The effect of chronic renal failure and hemodialysis on carbohydrate metabolism
In an attempt to better define the carbohydrate intolerance of uremia, five patients with abnormal glucose tolerance and chronic renal failure severe enough to require hemodialysis were investigated. After it was certain that calorie intake was adequate the patients were studied with tests of carbohydrate tolerance. In addition, serum immunoreactive insulin (IRI) and free fatty acids were determined in response to intravenous glucose (IVGTT). The patients then underwent frequent hemodialysis, after which they were reevaluated. The frequency of dialysis was subsequently varied in order to determine its effect on glucose metabolism. The data indicate: (1) There is a defect in carbohydrate metabolism present in uremia that is not related to secondary factors such as starvation or latent diabetes meli-tus. (2) This abnormality does not appear to be related to urea per se. (3) The glucose intolerance can be corrected with frequent hemodialysis, but a minimal ‘recovery period’ (approximately 2 weeks) is necessary. (4) The insulin sensitivity and abnormal response to intravenous tolbutamide is also corrected with dialysis. (5) The carbohydrate abnormality will reappear within 7 days if dialysis is withheld. (6) There is a decreased serum IRI response to the IVGTT noted primarily within the first ten minutes of testing. Mean values of IRI were compared with various ‘control’ groups and the ‘uremic’ patients best matched normal subjects after a 7 day fast. The ‘corrected uremics’ (IRI) matched well with normal patients who had similar ‘K’ values. (7) Free fatty acid levels were not significantly different during periods of ‘normal’ and ‘abnormal’ glucose tolerance. It is speculated that a small molecular weight substance(s) accumulates rapidly in uremia and effects carbohydrate metabolism (possibly by interfering with enzyme activity). This is manifest by a decreased serum insulin response to glucose loads and by a peripheral insensitivity to insulin. Author’s address: Dr. C.L. Hampers, Peter Bent Brigham Hospital, Boston, Mass. USA).

Chronic hemodialysis using venipuncture and a surgically created arterio-venous fistula
This paper describes a technique for repeated access to arterial and venous blood for chronic hemodialysis utilizing a surgically produced subcutaneous arterio-venous fistula. The fistula is created between the radial artery and a corresponding vein. Dialysis may be instituted the day following surgery and is performed by use of two venipunctures with 14 gauge thin walled needles. Arterial blood is collected by directing the needle toward the fistula. The venous blood is returned from a needle facing in the opposite direction. Thirteen of sixteen patients were treated by such a fistula for a total of 110 dialysis months. Only two fistula attempts were unsuccessful. Of the established shunts all have continued to work well without complications. Blood flow delivered in the shunt is between 250 and 300 ml/min. There has not been a single episode of fistula cloting, infection, or pulmonary embolae. In addition, no detectable change in
Cardiac output has been observed. The authors conclude that this technique provides a dependable method for repeated access to vessels for hemodialysis and largely removes the clinical and psychological problems associated with external silastic-teflon shunts.

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The electroencephalogram and spinal fluid during hemodialysis


Electroencephalograms (EEG), spinal fluid (CSF) examinations and blood chemistries were compared before and after six hours of hemodialysis with the twin-coil artificial kidney and again twenty-four hours later in nine patients with chronic renal failure. An attempt was also made to evaluate the effect of increasing the osmolality of the dialysate in order to prevent any ‘reverse urea effects’. This was accomplished by adding a higher concentration of glucose to the dialysis bath and reevaluating each patient.

Three-fourths of the patients studied demonstrated a worsening of the EEG after dialysis. In separating the patients into groups according to whether the EEG became ‘worse’ or remained the ‘same’, no statistical difference in any of the parameters measured was found. In particular, there was no difference in blood minus CSF osmolality or in CSF pressure.

The results only suggest that increasing the concentration of glucose in the dialysate may protect against a deteriorating EEG. If this is true, however, it must be due to factors other than by modification of the ‘reverse urea effect’ as no difference in osmolality or CSF pressure between the groups (‘high’ and ‘low’ CHO) was found.

