An experimental study of the nephrotoxic effects of oral cholecystographic agents

The effect of oral cholecystographic agents on the kidney was studied in 20 mongrel dogs after ligation of the common bile duct. The animals were divided into 4 equal groups. One group served as controls while the other groups received 1 of 3 contrast agents. The contrast agents used were iopanoic acid, bunamidyl, and ipodate sodium. Laboratory tests of renal and hepatic function were performed on all animals before and after operation, and after the administration of the contrast agent. Each animal was necropsied with histological examination of the liver and kidneys. Definite functional and morphological changes were produced in the experimental groups with production of abnormal blood urea nitrogen and serum creatinine levels with tubular degeneration. The findings correlate with the high incidence of liver disease, with or without jaundice, in the group of 27 cases of acute renal failure, reported in the literature, which occurred after the ingestion of oral cholecystographic agents.

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The renal vascular response to hemorrhage

In the chloralose anesthetized dog, renal blood flows were measured (rotameters) simultaneously from acutely denervated and innervated kidneys. Graded hemorrhages of 10, 20, and 30 ml/kg demonstrated an increasingly greater increase in renal vascular resistance in the innervated kidney. Prior administration of guanethidine eliminated the differential changes in renal vascular resistances of the denervated and innervated kidneys. Adrenalectomy did not alter the observed changes. A continued reduction below control values of renal blood flows and an associated pressor response frequently followed rapid restoration of the blood volume to normal. This pressor effect which was augmented by guanethidine and terminated by phentolamine, was not observed in adrenalectomized animals. It is concluded that the changes in renal vascular resistance during hemorrhage were determined largely by augmented sympathetic nervous activity. A post-hemorrhagic pressor response which occurred in 14 of 38 dogs was due to catecholamines from the adrenal medulla.

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Production of hypertension and vascular disease by kidney extracts

Hypertension was induced in rats by constricting the aorta between the origins of the renal arteries. The left kidney, which became ischemic and atrophic (*endo-
Aqueous extracts of ischemic kidneys, of kidneys contralateral to ischemic kidneys and of normal kidneys were prepared and the supernatant solutions were injected subcutaneously into test rats which had been uninephrectomized a few hours previously. Extracts of ischemic kidneys caused hypertension, cardiac hypertrophy, weight loss, and renal and vascular lesions mimicking the signs which result from renal ischemia. The extracts from the other kidneys were inactive.

It is proposed as a working hypothesis that renal hypertensive disease results not only from increased secretion of renin and formation of angiotensin but from simultaneous release from kidneys with reduced perfusion pressure of a substance which augments the enzymatic formation of angiotensin. This substance is presumably absent from normal kidneys and from semipurified renin preparations.

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Hemodynamic effects of renal transplants in hypertensive and control rats

Transplantation of a normal kidney to a renal hypertensive rat produced a decrease in mean arterial pressure of 171 to 138 mm Hg and a decrease in cardiac output from 258.9 to 167.3 ml/kg/min. There was no significant change in calculated total peripheral resistance or in regional vascular resistance in the perfused hind leg. The decrease in mean arterial pressure is caused by a decrease in cardiac output resulting from a decrease in stroke volume. Kidney transplantation to a normal rat elicits a lesser decrease in mean arterial pressure, which is caused by a decrease in both cardiac output and in total peripheral resistance.

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Quantitative assay and disappearance rate of circulating renin

In isovolemic cross-circulation experiments, a nephrectomized donor rat, into which various doses of hog renin were injected, was connected to a nephrectomized indicator rat. The blood pressure increase thus produced in the indicator rat was compared with the blood pressure response obtained during cross circulation using either intact normotensive or renal hypertensive rats as donor animals. An exponential dose-response relationship was found between hog renin injected into a nephrectomized donor and the blood pressure increase of the indicator rat. Using the cross-circulation technique, the disappearance rate of endogenous renin-like material in the blood of donor animals and of exogenous renin injected into
nephrectomized donor animals was examined. If an intact normotensive animal or a unilaterally nephrectomized hypertensive animal is totally nephrectomized, renin-like material disappears from the blood within 1 h. In renal hypertensive rats, with an untouched contralateral kidney which have a higher concentration of renin-like material in the blood, it takes about twice the normal time until renin-like material disappears from the blood after nephrectomy. The increased and prolonged blood pressure response of the nephrectomized animal to renin is not connected with a prolonged persistence of renin in the blood.

