Polyfructosan-S: A new Inulin-like Substance for the Determination of Glomerular Filtration Rate and Physiologically Active Extracellular Fluid Space in Man

Polyfructosan-S: Eine neue inulinartige Substanz extrazellulären Flüssigkeitsvolumens beim Menschen

D.P. Mertz and H. Sarre

Polyfructosan-S (PFS) is a new inulin-like substance. In comparison with inulin (In) there are a number of advantages: (1) PFS is totally soluble in cold water, (2) it is alkali-stable and (3) with weak acids it hydrolyzes half as fast as In. Since PFS and In. form the same products by hydrolysis, the chemical analysis of both substances in plasma and urine is identical. Consequently, only successive studies in comparing the renal clearance (C) and the volume of distribution (VD) of PFS and In. were possible. Under standardized basal conditions in water, electrolyte and protein metabolism, the clearance ratio PFS/In. was 1.016 ± 0.099 (range: 0.91-1.22) in adults with and without renal impairment. There was no difference in the variation of values between normals and persons with renal disease. The VD ratio PFS/In. was 1.005 ± 0.093 (range: 0.84-1.19). PFS-Clearances of patients with renal disease and of normal controls are independent of PFS plasma concentration over a range from 21.5 to 104.8 mg/100 ml. In all experiments (124) PFS was non-toxic and produced no pyrogenic action.

According to the present data, it is suggested that PFS may be qualified as a substance for the determination of glomerular filtration rate and physiologically active extracellular fluid space both in normal and renal diseased man. This hypothesis is supported by the fact that PFS, like In., is not bound to serum protein, as demonstrated by separation with gel filtration (D.P. Mertz and H.E. Franz: Is Polyfructosan-S bound to serum protein? Klin. Wschr. 42: 555 [1964]).

D.P. Mertz
Medizinische Poliklinik der Universität Freiburg, Freiburg L Br. (Germany).

Formation of an Erythropoietic Factor in the Kidney
Experimentelle Untersuchungen über die Bildung von Erythropoetin in der Niere

P. Andreadis, G. Bromig and J. Scharz

Renal insufficiency is often accompanied by anaemia which is difficult to treat. Earlier investigations suggest that this anaemia is caused by lack of an erythropoietic substance, said to be formed by endo-crinial action of the kidney. By irradiation of the kidneys of rabbits with fast electrons using the ‘Betatron’ it was possible with a careful dosage to produce anaemia without damaging the excretory function of the kidney, the NPN (nonprotein nitrogen) remaining normal. If the irradiated animals received serum of animals untreated by irradiation, but with an
excessive erythropoietin content increased by bleeding, an excessive erythropoiesis was obtained. Histological differences in the bone marrow before and after treatment were demonstrated. Finally treatment in cases of renal anaemia by chronic pyelonephritis is discussed.

G. Bromig
Chirurgische Klinik der Universität, Frankfurt a. M. (Germany).

The Action of Synthetic Eledoisin on Renal Function, Water and Electrolyte Metabolism in Man
Über die Wirkung von synthetischem Eledoisin auf die Nierenfunktion, den Wasser- und Elektrolythaushalt beim Menschen

D.P. MERTZ
Arch. exp. Path. Pharmacol. 246: 338-354 (1964)

The influence of intravenously injected synthetic eledoisin on renal function, water and electrolyte metabolism has been investigated in 26 adults with and without renal impairment under standardized dietetic and technical conditions. The threshold dose of eledoisin, which affects renal function, is 0.001 to 0.002 µg/kg body weight.

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Like in former studies on the renotropic effects of bradykinin (D. P. Mertz: Arch. exp. Path. Pharmacol. 244: 405 [1963]) there is no dose-action relation in doses between 0.002 and 0.33 µg/kg body weight. Furthermore healthy individuals react qualitatively in the same way to eledoisin as do persons with kidney malfunction.