In separating patients into two groups according to changes in their post-dialysis EEG, regardless of the glucose concentration used in the dialysate, no single factor appeared to separate the two. It was concluded from the results that either the critical factors separating the groups were not measured or the changes in the EEG are determined by multiple factors, one or a number operating in the individual case.

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Immunoglobulin class and pattern of nuclear fluorescence in systemic lupus erythematosus


Studies were made on one hundred consecutive patients with multiple-system disease compatible with systemic lupus erythematosus in addition to a positive LE-cell preparation at some time during the course of their illness.

LE-cell preparations were made according to the method of Zimmer and Hargraves (Proc. Staff Meet., Mayo Clinic 27: 424, 1952). Nuclear fluorescence were performed using an indirect fluorescent antibody technique. Patterns of nuclear fluorescence were graded as diffuse (homogeneous), speckled (fluorescence localized in 4 or more discrete spots in the nucleus), or peripheral (shaggy) pattern in which the fluorescence was located along the rim of the nucleus. Anti-serums monospecific for IgG, IgA and IgM conjugated with fluorescein isothio-cyanate.

Antinuclear factor was present in sera from all 100 patients with systemic lupus erythematosus whereas a positive LE-cell preparation was found in only 53 of the patients. All 3 immunoglobulin classes of antinuclear factor were present, and the most common class was IgG.
The peripheral pattern of nuclear fluorescence was present in a significantly higher incidence in serums from patients with clinically active disease than from those in remission. The diffuse and peripheral patterns were seen most frequently in serums from patients with systemic lupus erythematosus, whereas only a few produced a speckled pattern. All 3 patterns were found to be produced by all 3 immunoglobulin classes of antinuclear factor. Although the diffuse and speckled patterns were seen in serums from patients with other diseases, the peripheral pattern appeared only in those from patients with systemic lupus erythematosus.

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Effects of chronic excess salt ingestion: Lack of gross salt retention in salt-hypertension

Two inbred strains of rats were utilized, the ‘sensitive’ strain having a genetic susceptibility to salt-induced hypertension and the ‘resistant’ strain lacking this susceptibility to salt-induced hypertension. The animals were placed on either a high salt (8% sodium chloride) or a low salt (0.35% sodium chloride) diet. Measurements were made of total exchangeable sodium, whole body sodium, sodium turnover, total exchangeable potassium, whole body potassium, and potassium turnover. The biological half life of radioactive sodium-22 was found to be shorter in the ‘sensitive’ strain predisposed to hypertension and this shortened biological half-life of sodium did not appear to be related to elevation in blood pressures per se. Tissue sodium was not found to be increased in the animals with hypertension nor was there evidence of potassium depletion. It was suggested by the authors that the shorter biological half-life of sodium in the ‘sensitive’ hypertensive group was probably due to a slightly greater food intake as compared to the animals resistance to the development of hypertension. It was concluded that experimental hypertension induced in the genetically susceptible rat by excessive salt intake does not occur through gross accumulation of sodium, or depletion or potassium in tissues.

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Association of accelerated (malignant) hypertension in a patient with primary aldosteronism

Clinical observations and metabolic balance studies are presented on a 37 year old female hospitalized with complaints of decreasing vision, ankle edema, dyspnea.

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She was known to have had hypertension for at least 9 years. Admission blood pressure was 230/160 mm Hg. Examination of eyegrounds revealed hemorrhages, exudates and papilledema. Prominent edema was present in the lower extremities and examination of the chest was consistent with congestive heart failure. Admission chemistries were as follows: BUN 13 mg%; serum sodium 134 mEq; potassium 2.4 mEq/l; chloride 100 mEq/l; CO2 content 32 mM/l. Urine pH was 7.0. Urine protein 3+. Divided renal function studies did not reveal unilateral renal ischemia. Urinary 17-hydroxysteroids were 4 mg/day. Salivary sodium/potassium ratio ranged between 0.6 to 0.8. Urine aldosterone excretory rates were elevated, ranging between 34 and 52 µg/d and did not suppress to the normal range during oral salt loading. Plasma renin measurements were not made. The patient underwent adrenal exploratory surgery at which time a 1.8 g adenoma was removed from the left adrenal gland. The right adrenal gland was normal.
The patient’s hypertension was noted to have improved in terms of ease of therapeutic management during a 5 year post-operative period.

