Summaries – Résumés

Hemoperfusion through a charcoal column for glutethimide poisoning
Extracorporeal hemoperfusion through an activated charcoal column of blood containing glutethimide was performed under in vitro and in vivo experimental conditions. In vitro, 100 g of charcoal appeared to be saturated after adsorption of 3-4 g of glutethimide. During experiments with dogs, good results were obtained as judged by the decrease in blood level, reduction in duration of coma, and increased survival rate. Of seven dogs treated, five survived, while all control animals poisoned with the same doses died. Blood clearance appeared to be about 10 times greater than that obtained with hemodialysis using a lipid bath, which has been shown to be superior to an aqueous dialysate. This method appears to be relatively safe, despite a reduction in platelet count. The thrombocytopenia, however, never led to abnormal bleeding. That this is a preliminary evaluation of a new method for treatment of poisoning is stressed by the authors. They cannot as yet unequivocally recommend this technique for clinical use. However, its very high adsorption rate for glutethimide allows its consideration for therapy of severe glutethimide poisoning and a desperate clinical picture.

Author’s address: Dr. J.F. Maher, Department of Medicine, Georgetown University, School of Medicine, Georgetown University Hospital, Washington, D.C. (USA).

Correlation of autopsy findings and clinical experience in chronically dialyzed patients
Autopsy findings are correlated with clinical experience in five patients who expired after being maintained with regular hemodialysis. One patient died after transplantation following 32 months of hemodialysis, another patient, after 7.5 months of home dialysis, and the remaining expired after 5, 25 and 30 months of therapy. Significant anatomical findings included adherent fibrinous pericarditis in three cases and severe coronary atherosclerosis in 2. Two of the five individuals, both with severe hypertension, died of massive hemorrhage involving the pontine area. Two of the five autopsy cases showed parathyroid hyperplasia. Three cases showed osteoporosis, one osteitis, and another osteomalacia. Microscopic examination of the testes revealed a thickening of the basement membrane with arrested spermatogenesis at the spermatocyte and spermatid stages in all patients. The average transfusion requirement was 2.1 units/month. At autopsy, the bone marrow was found to be normal to mildly hypoplastic. Extensive hemosiderosis was found in the liver, spleen, and pancreas in three of the five patients. Despite the dense deposits of hemosiderin portal fibrosis was present in only one patient who had moderately disordered hepatic function. It is of interest that the degree of saturation of the serum iron-binding capacity of the five patients examined at autopsy was substantially elevated in only one.

Author’s address: Dr. A. Sokol, Chronic Dialysis Unit, Veterans Administration Center, Los Angeles, Calif. 90013 (USA).
The effect of long-term dialysis treatment on the course of uremic neuropathy
This study includes a total of 31 patients on maintenance dialysis at the university hospital since 1960. Clinical data are presented on all patients, and 18 patients were studied repeatedly by means of motor nerve conduction measurements. In the entire group there were four patients who presented with and six who developed sensory or motor neuropathy during the first year of dialysis. All patients improved after institution or intensification of dialysis treatment. In addition, all patients for at least one year had a significant improvement in their motor nerve conduction velocities. Clinical neuropathy did not develop or worsen in any of the 20 consecutive patients started on maintenance dialysis in the 22 months prior to the report. During this time the center had increased the intensity of dialysis. Institution of adequate dialysis before motor neuropathy has developed is felt to prevent its occurrence. The authors also feel that if neuropathy progresses or develops in patients maintained on dialysis, the amount of dialysis is by definition inadequate and should be increased.
Author’s address: Dr. H. Tenckhoff, Department of Medicine, University of Washington, School of Medicine, Seattle, Wash. (USA).

Allotransplantation of the pancreas and duodenum along with the kidney in diabetic nephropathy
Two patients are reported with juvenile onset diabetes mellitus and renal failure who underwent simultaneous renal and pancreatic homotransplants from cadaveric sources. In one case the body and tail of the pancreas of the donor were transplanted to the left iliac fossa extraperitoneally with anastomosis of the celiac axis and portal vein end to side to the left common iliac vessels. The superior mesenteric vein of the transplant was anastomosed end to side with the external iliac vein of the recipient with ligation of the external iliac vein proximal to the anastomosis. The venous segment of the transplant was used as a bypass graft. The pancreatic duct was ligated and the cut end of the pancreas oversewn. In the second case the entire pancreas and attached duodenum of the donor were transplanted extraperitoneally to the left iliac fossa of the recipient. The celiac axis and superior mesenteric artery and a small cuff of aorta were anastomosed end to side to the left common iliac artery and the portal vein was anastomosed end to side to the left common iliac vein. In both cases reported there was evidence of insulin secretion by the transplanted pancreas. In the first patient function was evidenced only for a brief period of six days during which time the serum plasma insulin level was in the normal range. Neither pancreas nor kidney survived in this patient. In the second patient a more prolonged state of function of the transplanted pancreas was achieved and, even though it was necessary to reinstitute insulin therapy after two months, with a lowering of the steroid dosage, there was evidence of pancreatic function four months after transplantation. The second patient is also of interest with respect to the transplantation of the bowel in the human, since the entire duodenum and the first portion of the jejunum formed an integral part of the graft. With the abatement of rejection episodes, the bowel had grossly recovered. The patient was, however, bothered with intermittent bleeding. The authors are
undecided as to which technique should be used for transplantation of the pancreas, i.e., with or without bowel graft and discuss the advantages and disadvantages of each.