On intravenous injection with 0.002 to 0.033 µg/kg body weight eledoisin inulin and PAH clearances, nitrification fraction, osmolar clearance, plasma osmolarity, serum concentrations and renal excretion rates of Na, K, and Ca, respectively, do not change significantly. Under the influence of eledoisin urine flow is decreased by an average of 24.4%, while UOSm and U/P osm are increased by an average of 24.9 and 25.2%, respectively, of the average control values. C%O is reduced in each case. Eledoisin elevates the total renal vascular resistance and leads to a vasodilation in head region.

D. P. Mertz
Med. Poliklinik der Universität Freiburg, Freiburg i. Br. (Germany).

Hyperparathyroïdie secondaire de Γinsuffisance rénale

Malgré la rareté de tels cas, il est des urémies chroniques auxquelles est secondairement surajoutée une hyperparathyroïdie patente. Après resection subtotale des parathyroïdes, les manifestations osseuses et humorales se modifient et deviennent celles de l’urémie courante.

Chez 35 insuffisants rénaux chroniques de toute origine mais in-dennes de lithiase urinaire, présente ou passée, on a étudié le syndrome humoral ainsi que l’aspect radiologique et histologique de Patteinte osseuse de façon à mettre éventuellement en evidence Pexistence des signes constates chez les malades du groupe precedent, ce moyen indirect étant le seul permettant d’apprécier l’intensité de la secretion parathyroïdienne. Dans quelques cas on a pu noter des anomalies qui pourraient être expliquées par une réponse parathyroïdienne excessive mais, à l’exception d’un ou deux malades, le groupement des symptomes

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interdit de porter une telle conclusion, si bien que le premier groupe d’urémiques se sépare de celui des insuffisants chroniques tout venant. Las discussion des faits conduit à émettre trois remarques:
Il n’est pas exclu que les cas d’hyperparathyroïdie patente co-existant avec une urémie chronique soient en réalité ou bien des hyper-parathyroïdies primaires, adénomateuses ou hyperplasiques, compliquées d’atteinte rénale, ou bien des coïncidences fortuites;
L’augmentation de volume des parathyroïdes, assez souvent constatée chez les insuffisants rénaux, peut fort bien ne pas correspondre à une activité endocrinienne accrue, laquelle n’apparaît pas du tout certaine d’après les documents que nous avons recueillis;
c) La discordance entre la morphologie des parathyroïdes et l’absence de manifestations suggérant la secretion d’un principe hypercalcémiant pourrait relever de l’intervention d’une autre action hormonale hypocalcémiant, dont l’existence est avancée par quelques travaux récents.

G. Richet
Hôpital Tenon, Paris XXe (France).

Les lesions du parenchyme renal au cours des septicémies
L’analyse de 28 dossiers de malades atteints de lesions rénales au cours de septicémies a permis les conclusions suivantes.
Une septicémie peut être responsable d’une atteinte rénale. Les germes les plus fréquemment en cause sont le staphylocoque, l’entéro-coque, le colibacille et le pyocyanique.
Il n’existe pas de tableau clinique et biologique univoque dans les atteintes rénales survenant au cours des septicémies.
Les aspects histologiques rencontrés sont variables. Certains semblent en relation directe avec l’infection microbienne: abcès du rein (4 cas), infiltrat interstitiel diffus à polynucléaires (1 cas), lesions glomérulaires (6 cas), infarctus (associé d’ailleurs à d’autres lesions) (3 cas). D’autres, par contre, paraissent la traduction de complications évolutives de la septicémie, collapsus ou désordres hydro-électrolytiques,
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Les injections de doses letales de Salmonella typhosa endotoxin dans le chien produisirent un initial (18 sec) vasoconstriction rénale suivie d’une vasoconstriction intense entre 5-10 min. Le vasoconstriction initial était attribuée à l’effet vasoconstricteur de l’endotoxin quand celui-ci n’était pas altéré par l’infusion de phentolamine, pré-traitement avec reserpine et ne pouvait être dupliqué par l’administration de sérotonine. La pression artérielle rénale resta élevée pendant 30 min. Depuis l’infusion locale de phentolamine a bloqué la vasoconstriction secondaire rénale.
vasoconstriction it is suggested that the persistent vasoconstriction was due to catecholamine release during the systemic hypotension. After endotoxin injection there was a marked decrease in all renal functions. The hemodynamic effect was eliminated in one kidney by infusing phentolamine locally and holding renal blood flow constant in one group of animals thus enabling comparison of this kidney with the contralateral undisturbed kidney. In the kidney in which vascular effects were eliminated there was no alteration in renal functions after systemic or local endotoxin injection.