In summary, the patient had coexistence of accelerated (malignant) hypertension and primary aldosteronism.

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Subjects with normal circulation or congestive failure received a loading dose and continued infusion of labeled aldosterone. Measurements were made of the concentrations of labeled aldosterone in arterial and renal venous plasma and these were compared with the prediction of certain simulated models programmed with an electrical analog computer in order to determine the distribution of aldosterone and its removal from plasma by the kidneys and liver. In addition, the appearance of labeled conjugate in plasma and urine was examined to determine the formation, distribution and excretion of the acid-labile conjugate. Five control subjects without known disease and one patient with asymptomatic heart disease were studied along with 16 patients undergoing cardiac catheterization. Renal plasma flow was measured by Hippuran-131I. It was found that congestive heart failure affects the regulation of plasma aldosterone in two different ways: (1) Reduced hepatic extraction and clearance of aldosterone tended to increase the steady state concentration of aldosterone in plasma at any given rate of secretion; (2) Plasma aldosterone levels show more rapid and larger response to changing rates of aldosterone input than were seen in normal controls. This was thought to be due to a reduction in the volume of the inner pool of aldosterone. The authors confirmed their earlier observation of a progressive fall in the hepatic clearance of aldosterone with advancing heart failure.

The acid-labile conjugate of aldosterone was consistently found in greater concentration in the renal venous plasma than in arterial plasma demonstrating that the acid-labile conjugate was produced in the kidneys and released into plasma. It was calculated that two-thirds of the urinary acid-labile conjugate was formed in the kidneys in two asymptomatic patients and in six patients with moderate congestive heart failure. No significant renal production of tetrahydroaldosterone glucuronide was detected. About 20% of aldosterone was noted to be extracted from plasma passing through the kidneys over a wide range of renal blood flow. Thus about two-thirds of the acid-labile conjugate of aldosterone (thought to be aldosterone-18-glucuronide) was found to be produced by the kidneys while the remainder of the acid-labile conjugate would appear to be produced by the liver. The principal metabolite of aldosterone in hepatic venous blood is tetrahydroaldosterone glucuronide and this metabolite does not appear to have appreciable extra-hepatic production.

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17-hydroxylation deficiency in man

A 35 year old female patient with deficiency of 17-hydroxylation activity in the adrenal glands is reported. A similar defect in the ovary was postulated. Cortico-sterone and deoxycorticosterone
in excess produced a ‘mineralocorticoid excess’ syndrome characterized by hypertension and hypokalemic alkalosis. The virtual absence of aldosterone secretion by the patient may have represented a second biosynthetic defect. Amenorrhea, hypertension, and hypokalemic alkalosis are the indicators of a 17-hydroxylase deficiency. 17-hydroxylation of steroids occurs only in the adrenal glands and the gonads. The absence of secondary sex characteristics and the negligible excretion of estrogens strongly suggest that the demonstrated 17-hydroxylase deficiency in the adrenal glands also occurs in the ovaries.

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Observation on the diuretic activity of antidiuretic hormone
The effects of physiologic doses of arginine-8-vasopressin on urine flow, urinary chloride concentration, and excretion of alcoholized and hydrated rats were studied following single intravascular injections as well as during slow infusion of the hormone. One hundred fifty-five experiments were carried out on 120 rats.
The ‘antiuretic’ hormone appeared to possess a dual effect on water excretion. It regularly cause diuresis as well as antiureasis. The type of action was dose-dependent. Under the reported experimental conditions, single injections of one milli-micro-unit or infusion of 0.1 mµU/min of arginine-8-vasopressin elicited diuresis while 5 mµU or 0.4 mµU/min, respectively, caused antiureasis. Intermediate doses produced wide individual variations: Diuresis, antiureasis or no response.
For the demonstration of the diuretic effect, the infusion technique proved to be superior to single injection. Greater regularity, higher degree and longer duration characterized the diuresis when elicited by this technique.
Chloride excretion increased in all antiureasis experiments as well as during diuresis when produced by infusion. Diuresis elicited by single injection was accompanied by very variable excretion patterns. Chloride concentration of urine consistently increased during antiureasis with both techniques. However, during

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diuresis following single injection, it decreased in 85% of the cases. Infusion-diuresis gave variable results with the majority showing an increase or a biphasic pattern.
Infusion-diuresis was associated with a much greater increase in chloride concentration and excretion than infusion-antiureasis.