Author’s address: Dr. W.B. Kelly, Department of Surgery, University Hospital, University of Minnesota, Minneapolis Minn. (USA).

Reversible cardiomyopathy in uremia

The use of a low protein diet for the treatment of severe uremia has been resurrected recently with gratifying results. It has prolonged the useful existence of many patients and has been particularly effective in controlling the gastrointestinal manifestations of renal failure. Not all systems are favorably effecting, however, and we have noted the progression of a peculiar cardiomyopathy in five of 35 patients who were maintained on the ‘diet’ for from 1-10 months. The clinical picture is one of a progressive, severe, biventricular failure manifested by: (1) massive cardiomegaly, (2) gallop rhythm, (3) a fall in mean blood pressure, (4) pericarditis, (5) arrhythmias and a marked sensitivity to cardiac glycosides. Pericardial tamponade was considered because of the ‘rightsided’ clinical picture and ruled out by pericardiocentesis and/or cardiac catheterization in four of the five. One patient suffered a cardiac arrest and required resuscitation. All patients survived with intensive dialytic treatment, but the time required for rehabilitation was considerably longer than that necessary for the ‘routine’ uremic individual. All abnormal findings improved markedly or disappeared after treatment. In order to determine the role of the diet itself, one patient was maintained with strict protein restriction while being dialyzed, and he recovered. It is concluded that the heart disease seen in these patients is most likely a progression of their uremia (uremic cardiomyopathy). It is also recommended that patients with chronic renal failure being maintained with a low protein diet be watched carefully for incipient heart failure. If it is noted, definitive treatment (dialysis or transplantation) should be instituted as soon as possible in order to decrease morbidity.

Author’s address: Dr. G. L. Bailey, Peter Bent Brigham Hospital, Boston, Mass. (USA).

The cytology of the urine sediment

Urine from 15 recipients of renal homotransplants, seven of which experienced episodes of threatened rejection were studied during a ten-month period. The sediment of the urine from each of the 15 patients contained many epithelial cells and histiocytes. Varying numbers of lymphocytes and plasma cells were also found in the majority of the specimens. In addition to the usual squamous and transitional cells, two distinct kinds of epithelial cells were recognized. These were classified as type 1 and type 2. The type 1 cells were small and clustered in groups, possessed scant cytoplasm and hyperchromatic nuclei that varied somewhat in size but not in shape. Type 2 cells were larger and were scattered individually in the sediment. They often had irregular cell margins, enlarged nuclei and clumped nuclear chromatin. Clusters of type 1 epithelial cells were found in the urine of patients during the period immediately following transplantation and shortly before death. They also were present during episodes of threatened rejection. It seemed likely that these cells were exfoliated from the renal tubules as a result of ischemia. Lymphocytes, plasma cells, and histiocytes were found in most specimens of urine. Their presence did not correlate with episodes of rejection. Varying numbers of enlarged type 2 cells were seen in the urine of each of the 15 patients. They were not associated with
rejection ‘crises’ or episodes of renal ischemia. In addition, characteristic cells of cytomegalic inclusion disease were not recovered from patients with established urinary tract viral infection and disseminated cytomegalic inclusion disease. The authors conclude that cells diagnostic of immunologic rejection of the homograft were not observed.

Author’s address: Dr. J. E. Craighead, Department of Pathology, Peter Bent Brigham Hospital, Boston, Mass. (USA).

Preservation of kidneys assessed by a biochemical parameter


Aerobic respiration of renal cortical tissue was measured in a crude renal cortex homogenate at 37.5°C using succinate as substrate. This system was used to assess preservation of kidney tissue after various storage procedures at 37.5°C, namely, blood, low molecular weight dextran-saline, low molecular weight dextran-saline exposed to five atmospheres of oxygen as well as continuous insufflation of a gas mixture of 95% O2 and 5% CO2 into the renal artery. The latter was the most effective, and normal respiration was preserved for three hours as compared with one hour for blood or unmodified low molecular weight dextran-saline. Kidney storage at 2°C after initial perfusion with cold, low molecular weight dextran-saline preserved normal respiration in this system for almost 24 h. Decrease of respiration at a room temperature of 20°C is more rapid in tissue which has been previously stored at 2°C than in freshly excised kidney tissue. Preservation of respiration in this system when compared with data for renal function after ischemia or reimplantation in the literature indicates this biochemical parameter may be used to assess both the deleterious effect of renal ischemia and different methods of kidney storage.

