 1. Chronic proliferative glomerulonephritis, showing thickening and splitting
of capillary basement membrane, hyalinized lobules, and capsular adhesions
adjacent to fibrous crescent. (Hematoxylin and eosin; × 375.)

Fig. 2. Chronic pyelonephritis, showing capsular fibrosis, collapse and early
hyalinization of glomerular tufts, and a dense interstitial infiltrate of lymphocytes
and plasma cells. (Hematoxylin and eosin; × 325.)

Roland, A.S. and Dimond, E.G.: The value of percutaneous renal biopsy in the hypertensive


Author’s address: Dr. Arnold S. Roland, 2290 Sixth Avenue, San Diego, Calif. 92101. (USA).

By Jick, H.; Snyder, J.G.; Finkelstein, E.M.; Cohen, J.L.; Moore, E.W. and Morrison, R.S.: J.
The effects of methyl prednisolone on maximum water conservation, sodium and potassium excretion and G.F.R. were measured. In three patients who received the drug orally for a period of eight days there was a substantial increase in maximal concentrating ability (Umax) and maximum negative free water clearance (Tm%). No consistent effect on G.F.R. was noted. Eight hydropenic patients received methyl prednisolone intravenously only, during a steady state of osmotic diuresis induced by mannitol. A small but highly reproducible rise in Tm¾o (+ 0.6 ± 0.07 ml/min fl S.E.) occurred within two hours. Concomitantly sodium excretion consistently fell (– 86 ± 32 mEq/ml). There were no consistent changes in potassium excretion or G.F.R.

The data are interpreted to indicate that the primary effect of this agent is to increase sodium reabsorption in the ascending limb of Henle’s loop. By enhancing delivery of more sodium to the medullary interstitium, the hormone contributes to the reabsorption of more solute free water from the collecting duct in the presence of a maximal antidiuretic hormone stimulus. An action in this portion of the tubule could also explain the increase in free water clearance previously reported in maximally hydrated subjects who were given glucocorticoids.


Evidence against a single renal transport defect in cystinuria

Cystinuria is generally thought to be due to a defect in a single renal tubular re-absorptive mechanism shared by cystine, lysine, arginine, and ornithine. However, this hypothesis is not supported by direct in vitro studies of amino acid transport in rat kidney cortex slices (1) which indicate that cystine does not share such a transport pathway with the dibasic amino acids.

Further investigations regarding the pathogenesis of cystinuria were carried out by measuring amino acid transport directly in human kidney cortex slices obtained at surgery from seven control subjects and three patients with cystinuria. These slices were incubated for 30-90 min with labelled cystine, lysine, or arginine at concentrations varying from 0.01 mM to 1.2 mM, and the intracellular accumulation of these amino acids was measured by methods previously described (2). Kidney slices from patients with cystinuria demonstrated a 50% reduction in the ability to accumulate lysine.

In summary, kidney slices from patients with cystinuria accumulated cystine normally, but were markedly impaired in their ability to accumulate lysine, and arginine. In control and cystinuric tissue, lysine, arginine, and ornithine competed for a common renal transport mechanism that was not shared by cystine. These studies suggest that in cystinuria a single defective tubular transport mechanism may be responsible for the increased urinary excretion of lysine, arginine, and ornithine, but not of cystine.

References

189


Authors’ address: M. Fox, M.D.; S. Thier, M.D.; L. Rosenberg, M.D.; W. Kiser, M.D. and S. Segal, M.D., Department of Medicine, San Francisco Medical Center, University of California, San Francisco, Calif. (USA).

Treatment of the adult Fanconi syndrome with oral phosphate supplements and alkali. Report of two cases associated with nephrolithiasis


Two patients with the adult Fanconi syndrome are described in which no underlying cause was found and in which there was the unusual added feature of renal calculi. Both patients had osteomalacia (with onset at age 42 and 65), hypophosphatemia, glucosuria, gross aminoaciduria, proteinuria consisting largely of alpha 2 and beta globulin, systemic acidosis and hypouricemia. Renal biopsy showed diminished numbers of proximal convoluted tubules. The diurnal variation in serum phosphorus level was absent in both cases while the diurnal variation in urinary phosphorus was absent in one. The response to calcium infusion was abnormal in both cases. There appeared to be a normal response to parathyroid extract administration. Dietary phosphorus deprivation resulted in a less than normal decrease in urinary excretion of phosphorus. The response to oral and intravenous phosphate loading was abnormal in both patients. Nephrolithiasis was not associated with decreased urinary citrate but may have been related to the presence of hypercalciuria and of urinary tract infection in these cases. Both patients were treated with large supplements of phosphate by mouth in the form of an isotonic neutral solution of disodium phosphate and sodium acid phosphate. In addition they were given alkalis but not vitamin D. On this regimen, serum phosphorus levels are maintained within the normal range for most of the day and there was prompt relief of symptoms. There was rapid radiologic evidence of bone healing in the first case. In the second patient, who did not take his medication regularly, histologic evidence of osteomalacia is still present, although less severe, despite the complete subsidence of symptoms.

Authors’ address: D. R. Wilson, M.D., E. R. Yendt, M. D. Department of Medicine, University of Toronto, Toronto, Ont. (Canada).