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These data, therefore, show that the principal effect of endotoxin on the kidney is hemodynamic and not nephrotoxic.

Jay Y. Gillenwater
Graduate Hospital of the University of Pennsylvania, 19th and Lombard St., Philadelphia 46, Pa. (USA).

Retrograde E. Coli Pyelonephritis in the Rat: A Bacteriologic, Pathologic and Fluorescent Antibody Study


Retrograde infections of the urinary tract in rats can be accomplished by inoculation of E. coli into the bladder. In contrast to the results obtained when Proteus was used as the infecting organism, the renal lesion produced with E. coli is generally mild and limited to pyelitis although a small number of animals develop pyelonephritis. The organisms are initially present in the kidneys but disappear progressively during the subsequent weeks so that the kidneys are invariably sterile by the fourteenth week after infection and free of bacterial antigen as determined by fluorescent antibody study. When glass beads are placed in the infected bladder, bacteriuria and positive cultures of the kidney persist for at least 14 weeks, but the renal lesions continue to be mostly limited to the pelvis. Bacteriuria may be present when the kidneys have become sterile, and in the absence of apparent renal lesions. The observations indicate that in retrograde infections of the urinary tract pyelonephritis of wide ranges of severity may be produced by varying the infective organism, and that in infections with a relatively avirulent organism, persistence of bacteria in the urinary tract may not be necessarily associated with significant renal lesions. It is suggested that a comparable situation in man may account for incidences of persistent bacteriuria in the absence of a demonstrable renal lesion.

Ramzi S. Cotran
Department of Pathology, Harvard Medical School, 25 Shattuck Street, Boston //, Mass. (USA).

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Kidney Homotransplantation in the Human R. Shackman, W. J. Dempster and O. Wrong

Together with twenty-nine relevant cases recorded by other writers, seven human kidney homotransplantations carried out at Hammersmith Hospital since January 1961 are reported in detail and the successes and failures have been defined and analysed. With the proviso that the maximal reported follow up period is only three and a half years, complete success may be claimed for two patients; one is well three and a half and another two and a half years after homotransplantation. The fact that both successes occurred in non-identical twins may be significant.
Partial success meaning that an individual’s life was significantly prolonged by homotransplantation was achieved in seven cases. Renal functional deterioration, not necessarily fatal, subsequently occurred in six; death ascribed to malignant metastases occurred in one. One patient in the Hammersmith Hospital series is at work two years after the homotransplantation. Immediate failure occurred in nine cases and was associated with vascular thrombosis in six, ischaemic necrosis of a cadaver kidney in one, ‘humoral’ shut-down with cortical necrosis in one, and acute tubular necrosis in one.

Early failure, within five days, occurred in nine cases and was associated with vascular thrombosis in five.

Infection and haemorrhage, sometimes occurring concomitantly, featured prominently as complications; infection occurred in twelve instances and haemorrhage in nine.

While it is not unreasonable to anticipate immediate success in a majority of cases of human kidney homotransplantation, early and late failures due to thrombosis, infection, haemorrhage, or renal functional deterioration, a manifestation of rejection, may vitiate the achievement.

Ralph Shackman
Department of Surgery, Postgraduate Medical School of London, Hammersmith Hospital, London (England).

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Effects of Long-Term 6-Mercaptopurine Treatment Upon Kidney Homotransplants in Dogs

Experiments in rabbits and dogs have demonstrated that 6-mercaptopurine (6-MP) can significantly prolong the survival of skin and kidney homografts but these earlier experiments also indicated that homografts survive only as long as they are protected by continuous 6-MP treatment of the host. In the present experiments, renal homo-transplants in three dogs treated with 6-MP for periods ranging from 6 to 8 months continued to function after the termination of 6-MP therapy for periods totaling 508, 516 and 679 days after transplantation.