Author’s address: Dr. S.G. Lannon, Renal-Urological Research Laboratories, Royal Victoria Hospital, Montreal (Canada).

Vascular and extravascular volumes of the kidney of man


Indicator dilution techniques were used to determine the vascular and extravascular volumes of the normal human kidneys in five normotensive patients. Renal artery and vein catheterizations were done for injection of the indicator and collection of renal venous serial samples. The volumes were corrected to 1.73 m2 per kidney. Renal blood volume was found to be 34.8 ± 3.1 ml as judged by indocya-nine green. The distribution volume of labelled inulin averaged 48.8 ± 9.0 ml and that of tritiated water 152 ± 20 ml. The distribution volume of inulin was used as an index of the extracellular fluid space of the kidneys exclusive of the tubular lumina; volume distribution of tritiated water was interpreted to represent the total exchangeable water content of the kidney. Intertstitial fluid volume and tubular-cellular volume were derived and averaged 27.4 ± 6.2 ml and 93.7 ± 14.3 ml, respectively. Future studies are to be reported using these methods in patients with essential hypertension.

Author’s address: Dr. R.M. Effros, Department of Medicine, New York University School of Medicine, Bellevue Hospital, New York, N.Y. (USA).

Antidiuretic hormone inactivation by isolated perfused rat liver

The disappearance of ADH from circulating perfusate and the fractional inactivation of ADH added to blood was studied in 13 separate perfusion experiments utilizing the perfused isolated rat liver. The hepatic clearance rate of ADH was found to be concentration dependent. No ADH activity was noted in bile. The average ADH extraction ratio ranged from 0.24 at plasma concentrations of ADH in the 15-25 µU/ml range to 0.63 at plasma concentrations between 1000-5000 µU/ml. ADH measurements were made by intravenous injection into ethanol-anesthetized water-loaded rats. The authors conclude that the hepatic extraction ratio of ADH in the rat is quite low at physiological plasma ADH levels and suggest that the liver may play a less important role than previously had been supposed in the regulation of ADH under such conditions.

Author’s address: Dr. J. B. Little, Department of Physiology, Harvard School of Public Health, Boston, Mass. (USA).

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Effet de la thyrocalcitonine sur l’excrétion rénale du sodium et du chlore chez l’homme normal

L’hypercalcémie et l’hypercalciurie déterminent, entre autres modifications urinaires, une excretion accrue de sodium et de chlore chez l’homme comme chez le chien. Il est possible que cette réponse soit induite, en partie ou en totalité, par un excès de thyrocalcitonine (TCT) secrétée sous l’influence de l’hypercalcémie.

Une préparation partiellement purifiée de TCT détermine chez l’homme une augmentation de l’excrétion urinaire de sodium et de chlore. Ce phénomène est rapporté à une diminution de la réabsorption tubulaire de ces deux ions indépendante de l’aldostérone ou de la parathormone endogènes. L’analyse statistique démontre que l’augmentation de la natriurie est indépendante de celle de la calciurie.

Adresse de l’auteur: Dr. R. Ardaillou, Service de Néphrologie, Hôpital Tenon, 4, rue de la Chine, 75 Paris XXe (France).

Renal handling of calcium, magnesium and inorganic phosphate in chronic renal failure

The correlation among the renal excretion of sodium and that of calcium and magnesium in normals undergoing urea-saline diuresis (obtained previously [1]) was compared with that found in a group of 49 patients with stable chronic renal failure. Patients with stable failure as a group, excreted a greater fraction of filtered divalent ions than normals. Obligatory solute diuresis accounted for the increased clearance ratio of calcium (excreted Ca/filtered Ca) in patients with predominantly glomerular lesions, but was inadequate to explain the increased clearance ratio of calcium in patients with predominantly tubular lesions. The increased clearance ratio of magnesium was in excess of the value expected for the degree of obligatory solute diuresis found.

The increased clearance ratio of phosphate was due to increased filtered load and secondary hyperparathyroidism. Ionic composition of tubular fluid was a major determinant affecting magnesium and calcium excretion. Statistically, endogenous filtered loads of calcium and magnesium were not important determinants affecting the clearance ratio of calcium and magnesium.

Reference
          saline diuresis on renal clearance of calcium, magnesium and inorganic phosphate in man. 
          Author’s address: Dr. O. S. Better, Renal Unit, Ramban Government Hospital, Haifa (Israel).
          Influence of thyrocalcitonin on phosphaturia


          Thyrocalcitonin extracted from hog thyroid glands caused a fall in serum calcium within 30 min in 
          the dog and within 45 min in the rat. The most effective dose of thyrocalcitonin on serum 
          calcium in the intact rat induced a small but significant increase of the urinary output of 
          radiophosphate in the parathyroidectomized rat. When thyrocalcitonin and PTH were injected 
          simultaneously a decrease in the effect of parathyroid hormone on phosphaturia was observed. 
          Triiodothyronine did not influence the phosphaturia. Perhaps thyrocalcitonin inhibits 
          competitively the activity of PTH on the kidney tubules. So far the phosphaturic effect of 
          thyrocalcitonin has not been defined in terms of specificity.
          Author’s address: Dr. R. Ziegler, Zentrum für Innere Medizin der Medizinisch- 
          Naturwissenschaftlichen Hochschule Ulm, Steinhövelstrasse 9, 79 Ulm-Donaun (Germany).