Author’s address: Dr. F. Gross, Research Laboratories of the Pharmaceutical Department of Ciba Limited, Basle (Switzerland).

Hyperresponsiveness of renal hypertensive rats to intravenous angiotensin II
Renal hypertensive rats were found to have a pressor response to angiotensin which exceeded that of normal rats in both magnitude and duration. The results would appear to be in keeping with an intrinsic increase in pressor reactivity of the hypertensive organism, but are not compatible with the production of a specific angiotensinase as an adaptive mechanism to prevent chronic angiotensin-emia.

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Loss of the renal vasoconstrictor activity of angiotensin II during renal ischemia
In dogs anesthetized with morphine-chloralose the induction of renal ischemia resulted in the loss of the renal vasoconstrictor activity of angiotensin II during the period of ischemia. Before renal ischemia, intravenous administration of morphine-chloralose the induction of renal ischemia resulted in the loss of the renal vasoconstrictor activity of angiotensin II during the period of ischemia. Before renal ischemia, intravenous administration of angiotensin II (0.1 µg per kg) elicited a 49% reduction in renal blood flow (RBF). Constriction of the renal artery reduced the RBF 59% (from 174 ml per minute to 72 ml per minute). After induction of renal ischemia, intravenous administration of angiotensin II (0.1 µg per kg) produced a 67% increase in RBF (mean of 42 observations in 24 experiments). An equipressor dose of levarterenol during renal ischemia produced a further reduction in RBF (35%). Renal denervation resulted in the loss of the renal vascular action of angiotensin II in the nonischemic state. A reduction or loss of the renal vascular response to angiotensin II in the nonischemic kidney developed frequently, particularly after prolonged periods of renal ischemia.

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Electrolyte and juxtaglomerular changes in adrenal regeneration hypertension
A time sequence study was made of electrolyte and juxtaglomerular cell changes during development of the hypertension which occurs in unilaterally nephrecto-

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mized rats fed 1% saline following adrenal enucleation and subsequent adrenal cortical regeneration. Control and adrenal enucleated rats were killed at 1, 2, 4, 6, and 8 weeks after operation. At one week skeletal muscle and serum electrolytes followed a pattern similar to adrenal insufficiency. However, at the 2nd week of adrenal regeneration there was a marked shift of sodium into and potassium out of skeletal muscle cells which persisted through the 8th week. These cation shifts correlated with increases in blood pressure and renal and heart weights. In
two subsequent experiments increased sodium and decreased potassium in skeletal muscle cells and increased blood pressure and increased renal and heart weights were potentiated by saline and failed to occur with adrenal regeneration in the hepatic portal circulation. The cause of these marked skeletal muscle electrolyte shifts with adrenal regeneration is unknown but it seems unlikely that they are due to excess mineralo-corticoid production by the regenerating adrenal since serum sodium remained constant throughout the 8 week period and serum potassium rose transiently at 1 and 2 weeks returning thereafter toward control levels. One would expect increased serum sodium and lowered serum potassium with excess mineralocorticoid production.

The correlation between skeletal muscle electrolyte shifts and blood pressure was interpreted in terms of the theory proposed by Friedman et al. that smooth muscle tension is directly related to the ratio: intracellular Na concentration/ extracellular Na concentration. Thus if the skeletal muscle electrolyte shifts found here reflected similar changes in smooth muscle cells of vessels, then one would expect the relationship between skeletal muscle sodium (and potassium) and blood pressure which was found.

Juxtaglomerular cells were examined in the rats killed at 1, 2, 4, 6, and 8 weeks after adrenal enucleation. No change such as hypergranularity or hyperplasia which might be expected to initiate a blood pressure increase was found to precede the development of hypertension. The degranulation which was observed was interpreted as the result rather than the cause of the blood pressure change.

Reference

Author’s address: Dr. John P. Rapp, Penrose Research Laboratory, Zoological Society of Philadelphia and Dept. of Pathology, University of Pennsylvania, Philadelphia, Pa. (USA).