In one of these dogs the transplant supported the life of the host as its sole kidney for 467 days when it became obstructed by renal stones. In the other two dogs the kidney homotransplants had been reciprocally exchanged by implantation into the necks of the recipients. This permitted testing of the state of tolerance by subsequent exchange of the remaining kidneys. These were implanted into the pelvis about 9 months after the termination of 6-MP treatment so that it was possible to observe the urine outputs of the primary transplants in the neck and these secondary transplants in the pelvis, independently. The secondary transplant in one host was rejected after functioning for 11 days while the primary transplant continued to excrete urine until death of this host 7 days later. The secondary transplant in the other host continued to function together with the primary transplant despite mild homograft reaction processes until the death of the host 27 days after secondary transplantation.

These experiments suggest that if a homograft is maintained by a drug for a prolonged period of time, the drug can be ultimately discontinued without subsequent rejection of the homograft. They further indicate that mechanisms of immunological tolerance and graft adaptation were both operative in the maintenance of the renal homotransplants after the termination of 6-MP therapy.

James C. Pierce
Department of Surgery, University of Minnesota Medica School, Minneapolis, Minn. (USA).

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The Estimation of Vasopressin in the Blood and Urine of Hydrated and Dehydrated Subjects
J. Lee J. Physiol., Lond. 167: 256-262 (1963)
(1) A method for the assay of antidiuretic activity in blood and urine is described.
Vasopressin was never detected in the blood from the ante-cubital vein of hydrated or dehydrated subjects.
The daily urinary excretion of vasopressin in normal hydrated subjects at rest was &lt; 10 mu/day.
Dehydration for 24 h resulted in increased excretion of the hormone to rates between 2 and 3 mu/h; with more severe dehydration, the rate rose to 10-12 mu/h.
Reasons are given for believing that the antidiuretic activity which is destroyed by treatment with sodium thioglycollate is due to vasopressin.
J. Lee
Department of Physiology, Charing Cross Hospital Medical School, London, W.C. 2 (England).

Dissociation Between Filtered Load of Sodium and its Rate of Excretion in the Urine
Urinary sodium under most circumstances represents only about 1% of the filtered load; thus, minor changes in filtered load might result in major changes in the rate of urinary sodium excretion (U\text{\textit{jsiaV}}). Since it is not possible at present to assess small changes in filtered load of sodium because of the magnitude of error involved in measuring glomerular filtration rate (GFR), it is not reasonable to ascribe a change in \text{\textit{UNaV}} to a variation in tubular reabsorption simply because there is no apparent change in the filtered load. Furthermore, the un-
certainty involved in measuring small changes in filtered load of sodium has afforded difficulty in delineating the role of each of its components, plasma sodium concentration (PNa) a\text{\textipa{}}d GFR, in regulating sodium excretion.
The bulk of evidence supports the view that acute changes in \text{\textit{UNaV}} can be accounted for by fluctuations in filtered load.
The present study examines in dogs the relationship between filtered load of sodium and U\text{\textit{jsiaV}} when PNa is increasing and filtered load is decreasing as a consequence of the infusion of a solution of hypertonic saline and the simultaneous disproportionate depression of GFR.
No direct relationship between filtered load of sodium and \text{\textit{UNaV}} was found. \text{\textit{UNaV}} was markedly elevated over control values despite a depressed filtered load. Linear correlation between log. \text{\textit{UNaV}} and PNa was observed.
We concluded that factors other than filtered load influence \text{\textit{UNaV}}, and the data imply that plasma sodium concentration may be one of the regulating influences.
William B. Blythe
Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, N.C. (USA).

Pressor Activity of Renal Venous Effluent of Normal and Hypertensive Rats
H. Sokabe and A. Grollman Amer. J. Physiol. 205: 264-266 (1963)
The problem as to whether the kidney secretes an agent (specifically, renin) responsible for the elevation in blood pressure observed in hypertension has preoccupied the attention of many workers. The determination of the rate of release of renin by the kidney offers a direct means for evaluating this problem and is superior to such indirect procedures as measuring the renin
content of the kidney, determining the juxtaglomerular granulation index, etc. However, the
procedure of grafting the kidney to a bilaterally nephrectomized recipient as a means of
determining the resting renin secretion of the kidney was shown to be accompanied usually by
alterations in blood pressure