          Isolated hypercystinuria in a family with idiopathic hypoparathyroidism


          An isolated hypercystinuria was observed in 2 siblings. The hypercystinuria was caused by a 
          hereditary defect of the tubular reabsorption of cystine and was not accompanied by an increased 
          excretion of lysine, ornithine or arginine. One of the two children suffered from idiopathic 
          hypoparathyroidism, which is familial too since two other children of the family had 
          hypocalcemic tetany. Parathormone and vitamin D reversed the hypocalcemia and 
          hyperphosphatemia but did not change the hypercystinuria. It is suggested that cystine and the 3 
          amino acids lysine, ornithine and arginine do not share a common renal transport mechanism, 
          but that the tubular reabsorption of cystine is a unique process.
          Author’s address: Dr. J. Brodehl, Universitäts-Kinderklinik, Koblenzerstrasse 119, 51 Bonn 
          (Deutschland).

          Prevention of urolithiasis

          By Frank, M. and Vries, A. de

          A study was carried out on the effect of education to high fluid intake on urine output and on the 
          incidence of urolithiasis in the newly established town of Arad,
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          situated in the arid Judean desert mountain region. Settlers of the nearby town Beersheba, not 
          subjected to the educational program, served as a control. At the end of a three-year period 
          (1962-1965), the prevalence of urolithiasis in Arad 2.8%o) was significantly lower than in 
          Beersheba (8.5%o), and daily urine output higher in the former. These preliminary results 
          suggest the value of education to fluid intake in the prevention of urolithiasis in a hot climate.

          References

          Frank, M. et al.: Epidemiological investigation of urolithiasis in the Hot Southern Arid Region of 
          Author’s address: Dr. M. Frank and A. de Vries, Belinson Hospital, Petah Tikva (Israel).
The effect of beta adrenergic blockade on patterns of urinary sodium excretion

The effect of oral administration of the beta adrenergic blocking agent, propranolol (Inderal®), on the pattern of urinary sodium excretion was examined in six normal volunteers and in ten patients with heart disease. Isocaloric diets of varying sodium content were given using standard metabolic balance technique. Propranolol was given in total daily doses ranging between 60 to 240 mg. Diurnal sodium excretion patterns were determined in five subjects utilizing six hour collection periods and in eight subjects day/night sodium excretion ratios were determined.

In all subjects propranolol altered the diurnal patterns of sodium excretion; a greater percentage of the total 24 h sodium output was excreted at night and during the early morning hours, but no change occurred in the total 24 h sodium excretion. An intermediate degree of impairment was seen in some patients with heart disease in whom propranolol retarded the rate at which sodium conserving mechanisms were turned off as sodium intake was progressively increased. Although propranolol prolonged the time for the achievement of sodium balance, the latter ultimately did occur and progressive sodium retention was not observed. The latter was observed in only one subject, a patient in functional class IV.

It was noted that beta adrenergic blockade can occasionally precipitate dangerous cardiac decompensation in cardiac patients not preceded by sodium retention and weight gain.

It is concluded that the sodium retention induced by propranolol in some patients with cardiac disease supports the concept of the importance of the role of the sympathetic nervous system in the integrity of myocardial performance.

Author’s address: Dr. Eugene Braunwald, Cardiology Branch, National Heart Institute, Bethesda, Md. 20014 (USA).

Red blood cell content of water, sodium and potassium in body fluid disturbances

The determination of the red blood cell (RBC) water and electrolyte content is fraught with uncertainties, mainly due to the variations in the amount of ‘trapped’ plasma even under rigidly standardized conditions of collection and centrifugation of the blood samples. The normal values reported in the literature vary considerably, and this is probably the reason why the changes in the RBC content of water and electrolytes have not been studied more extensively.

In a previous publication we described an improved method for measuring RBC water and electrolytes, based on the actual determination of the trapped plasma in each sample (1). By this method the normal range for water and electrolytes in the RBC was found to be narrower, and the values for Na were much lower than by most other methods – 7.8 ± 0.71 (S.D.) RBC sodium, potassium and water content was determined in blood from patients suffering from cirrhosis of the liver, from chronic renal failure and from congestive heart failure. Deviations from normal values were found especially in the RBC sodium content. Most of the patients with cirrhosis of the liver and with chronic renal failure had a lower RBC sodium content. In patients suffering from congestive heart failure, an increased frequency of deviations of the RBC sodium values in either direction was observed in the more severe stages of this condition. In mild and moderate congestive heart failure there was an increased frequency of low RBC sodium. In severe
congestive heart failure normal results were obtained only in 2 out of 29 cases. In 16 cases the sodium content was low and in 11 cases high.