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Evidence for a mucosal effect of aldosterone on sodium transport in the toad bladder
Studies on the mode of action of aldosterone were carried out on the isolated bladder of the toad, Bufo marinus. The increased rate of aerobic metabolism that is associated with the stimulation of sodium transport by aldosterone was found to be dependent upon the presence of sodium in the mucosal bathing medium. Amphotericin B, which increases sodium transport by reducing the permeability barrier to sodium at the apical surface, was shown to mimic the metabolic effects of aldosterone in this tissue.
The experimental evidence presented demonstrated the adequacy of the hypothesis that the action of aldosterone is to increase the entry of sodium into the transport pathway across the apical surfaces of the mucosal epithelial cells. The authors suggest that the metabolic effects of aldosterone are secondary to the entry of sodium into the tissue.

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Release of adrenal catecholamines by angiotensin II

The response of adrenal catecholamine output to intravenous infusions of angiotensin was studied in 34 anesthetized dogs. Angiotensin was infused for 10 min periods with doses of 0.025, 0.05 and 0.10 µg/kg per minute. Vena caval samples were drawn from above the adrenal veins and analyzed fluorometrically for epi-nephrine and norepinephrine content. It was found that angiotensin produced an increase in circulating catecholamines. Epinephrine was significantly increased by infusions of 0.05 and 0.1 µg/kg per minute. Plasma norepinephrine was significantly increased also. The rises in norepinephrine were more transient than those seen with epinephrine. These studies provide direct evidence of adrenal catecholamine release induced by pressor doses of angiotensin.

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Renal angiotensinase activity. Its localization and the effects of mercury

The renal pressor substance, angiotensin, is inactivated by an enzyme or group of enzymes referred to as ‘angiotensinase’. The present studies were performed to investigate further the locus and biochemical properties of the angiotensinase enzyme system. A rat bioassay technique utilizing the anesthetized rat was used to measure angiotensinase activity. The angiotensinase activity of renal homogenates was expressed in terms of the percentage by which control (zero incubation time) angiotensin pressor activity was reduced after 15 and 30 min of incubation.

Angiotensinase activity of the renal cortex at 15 or 30 min time was approximately four times greater than that found in renal medullary or papillary tissue. Complete destruction of proximal renal tubular cells by mercuric chloride resulted in losses of cortical angiotensinase activity averaging 40% of control values. The destruction of cells of both the proximal and distal renal tubules by sodium potassium tartrate caused a 90% reduction in angiotensinase activity. Marked reductions in cortical angiotensinase activity were measured in rats injected with meralluride 2 h previously. When meralluride was added to in vitro systems of normal rat kidney homogenates, similar depressions of angiotensinase activity was noted. The ability or meralluride to inhibit angiotensinase was interfered with by the presence of reduced glutathione. Ammonium ion in a concentration of 0.18 M inhibited angiotensinase activity of renal cortical hemogenates by a moderate degree.

These studies are consistent with the greater concentration of angiotensinase activity being present in the renal cortex in areas composed primarily of cells from the renal glomeruli and the proximal and distal convoluted tubules. Since the agents employed in these studies such as the mercurials, ammonium salts, and angiotensin are all known to affect renal tubular sodium and water metabolism, an interrelationship among these variables may thus be postulated.
Observations on the level and the composition of urinary mucopolysaccharides in patients with ophthalmological and internal arteriosclerotic diseases


Urinary mucopolysaccharides were determined in patients with ophthalmological and internal arteriosclerotic diseases. The values were compared with those of normal persons. No significant differences were found. Paper chromatography of the isolated MPS-fraction showed products of acid and neutral mucopolysaccharides. This method of demonstrating metabolic disorders of mesenchymal tissues is therefore very limited as the neutral mucopolysaccharides are extremely similar to those of the blood plasma.