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which induce a liberation of renin. Unavoidable manipulations involved in the procedure result
in the liberation of pressor material. The observed pressor response under these conditions is not
a result of the resting secretion of renin as has been claimed by previous workers. When properly
performed no pressor effect of the renal venous blood is demonstrable. An alternative procedure
in which a fixed period of ischemia is induced by preliminary flushing of the donor’s kidney
with saline is recommended for utilizing this procedure in evaluating the rate of secretion of
renin. In the rat, the resting rate of secretion of renin, if any, is insufficient to exert a pressor
effect.
The results of the present study confirm those of previous workers who have demonstrated that
there is a decrease rather than an increase in the renin content of the kidney of the hypertensive
rat as measured in kidney extracts or by the rate of secretion of renin from the kidney. There is
accordingly no basis for the view that renin is concerned in the pathogenesis of hypertension, a
view consistent with other available data (1). Renin apparently is concerned primarily with the
control of aldosterone secretion and is only secondarily affected by alterations in blood pressure
(2, 3).

References
Grollman, A.: Alterations in blood pressure with particular reference to hypertension, Chap. X,
in The functional pathology of disease: The physiologic basis of clinical medicine, 2nd ed.

Arthur Grollman
Department of Experimental Medicine, Southwestern Medical School, The University of Texas,
5323 Harry Hines Boulevard, Dallas ^/, Texas (USA).
Renal Water Reabsorption During Saline and Urea Osmotic Diuresis in the Dog
Free water reabsorption (T^) was measured in conscious dogs during a long-term, reasonably
steady-state osmotic diuresis induced either

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by sodium salts or by urea. After 4 to 8 hours the original solute was partially replaced by urea or
by sodium salts. Both the replacement of sodium salts by urea and the converse procedure were
associated with an augmentation in T|^.

During sodium diuresis T|^ always fell during the first 2
or 3 hours, a change which appeared unrelated to glomerular filtration rate (GFR) or to osmolar
clearance. During the course of urea diuresis T|^ steadily increased and showed a positive
correlation with GFR. A possible basis for such a correlation is discussed.

David L. Maude
Biophysical Laboratory, Harvard Medical School, Boston i), Mass. (USA).
Effect of Strophanthidin on the Fluxes of Potassium in Rabbit Kidney Slices
M. Burg and J. Orloff Amer J. Physiol. 205: 139-146 (1963)
The effect of the cardiotonic steroid strophanthidin on the K content and K42 exchange rates of rabbit kidney slices was determined. Strophanthidin decreased the influx of K into renal tubule cells, thereby accounting for an observed reduction in the K content of slices in vitro and a diminished rate of secretion of K in vivo. It is probable that the inhibitor also decreases the rate constant for efflux of K from the tubule cells. However, the latter conclusion requires qualification since the thickness and structure of kidney slices complicate the interpretation of isotope exchange data, particularly in this case with respect to the analysis of changes in K efflux.

A theoretical analysis of the effect of kidney slice structure on K42 exchange is given. It is emphasized that the relationship between K42 exchange observed using a whole slice and the true exchange rate across the individual cell membranes is not direct and, furthermore, varies with the experimental conditions. Although an approximate relationship can be calculated, this requires several assumptions and approximations which limit the usefulness of kidney slices (and other solid tissue) for the estimation of fluxes across cell membranes. The latter can be done more readily in kidney tissue by employing a suspension of tubules separated from rabbit kidney cortex, as reported in Burg and Orloff, Oxygen consumption and active transport in separated renal tubules’ (Amer. J. Physiol. 203: 327-330 [1962]), and Burg, Grollman and Orloff, ‘Sodium and potassium flux of separated renal tubules’ (Amer. J. Physiol. 206: 483-491 [1964]).

M. Burg and J. Orloff
Laboratory of Kidney and Electrolyte Metabolism, National Heart Institute, National Institutes of Health, Bethesda, Md. (USA).