Reference

Authors’ address: Dr. J.W. Czaczkes, Dr. A. Aviram, Dr. A. Keynan and Dr. T.D. Ullmann, Laboratory of Clinical Research, Hadassah University Hospital and Hebrew University, Hadassah Medical School, Jerusalem (Israel).

Action of tonephin on the renal excretion of electrolytes and urea during the infusion of glucose and sterofundin


The effect of an ADH-infusion during water diuresis and infusion of sterofundin in healthy subjects and patients with diabetes insipidus centralis on the following topics was examined: Excretion of sodium, chloride, potassium, and urea. The following results were obtained:

(1) Sodium and chloride excretion decrease significantly until a maximal U/Posm is achieved; however, they often increase again still during maximal urine concentration. Not only the sodium output but also the excretion fraction of sodium (TRNa) shows similar changes. The acute NaCl retention is absolutely lowest in water diuresis and highest in isotonic saline loading.

In the beginning of an ADH-infusion urea excretion decreases considerably, it shows some increase still during maximal antidiuresis and raises up to the initial values or above when the urinary flow increases again. With infusion of isotonic saline solution urea retention is distinctly lower than in water diuresis.

Potassium excretion during ADH-infusion shows a significant increase in patients with diabetes insipidus centralis.

The present results are consistent with the concept that in antidiuresis a temporarily increased tubular reabsorption of sodium and urea results in an increased sodium and urea content of the medullary interstitial fluid.

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An effect of antidiuretic hormone on the flow of blood through the vasa recta of the rat kidney


The injection of a fluorescent dye which stained the vessel walls showed the pathway taken by the blood in the renal medulla in rats. The vasa recta stained in normal rats given water; they did not stain in dehydrated rats, nor did they stain in rats given an antidiuretic dose of vasopressin in addition to water. The vasa recta stained in all rats with diabetes insipidus whether they were given water or dehydrated.

These results suggest that antidiuretic hormone increases water conservation in the medulla by reducing blood flow through the countercurrent system as well as by increasing the permeability of the collecting ducts to water.

Authors’ address: Dr. Julia Fourman, Department of Anatomy, Leeds (England).
Antidiuretic hormone content of the hypothalamo-neurohypophysial system and urinary excretion of antidiuretic hormone in rats during the development of diabetes insipidus after lesions in the pituitary stalk


The antidiuretic hormone (ADH) content of the hypothalamo-neurohypophysial system (HNS) and the excretion of AD-activity in the urine has been examined after pituitary stalk lesion in rats. In the oliguric phase which developed approximately 24 h after stalk destruction and lasted for about 3 days, the HNS was greatly depleted of ADH and the excretion of AD-activity in the urine was much above normal.

Implantation of posterior lobes obtained from intact adult rats under the kidney capsule of stalk-lesioned animals with a manifest diabetes insipidus produced oliguria similar to that found after stalk destruction. However, the antidiuretic effect of the implant lasted somewhat longer and the amount of AD-activity excreted in the urine was twice as high as that excreted in the oliguric period after stalk destruction.

Subcutaneous injection of lysine or arginine vasopressin in various vehicles into rats with manifest diabetes insipidus showed that the effect of these preparations on water intake and urine output was independent of the dosage used but seemed to depend on the rate of absorption from the subcutaneous tissue. The results indicate a relationship between duration of action and the amount of AD-activity excreted in the urine.

Hyperosmoticity induced by the subcutaneous injection of a 15% NaCl solution failed to release ADH irrespective of the hormone content of the HNS of stalk-lesioned rats.

In a number of stalk-lesioned rats the polyuria gradually disappeared several weeks after stalk destruction. The ADH content of the hypothalamus of these animals was nearly normal, but that of the posterior lobe was only about 10% of that of intact controls. The urinary excretion of AD-activity in these animals was about half of that of the controls. In such rats ADH could be readily released from the HNS after loading with 15% NaCl, indicating that animals with a regression of the diabetes insipidus had resumed the production of ADH.

Authors' addresses: Dr. F.A. László, Research Fellow of the Organization for the Advancement of Pure Research in the Netherlands (Z.W.O.) on leave of absence from the First Department of Medicine, Medical University of Szeged, Szeged (Hungary). Dr. D. de Wied, Department of Pharmacology, Medical Faculty, University of Utrecht, Vondellaan 6, Utrecht (The Netherlands).