Studies of mechanism by which phosphate infusion lowers serum calcium concentration


One to 2.8 mM phosphate per kg of body weight as neutral isotonic sodium-potassium phosphate was given intravenously to normal subjects (8), patients with hyperparathyroidism (3), and patients with hypercalcemia due to hyperparathyroidism (4), or cancer (7).

Phosphate infusion lowered serum calcium in all subjects without causing simultaneous losses of calcium from the body. Evidence is presented which indicates that the calcium-lowering effect of phosphate was not hormonally mediated.

The subsequent response to the fall in serum calcium levels induced by phosphate infusion appeared to depend upon the presence and responsiveness of the parathyroid glands.

Effects of hypertonic glucose and mannitol on plasma volume

By Hoff, H. E.; Deavers, S. and Huggins, R. A.: Proc. Soc. exp. Biol., N.Y. 122: 630-634 (1966). The influence of hypertonic glucose and mannitol on blood volume was tested in normovolemic-normotensive and hypovolemic-hypotensive dogs. Twenty-nine fasting dogs anesthetized with pentobarbitol were used. Control dogs received infusions of either a 25% solution of mannitol (1 g/kg in 10 min) or a 25% solution of glucose (1 g/kg in 10 min) via a femoral vein. An additional 17 dogs were given comparable infusions after hemorrhage, sufficient to reduce mean carotid arterial pressure to 50 mm Hg.

Neither glucose nor mannitol has any effect on the blood volume of normovolemic dogs. In hypovolemic-hypotensive dogs, mannitol produced a significant increase in the plasma volume by mobilizing fluid from the extravascular spaces. The fluid entering the circulation was
accompanied by a significant amount of protein. Also, plasma volume increased after hemorrhage with glucose, but the increase was small and was not accompanied by protein. Thus, both glucose and mannitol, but particularly the latter increased the blood volume in hypovolemia.

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Renal hemodynamics and hemorrhagic hypotension / Renale Hämodynamik und hämorrhagische Hypotension


Intrarenal distribution of blood flow and local renal blood flow rates were measured using the inert gas wash-out technique of Thorburn et al. During acute and prolonged arterial hypotension marked redistribution of intrarenal blood flow occurred: The cortical flow fraction decreased from 80% to about 10% of total renal blood flow, while the corticomedullary fraction increased from 14 to 80%. The flow fractions of the inner medulla and perirenal fat increased to a minor extent. No significant changes in local blood flow rates were observed. This typical pattern suggests a decrease in perfused cortical tissue mass. This conclusion was confirmed by radioautography: Areas of cortical ischemia alternate with apparently normally perfused segments. The areas of hyperperfusion expand as hypotension is prolonged. Concerning the clinical picture of acute tubular necrosis (ATN) it is suggested that the initial acute anuria is due to marked cortical vasoconstriction with a primary decrease in glomerular filtration rate. No conclusions are drawn from these observations as to the pathogenesis of the persisting anuria and of the poly-uric phase of ATN.

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Electrolyte excretion in uraemia


Water and solute excretion in twenty-one patients with plasma urea concentrations between 135 and 210 mg/100 ml were compared with those of five healthy students with comparable degrees of uraemia induced by ingestion of urea. The students were studied both before and after receiving 1 mg of aldosterone intravenously.

Patients with different types of renal disease could not be distinguished by their urinary electrolyte excretion. In the patients, the percentage of filtered water excreted seemed to be determined by solute excretion. At constant plasma urea concentration the chief variant in solute excretion was sodium. Seven patients excreted a smaller proportion of their filtered sodium than the students who had received aldosterone. Nine patients excreted a much higher proportion of their filtered sodium than the students and exhibited the features of a physiological sodium diuresis. The patients retaining sodium had significantly higher creatinine clearances, urine osmolality and urine urea concentrations than patients with similar plasma urea concentrations who were having sodium diuresis. Renal function in the patients and students was remarkably similar when considered as solute excretion per unit of glomerular filtrate. The patients had, however, consistently lower urine osmolarities than the students. This defect was not entirely due to solute diuresis.
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