Radiomercury-Labelled Chlormefodrin for in vivo Uptake Studies and Scintillation Scanning of Unilateral Renal Lesions Associated with Hypertension
R.C. Reba, J.G. McAfee and H.N. Wagner, Jr.
Medicine 42: 269-296 (1963)

(1) Following the intravenous injection of radiomercury-labelled chlor-merodrin, a combination of two radioisotopic techniques proved to be an accurate means of detecting unilateral renal disease in a series of 147 patients with hypertension. First, the rate of accumulation of the radiomercurial for each kidney was measured independently by paired external scintillation detectors during a 30 to 60 minute period. Second, the distribution of the labelled diuretic within the renal parenchyma was delineated by scintillation scanning.

(2) The results of the chlormerodrin accumulation test were expressed as a ratio of the count rate at any time t, divided by the count rate at five minutes (Q/C5) after intravenous injection. The Q/C5 ratios on the right were then divided by the corresponding ratios on the left. The normal ranges of these right/left ratios were defined as the 95 percentile values obtained in a group of normotensive individuals. The ratios in 116 patients with hypertension not associated with unilateral renal disease did not statistically differ from the group of normotensive controls.

(3) The right/left ratios were beyond the normal ranges in 30 out of 31 patients with unilateral renal diseased associated with hyper-
tension. The evaluation of the exponential half-times of accumulation, or comparisons of the absolute count rates at 30 or 60 minutes proved inferior as criteria for selecting those patients with unilateral renal disease.

(4) The chlormerodrin accumulation test was not influenced by variations in urine flow, changes in specific activity of the organic mercurial in the range 4 to 80 µg Hg/kg body weight, variations in the rate of intravascular mixing phase which follows an intravenous injection, or by differences in the absolute count rates recorded. Possible sources of error in the test included malposition of the detectors, subcutaneous infiltration of the administered dose, and the presence of free mercury in the organic mercurial preparation.

\[
\begin{array}{cccc}
Ei & C5 & Ei & C5 \\
\hline
\text{NORMAL} & \\
\text{Right Kidney} & \\
\text{ESSENTIAL HYPERTENSION} & \text{Right Kidney} \\
\end{array}
\]

Comparison of Right/Left

\[
\begin{array}{c}
\text{Ct} \\
1.3 \\
\text{RIGHT} 1.2 \\
\text{LEFT} 1.1 \\
Ei \text{ LEFT} & \text{H} \\
C5 & 9 \\
.8 & .7 \\
\end{array}
\]

Comparison of Right/Left

\[
\begin{array}{cccc}
0 & 5 & 10 & 20 30 40 50 60 \\
\text{MINUTES} & \\
\end{array}
\]

Fig. Method of evaluating the rate of chlormerodrin accumulation, with comparison of 17 selected normal individuals and 58 patients with essential hypertension. The count rates at any time, \( t \) are divided by the five minute count rate. These ratios for the right kidney are then divided by those of the left (bottom figures). Shaded areas represent the 95 percentile normal ranges.

Renal scintillation scanning as an isolated procedure was not a satisfactory screening method. In 6 out of 31 patients with unilateral renal lesions, this procedure failed to show any abnormalities. It was valuable, however, in demonstrating differences in renal size, segmental areas of ischemia, and infarction.
Radioactive I\textsuperscript{131} Hippuran® renograms were positive in only 10 of 18 patients with unilateral renal disease. The remaining eight studies gave misleading information. Furthermore, symmetrical tracings were obtained in 17 of 28 renograms in patients with essential hypertension. Frequently the ‘symmetrical’ renograms were bizarre in configuration.

(7) The accumulation of labelled chlormerodrin is primarily dependent on renal blood flow and renal extraction efficiency. The variabilities due to changing rates of urinary flow, encountered with I\textsuperscript{131} Hippuran®, are virtually eliminated.

The combination of chlormerodrin accumulation test and renal scintillation scanning is a relatively simple procedure, free of complications or morbidity, with reproducible results. Both functional and morphological information about the kidneys are provided by a single intravenous injection.

To reduce the radiation dosage to the kidney, it is recommended that Hg\textsuperscript{197} labelled chlormerodrin be used rather than the nuclide Hg\textsuperscript{203}.