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Action of oral water intake on the renal excretion of sodium in normal and hypertensive subjects

(Einfluß einer oralen Flüssigkeitsbelastung auf die renale Natriumausscheidung bei gesunden und bei Hochdruckpatienten)


The influence of a repeated oral fluid loading on renal sodium excretion was analyzed in 12 normal persons and 14 patients with hypertensive disease of various origin.

In normal persons, the oral hydration produced a continuous increase of renal sodium excretion, whereas urine volume, endogenous creatinine clearance and tubular sodium load remained essentially unchanged.

In hypertensive patients, a maximal natriuresis occurred in the first hour after hydration and was followed by a decrease of sodium excretion together with a reduction of endogenous creatinine clearance and tubular sodium load.
As the cause of the increasing sodium excretion in normal persons after oral hydration an endogenous natriuretic principle is postulated, acting mainly on the sites of anisotonic sodium transport.

The mechanism of the initial natriuresis in patients with hypertensive disease after oral hydration is still not completely understood. It is concluded that the effect of hydration on sodium diuresis in normals is different from that in hypertensive patients.

Author’s address: Dr. F. Krück, II. Medizinische Universitäts-Klinik und Poliklinik, 66 Homburg/Saar (Germany).

Antidiuretic response to vasopressin during infusion of albumin into hypertensive and prehypertensive subjects

In previous reports from this laboratory it was shown that in hypertensive and pre-hypertensive subjects the infusion of reconstituted human plasma caused an increase in water excretion, without natriuresis, whereas in normal individuals an antidiuretic effect was observed. It was suggested that in the normal subjects the diuretic stimulus of the extracellular fluid volume expansion by the plasma infusion was balanced or suppressed by the antidiuretic hormone (ADH) like material present in the plasma. In the hypertensive subjects this antidiuretic effect was overcome by an increased reactivity of a volume regulating mechanism, which may be characteristic of these subjects.

An additional, or alternative, explanation for the observed difference could be that hypertensive subjects possess a lower tubular sensitivity to ADH, or a higher turnover rate for this substance, than do normotensive subjects. This would mean that in order to obtain a comparable antidiuretic effect during induced water diuresis, larger amounts of ADH would be required in hypertensive than in normotensive subjects. In order to test this hypothesis, normal subjects were infused with a 10% human serum albumin solution. They reacted with an increased diuresis suppressible by an infusion of 100 µU/min vasopressin. In hypertensive and prehypertensive subjects 160 µU/min of vasopressin were necessary in order to elicit an antidiuresis of comparable magnitude. It is suggested that this difference may be due either to a decrease in the tubular sensitivity to vasopressin or to an increased turnover rate of antidiuretic hormone in the hypertensive groups.

Authors’ address: Dr. J.W. Czaczkes, Dr. A. Aviram, Dr. A. Keynan and Dr. T.D. Ullmann, Laboratory of Clinical Research, Hadassah University Hospital and Hebrew University, Hadassah Medical School, Jerusalem (Israel).

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Anion concentration gradients and electrical potentials in distal tubule of dog

Stop-flow and slow-flow techniques were employed to study steady-state distal transtubular anionic concentration gradients in anesthetized dogs. The gradients established for SCN, Cl, and Br were not significantly different from one another, and are consistent with an absence of active transport of these anions. The U/P ratio for 131I was always higher than that for the other anions, and this was attributed to nonestablishment of a steady state for 131I due to its low degree of permanence. Transtubular potentials were calculated from Cl transtubular concentration gradients using the Nernst equation. The calculated potential was increased both by salt depletion and sodium sulfate infusion.
Micropuncture study of urea transport in rat renal medulla

Urea concentration may be higher in rat renal papilla than in urine under circumstances in which the urine urea is decreased (1). To investigate this further, anesthetized young rats were given urea-14C and inulin-methoxy-3H, and 14C and 3H activities were determined in vena cava plasma and in fluid obtained by micro-puncture from loops of Henle, vasa recta, and collecting ducts in the papilla, and from distal convolutions on the surface of the kidney. Mean urea concentration was greater in vasa recta (VR) than in adjacent collecting ducts (CD) in protein-depleted rats (mean VR/CD = 1.14; P < 0.02), and also in rats on a normal diet during osmotic diuresis (mean VR/CD = 1.08; P < 0.01). Urea binding to plasma proteins was insufficient to account for these differences. Urea concentration in loops of Henle did not differ significantly from that in collecting drugs in protein-depleted diuretic rats. Comparison of urea and inulin fluid-to-plasma ratios in distal convolutions and collecting ducts suggests movement of urea out of collecting ducts into the renal medullary interstitium. These results suggest active transport of urea out of collecting ducts.