Renal excretion of urate in patients with gout


Impaired renal urate excretion can be demonstrated in most hyperuricemic patients with gout as compared with normouricemic non-gouty subjects when the two groups are studied during periods when their plasma urate concentrations are similar. The plasma urate concentration of nongouty subjects can be raised to the levels of patients with gout by feeding 4 g of ribonucleic acid (RNA) each day for 3 days. The data in the figure are those of the authors plus published data of Yü et al. (1) and are based on studies of 21 patients with gout and a similar number of non-gouty subjects. In this illustration the urate excretion rate has been plotted as a function of the plasma urate concentration. Similar differences in renal urate excretion between gouty patients and non-gouty subjects are also apparent when urate/inulin clearance or urate clearance is plotted as a function of the plasma urate concentrations. The difference in renal urate excretion...
between the gouty and non-gouty groups when their plasma urate concentrations are similar is not attributable merely to the conditions under which the acute urate loading experiments were carried out (see data indicated by circles in figure). Non-gouty subjects fed urate precursors for month-long periods to cause chronic elevations

![Graph showing plasma urate concentration](image)

**PLASMA URATE CONCENTRATION mg PER 100 ml**

Fig. 1. The means for all individuals studied after three days of ingestion of 3 to 4 g of RNA per day in addition to their previous dietary intake are at the right ends of the lines. The means of the initial studies are at the left ends of the lines. The differences between the slopes of each non-gouty group as compared with the gouty group are significant at the 0.05 level. There was some overlap between the data of individuals in the gouty and non-gouty groups.

Summaries – Resumes

in plasma urate concentration (see data indicated by open squares in the figure) continued to excrete more urate than patients with gout who had similar plasma urate concentrations. The failure of most hyperuricemic patients with gout to excrete an acute load of urate with as great a facility as do normouricemic non-gouty subjects made hyperuricemic by longcontinued ingestion of ribonucleic acid leads to the conclusion that most hyperuricemic patients with gout have impaired renal urate excretion.


Author’s address: Dr. C. A. Nugent, Dept. of Internal Medicine, Salt Lake County General Hospital, Salt Lake City, Utah (USA).


Hyperuricemia is a characteristic finding in acute leukemia and is accentuated by various chemotherapeutic agents.

In the normal human the major source of uric acid is nucleoprotein degradation. A small amount of direct synthesis has been demonstrated through the precursor hypoxanthine ribotide (1). Purine analogs increase uric acid production by interrupting nucleic acid synthesis after the formation of hypoxanthine ribotide (2). Therefore urinary acid output increases because of (1) utilization of the hypoxanthine ribotide directly into uric acid, and (2) degradation of existing neoplastic cells. On the other hand, antifolic acid agents block nucleic acid production prior to hypoxanthine ribotide (2). Thus uric acid production may not be as great and results primarily from the catabolism of nucleoproteins.
A case of acute myeloblastic leukemia was treated with 6-mercaptopurine. There was a precipitous fall in the white cell count with a complete bone marrow remission. Concurrently a sharp rise in the serum uric acid to 55 mg % resulted in oliguria and acute renal failure. Peritoneal dialysis was successfully used to lower the serum uric acid and potassium levels. This was followed by a prompt diuresis and return to normal renal function. At least two factors contributed to the successful outcome: (1) dialysis removed a significant amount of uric acid, thus decreasing the total body pool and further renal deposition, and (2) dialysis was accompanied by an improvement in the metabolic acidosis with an increased solubility of uric acid from the renal tissue.

During a relapse in the leukemic process an antifolic acid agent was used. This resulted in a second complete remission but was not complicated by hyperuricemia. During the patient’s second and final relapse the antifolic acid drug was not effective and 6-mercaptopurine had to be used. There again was a significant hyperuricemia and azotemia but no hematologic improvement was obtained and the patient died.

The changes in uric acid metabolism and secondary renal complications seen in this patient correlated with the site of action of the chemotherapeutic agent employed. Peritoneal dialysis should be considered in the management of any patient with leukemia in whom renal function is severely compromised in association with hyperuricemia. This procedure has the advantages of being relatively atraumatic and unlike extracorporeal dialysis it is not contraindicated in the presence of thrombocytopenia.

References
Authors’ addresses: L. R. Weintraub, Department of Hematology, Walter Reed Army Institute of Research, Washington, D.C. and J.A, Pennerand Muriel C. Meyers, Simpson Memorial Institute, University of Michigan Medical Center, Ann Arbor, Mich. (USA).

Effect of reducing renal arterial blood pressure by balloon catheter on urate excretion in the dog
Reduction of mean renal arterial blood pressure of Dalmatian and mongrel dogs by inflating a balloon-tipped catheter inserted into the aorta just above the renal arteries resulted in a proportionate decrease in GFR and Cph, a precipitous fall in UNaV/FNa, no appreciable change in UκV/Fκ. In the Dalmatian, under conditions of net secretion of urate, UurateV/Furate was unchanged or rose somewhat. A comparable response of UurateV/Furate was obtained in mongrels under conditions of net reabsorption of urate, a result consistent with tubular secretion of urate masked by preponderant tubular reabsorption.

Author’s address: Dr. T. F. Yü, Department of Medicine, Mount Sinai Hospital, New York, N.Y. (USA).
The renal concentrating capacity in albino rats after long-term consumption of phenacetin, NAPA (N-acetyl-p-aminophenol) and acetylsalicylic acid
The renal concentrating capacity was studied in albino rats which had been given large amounts of phenacetin, NAPA or acetylsalicylic acid for 41-42 weeks. There was a marked and significant decrease of concentrating capacity in the phenacetin and NAPA groups as compared with a control group given no drug. There was a slight but not significant decrease of concentrating capacity in the acetylsalicylic acid group. No definite difference in the urinary sediments could be demonstrated between the groups with or without drug intake.

Author’s address: L. Angervall, M.D.; L. Lehmann, M.D.; U. Bengtsson, M.D., The Second Department of Pathology and the First Medical Service, Sahlgren’s Hospital, Göteborg (Sweden).