(10) For better demonstration of the kidneys by scintillation scanning in the presence of renal insufficiency, Hg\textsuperscript{197} chlormeprorodrincysteine complex should be used.

Richard C. Reba
Department of Isotope Metabolism, Walter Reed Army Medical Center, Walter Reed Army Institute of Research, Washington 12, D.C. (USA).

Mechanism by which Dietary Protein Enhances Renal Concentrating Ability

It is well established that protein feeding enhances, and protein deprivation depresses, the ability of the kidneys to concentrate urine.

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In the past this has been ascribed to the increased excretion of urea in the urine on a high-protein diet. Since urea permeates the walls of collecting ducts to appear in high concentration in medullary interstitial fluid, water is not obligated by urea to the same extent as by non urea solutes. Additional urea appearing in the urine would therefore raise total urinary solute concentration, by an increment not exceeding the increase in the concentration of urea itself. The present experiments indicate that renal ability to concentrate solutes other than urea is also improved in dogs by feeding protein. The effect is most apparent during osmotic diuresis induced by mannitol, when urea no longer makes up the bulk of the urinary solute. Though explicable in some animals by increases in glomerular filtration rate, it was also observed in dogs whose GFR did not rise with protein feeding. The increase in urinary concentration of non-urea solutes was associated with an increase in the concentration of sodium and potassium in the water of papillary tissue. The data therefore suggest that protein depletion may impair, and protein feeding enhance, the mechanism by which potassium is concentrated in the cells of the medulla and sodium is sequestered in the medullary interstitium.

Franklin H. Epstein
Department of Internal Medicine, Yale University School of Medicine, New Haven, Conn. (USA).

Effect of Glucose on Sodium Excretion and Renal Concentrating Ability after Starvation in Man
H. K. Wright, D. S. Gann and K. Albertsen Metabolism 12: 804-811 (1963)
Studies were conducted to delineate the renal mechanism of reduction in the rate of sodium excretion by glucose administration after a 5-day fast. Initially, solute diuresis with glucose did not differ from mannitol diuresis during maximum antidiuresis. However, after a lag period of 2 hours, sodium excretion was lower at all rates of solute clearance (COSm) during a similar glucose diuresis, and renal concentrating ability measured as Tc\(\frac{\text{TmO}}{\text{sm}}\) was increased simultaneously at any given Q > sm· These effects were independent of body sodium content and of serum sodium concentration. The reduction in sodium excretion may have led directly to augmented concentrating ability. In this case, it seems likely that, in fasted subjects, glucose acts to increase sodium transport into the renal medulla, probably across the ascending limb of the loop of Henle, thus decreasing sodium excretion and increasing renal concentrating ability.

Hastings K. Wright
University Hospitals of Cleveland, Cleveland, Ohio (USA).
Natural History of Acute Glomerulonephritis
A study has been made of the natural history of acute glomerulonephritis based on clinical observations and serial renal biopsies. The observations indicate that (1) the prognosis in patients with relatively mild initial glomerular abnormalities is favorable; (2) the intensity of the disease process reaches its peak early, and thereafter continuous regression of the initial exudative and proliferative changes in glomeruli occurs, proceeding at varying rates among different patients; (3) the intensity of the process subsides rapidly in patients who recover, although in some cases complete subsidence and clinical recovery may ensue only after many years; (4) in patients who failed to recover, regression of the proliferative changes occurs more slowly and is usually accompanied by increasing accumulation of basement membrane-like material; (5) true ‘exacerbations’, i.e., reappearance of exudative and proliferative changes, occur rarely, if at all; and (6) the nephrotic syndrome, if it occurs, does so early when proliferative changes are present and persists in patients with progressive renal insufficiency but subsides in others who are left with relatively unimpaired renal function and who may go on to recovery.
Based on our observations, a classification and nomenclature of the stages of glomerulonephritis are proposed.
Robert T. McCluskey
Department of Pathology, New York University Medical Center, 560 First Avenue, New York 16, N.Y. (USA).