Reference

Renal tubular reabsorption of urea in normal and protein-depleted rats

The concentration of inulin and urea was measured in samples of proximal and distal tubular fluid from normal and protein-depleted rats. The concentration of urea rose above that of plasma very early in the proximal tubule and showed a further rise in the distal tubule and collecting ducts of the normal rats. Proximal and distal TF/P urea ratios in protein-depleted rats were comparable to those in normal rats. However, in contrast to normal rats, the urea TF/P ratio fell from 6.9 (SD ± 1.7) in the distal tubule to 5.2 (SD ± 0.9) by the end of the collecting ducts. The papillary tissue water urea concentration in protein-depleted rats was consistently higher than that in final urine. The data strongly suggest that urea is actively reabsorbed from the collecting ducts of protein-depleted rats. However, the possibility that a portion of the papillary urea may exist in a bound or inactive form could not be excluded.

Effect of renal arterial pressure on the stop-flow sodium minimum

An increase in renal perfusion pressure in the rat and dog elevates the stop-flow distal sodium minimum concentration. The following studies were done to define the mechanism of this change. Dog kidneys were perfused at selected pressures during stop-flow. The sodium minimum concentration changed 0.8 mEq Na/l urine for each 10 mm Hg change in perfusion.
pressure. This was not modified by infusion of angiotensin II. Ureteral pressure varied directly with perfusion pressure. The point of maximum PAH secretion showed proximal displacement with increased perfusion pressure. The entrance of postocclusive filtration markers into more distal samples increased with elevated perfusion pressure. It is concluded that the increase in distal sodium minimum concentration occurring with increased perfusion pressure is probably due to an increase in filtration, intratubular pressure, and tubular dilatation, causing stop-flow distal sodium minimum concentration to equilibrate at a higher level.

Author’s address: Dr. J. W. Wilkins, Jr., Department of Internal Medicine, The University of Michigan Medical Center, Ann Arbor, Mich. 48104 (USA).

Bioassay of a humoral natriuretic substance in the urine of normal individuals


Recently we demonstrated an increased renal sodium excretion without changes in tubular sodium load after moderate continuous oral hydration in normal man. To evaluate the possible existence of a humoral factor responsible for the natriuresis, urine preparations of hydrated normal persons were tested for natriuretic activity in a specially developed bioassay in rats. Urines were dialyzed and ultra-filtered. The lyophilized residue was dissolved in isotonic saline. Sodium depleted rats received sodium in an amount of 750 µEq by gavage and 150 µEq intravenously. The animals were kept under standardized conditions in single metabolic cages. Urine was collected for five hours. Urine volume, osmolal clearance, sodium, chloride and potassium excretion were calculated for 100 g body weight/5 h. Of the given sodium load, control animals retained almost 50% (mean: 222 of 470 µEq/ 100 g/5 h). In spite of sodium loading the urinary sodium: potassium ratio was reduced to 0.88. Intravenous injection of urine preparations resulted in a dose-dependent decrease in sodium retention with an increase in the sodium: potassium ratio to 2.0 at doses of 25 µg, potassium excretion being unaltered. The free water reabsorption was significantly reduced. The effect of this dose exceeded that of 50 µg of hydrochlorothiazide. The results point to a decrease of tubular sodium reabsorption and give evidence for the existence of a humoral natriuretic factor present in normal man after moderate oral hydration.

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Renal tubular transport of fluoride compared with chloride


Simultaneous clearances of inulin, chloride, and radiofluoride (F18), given by priming injection and constant infusion, were measured in dogs depleted of chloride, undergoing mannitol or sulfate diuresis, and after chloride repletion. In the presence of appreciable chloruresis, fluoride and chloride reabsorption varied together independently of flow. However, when chloride reabsorption was nearly complete (> 99%), fluoride reabsorption became dependent on flow, urine-to-plasma concentration ratio averaging 1.6. It is inferred that passive reabsorption of fluoride occurs proximally, tubular permeability to fluoride being much less than to chloride, but that fluoride does not share in the distal tubular transport of the last traces of chloride.

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Influence of osmotic load on sodium reabsorption and oxygen consumption of the kidney

Natriumreabsorption und Sauerstoffverbrauch der Niere bei osmotischer Belastung
The relation of tubular sodium reabsorption to the filtered load of sodium and to the oxygen consumption of the kidney was examined after loading (i) with physiological saline, (ii) with hyperosmotic NaCl and (iii) with hyperosmotic mannitol solutions, respectively. The quantity of sodium reabsorbed is in all three series were proportional to the filtered load. With a given filtered load sodium reabsorption is less with higher plasma sodium levels; hypernatraemia leads to decreased tubular sodium reabsorption.

Oxygen consumption connected with the reabsorption of 1 mEq of sodium is less after salt loading than after mannitol loading (0.79 and 1.05 ml C\(^\frac{1}{8}\)/mEq Na, respectively).

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Urinary excretion of 5-hydroxyindoleacetic acid in relation to urine volume/5-Hydroxyindolëssigsäure-Elimination und Harnmenge
Measurement of the urinary excretion of 5-hydroxy-indoleacetic acid (5-HIAA) after ingestion of an excess of water, after application of a mercurial diuretic and a carbonic anhydrase inhibitor in normal men shows a conspicuous correlation between the amount of excreted 5-HIAA and the urine flow. Since most of the urinary 5-HIAA is excreted by tubular secretion, it is apparent, that alteration of tubular milieu by exogenous interference in the concentrative mechanism may lead to the variation of the 5-HIAA-elimination by influencing the concerning tubular transport without shifting the 5-hydroxy-indol mechanism.