Carcinoma of the Lung with Inappropriate Antidiuresis
T.T. Amatruda, Jr., P.J. Mulrow, J.C. Gallagher and W. H. Sawyer
A case of inappropriate antidiuresis associated with oat-cell carcinoma of the lung is described. The syndrome was not modified by administration of alcohol or chlorpromazine, vagal block, administration of nitrogen mustard or x-ray therapy. Antidiuretic-hormone-like activity was demonstrated in extracts of tumor obtained at autopsy. Previously reported cases reveal a striking association of this syndrome with oat-cell carcinoma of the lung. These observations raise, but do not establish, the possibility that the syndrome is due to the elaboration of a substance with antidiuretic-hormone-like substance by certain tumors.
Uric acid was administered intravenously to dogs and rats. In rats this caused blockage of renal collecting tubules and distal convoluted tubules by urate deposits, with dilatation of the more proximal parts of the tubules. In dogs, which received smaller proportionate doses than did the rats, some tubular casts were seen and tubular blockage was inferred from the finding of grossly dilated tubules, dilated glomeruli, and flattening of tubular epithelium although complete blockage of tubules by urates was not actually demonstrated.

A series of single daily injections of uric acid, 40 mg/kg, in dogs led to renal damage whereas a single injection did not appear to do so.

Subsequent work has shown that the renal clearances of PAH and creatinine in dogs with reduced renal reserve (i.e. unilateral nephrectomy, or impaired function) were greatly depressed by i.v. doses of uric acid which did not impair these clearances in the normal dog, (Duncan, H., Thesis, Univ. of Minnesota 1961).

The purebred Dalmation dog was better able to excrete the added load through the kidney though the oxidation rate of uric acid by the liver is impaired in this breed. [Duncan, H.; Wakim, K.G. and Ward, L.E., J. Lab. clin. Med. 58: 876 (1961)].

Many of the findings in human gouty nephritis were produced in these experimental animals by urate infusions. We suggest that mechanical blockage of renal tubules by urates is an important pathogenetic mechanism in gouty nephritis.

Trimethadione Nephrosis Treated with Cortisone and Nitrogen Mustard


Trimethadione, an anticonvulsant used to treat petit-mal epilepsy, is known to be nephrotoxic in rats, rabbits and guinea pigs. Eighteen cases of nephrotic syndrome following its use in humans are recorded in the literature. Although many of the clinical and laboratory findings are similar to those of idiopathic nephrosis, this entity differs by its frequent response to discontinuation of the drug and by its refractoriness to steroid therapy.

An eleven-year-old girl developed the nephrotic syndrome after ten months of therapy with this drug, 300 mg three times daily. Her condition failed to improve either after nine days’ withdrawal of trimethadione or during the three following weeks, when cortisone was administered in doses of 200 mg to 400 mg per day, along with hydro-chlorothiazide, intravenous albumin and reserpine. Improvement appeared to follow promptly the addition of nitrogen mustard, 5 mg intravenously on each of three days. A full recovery has since occurred, with return to normal of serum total protein, urinary protein and creatinine clearance.

Richard C. Talamo
Clinical Associate, Pediatric Metabolism Branch, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda 14, Md. (USA).
Influence of Analogues of Phenylbutazone on Renal Transport of 4-Aminohippurate
Analogues of phenylbutazone were tested for inhibitory potency in the renal transport
mechanism for 4-aminohippurate. In a series of ten compounds examined by an in vitro
technique, no correlation could be demonstrated between inhibitory potency and acidic strength
of the inhibitor either in rabbit or in dog tissues. In a further series of 16 paired analogues, the
hydroxylated member of each pair was 3-4 times less potent than its unhydroxylated counterpart.
Correlations between molecular structure and pharmacological activity are suggested. In contrast
to these observations, each of three selected phenylbutazone analogues (phenylbutazone,
metabolite II, and sulfin-pyrazone) depressed the maximum tubular excretory rate for 4-aminohippurate in intact dogs, but apparent inhibitory potencies by the clearance technique were
unrelated to inhibitory potencies in dog kidney slices. Differences in relative potencies thus
obtained are attributed to differences in metabolic alteration of each compound at extra-renal
sites in intact dogs.
A. Despopoulos
Department of Pharmacology, University of Louisville School of Medicine, L·omsville, Ky.
(USA).