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Stop-flow-examinations concerning the mechanism of saluretic action of Chlosudimeprimyl/Untersuchungen zum tubulären Wirkungsmechanismus von Chlosudimeprimyl im Stop-flow-Versuch
Stop-flow examinations on 3 dogs concerning the influence of 2 mg Chlosudimeprimyl (Brinaldix) per kilogram body weight show in the whole tubular system a decreased sodium, chloride and water reabsorption. The secretion of potassium in the distal tubular system is only slightly increased.

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Serum sulfate and sulfate clearance in persons with normal and diminished renal function/Serumsulfat und Sulfatclearance bei normaler und eingeschränkter Nierenfunktion
(1) As determined by means of a nephelometric method the average value of the inorganic serum sulfate was 0.75 mval/l with a σ of ± 0.13 in normal subjects.
In normal people on a normal diet sulfate clearance ranged between 39.1 and 26.6 ml/min. Serum sulfate is increased in renal insufficiency. Thus there are close positive correlations between serum sulfate on one hand and serum-BUN, -creatinine and phosphate in the other hand as well as a negative correlation between serum sulfate and serum bicarbonate.

A progressive increase of serum sulfate could be observed when creatinine clearance was lower than 70 ml/min. When renal function decreases creatinine clearance and sulfate clearance
parallel each other. There is a better correlation between a decreased sulfate clearance and a decreased creatinine clearance than between hypersulfatemia and a decreased creatinine clearance.

(5) Among the anions retained in renal insufficiencies which belong to the so-called ‘unidentified anions’ inorganic sulfate is often prominent and can rise to twentyfold the normal values. In the course of reversible or fluctuating renal insufficiency the level of serum sulfate is much more sensible than the level of serum phosphate.

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Regulatory function of the sodium gradient at the macula densa-cells in regard to glomerular filtration rate and systemic arterial blood pressure. A hypothesis about the stimulation of the renin-angiotensin system. Contribution to the pathogenesis of various hypertensive conditions.

Summaries – Resumes


A review of the experimental data in the literature concerning the regulatory function of the juxtaglomerular apparatus and the macula densa in regard to sodium metabolism and systemic arterial blood pressure has led to a new hypothesis:

Stimulus for the secretion of renin at the juxtaglomerular apparatus (and consequent formation of angiotensin) is the gradient of sodium concentration between serum and early distal tubular fluid, rather than the absolute sodium concentration in the early distal tubular fluid. It is assumed that both, increase and decrease of this gradient at the macula densa stimulate renin secretion. In addition, a decrease of the gradient is followed by local vasoconstriction at the vas afferens with consequent reduction of glomerular filtration. When the gradient is increased above normal this local vasoconstriction at the vas afferens is inhibited, and, when it is already inhibited renin is released into the systemic circulation with consequent rise of arterial pressure and glomerular filtration.

The validity of the new concept is seen in the fact that such a gradient would serve as a common denominator for the renin-angiotensin-system and thus could explain many of the mechanisms operative in various disease states, such as renal vascular hypertension, coarctation of the aorta, primary hyperaldosteronism, and perhaps essential hypertension and acute glomerular nephritis.

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Direct effects of glucagon on renal hemodynamics and excretion of inorganic ions


The direct renal effects of glucagon were studied in a series of dogs. Glucagon was infused in dilute solution directly into one renal artery for four clearance periods of twenty minutes each, by a method developed in this laboratory and previously described (Pullman, T. N.; Lavender, A. R.; Aho, I. and Rasmussen, H.: Endocrinology 67: 570 [1960]). The differences between kidneys with respect to glomerular filtration rate, effective renal plasma flow, filtration fraction, and the excretory rates of sodium, chloride, potassium, water, inorganic phosphate, calcium and
magnesium were compared with differences observed during the immediately preceding four 20
min periods during which physiological saline had been infused into one kidney. The differences
between kidneys during saline infusion were small or insignificant. Glucagon infusion produced
a bilateral rise in filtration rate and filtration fraction of about the same degree in each kidney. In
all except the initial glucagon period, however, there was no difference in filtration rate, plasma
flow, or filtration fraction between the infused kidney and its mate. There was a small
statistically significant rise in differential filtration rate for the first glucagon period, but not for
the remaining three periods. Glucagon produced marked differential increase in excretion of all
measured ions; the sodium increase was the largest. The results support the conclusion that
glucagon acts directly upon the renal tubule to decrease the reabsorption of sodium, chloride,
water, calcium and magnesium and to decrease the ‘net’ tubular reabsorption of potassium.
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