The effect of renal perfusion pressure on the net transport of sodium out of distal tubular urine as studied with the stop-flow technique


After a 55-minute perfusion of isolated kidneys at 170 mm Hg, the tubular cells in the distal part of the nephron have a relatively limited ability to effect a net transport of sodium out of the distal tubular urine in a stop-flow situation. In two series of experiments utilizing this high perfusion pressure, the lowest concentration of sodium in the stop-flow studies averaged 31 mEq/l and 25 mEq/l respectively. Conversely, after a 55-minute perfusion at 100 mm Hg, the distal tubular cells have a relatively enhanced ability to effect a net transport of sodium out of the distal urine. In a series of experiments utilizing this lower perfusion pressure, the lowest concentration of sodium in the stop-flow studies averaged 14 mEq/l. In a subsequent summary using a different stop-flow method, the high perfusion pressure resulted in an average minimal sodium concentration of 13.7 mEq/kg, whereas the low perfusion pressure produced an average minimal sodium concentration of 7.9 mEq/kg. This difference in net transport of sodium seems related more to the perfusion pressure than to the rate of blood or urine flow. Renal hemodynamics and the rate of flow in the renal tubules during the stop period cannot account for the difference. The difference in net sodium transport does not depend upon a changing rate of aldosterone secretion or upon neurogenic reflexes from the central nervous...
system. Apparently, changing the distention of the renal arterial bed by altering perfusion pressure somehow influences the ability of distal tubular cells to effect a net transport of sodium, underdistention increasing transport and overdistention decreasing it. The authors speculate that the varying levels of perfusion pressure are sensed by the granular juxtaglomerular cells, acting as stretch receptors. The juxtaglomerular apparatus (granular cells plus macula densa cells) then appropriately responds by changing its rate of secretion. The concentration of these secretory substances in the fluids of the kidney subsequently regulates the net transport of sodium in the distal convoluted tubule and collecting duct, acting in concert with the tissue levels of aldosterone. This mechanism is probably active in various sodium-retaining situations associated with underdistention of the arterial tree. It may also partially explain the phenomenon of the Howard test.

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Transport by diffusion in the terminal nephron segment
By Hills, A.G.
It is established that antidiuresis is accomplished by passive reabsorption of water from the terminal nephron (collecting ducts and distal tubules) down an osmotic gradient (1, 2). It immediately follows that urinary solutes which are highly diffusible in water and through membranes should tend to be increasingly reabsorbed, as urine flow declines, down an increasing concentration gradient resulting from water reabsorption. Two such urinary solutes—the gases CO2 and N\(\frac{1}{2}\)—are each a constituent of a buffer system; their reabsorption, while their charged congeners HCC\(\frac{1}{2}\) and NH4+ are restrained, should lead (1) to decreasing excretion of total CO2 and total ammonia as urine flow declines, both of which phenomena are regularly demonstrable (3, 4); and (2) to change in urine reaction, since evolution of CO2 is a H+-consuming reaction, and evolution of NH3 a HA-generating reaction:

1. \(\text{NH}_4^+ \rightarrow \text{N}\frac{1}{2} (\text{reabsorbed}) + \text{H}^+\)
2. \(\text{H}^+ + \text{HCO}_3^- \rightarrow \text{H}_2\text{CO}_3 \rightarrow \text{CO}_2 (\text{reabsorbed}) + \frac{1}{2}\text{O}\)

In more acid urines (pH < 6.4 at 37° at maximal diuresis), in which [HCO3-] is negligible, antidiuresis produces a decline of pH. Because of the high pK’ of NH4OH, at least 95% of total ammonia in all body fluids is always N\(\frac{1}{2}\); consequently the H+ generated within the nephron by reaction No. 1 above, as the flow-rate of bicarbonate-poor urine declines, must be chemically equivalent (to a close approximation) to the excess ammonia reabsorbed. This equivalence has been demonstrated in man by excretion data (3). Evidence direct and indirect has also been marshalled (3) to show that NH3, having diffused into the acidified fluid of the distal tubule, subsequently diffuses out of the nephron as a result of water re-absorption. In experiments where urine pH at maximal flow exceeds 6.7, relatively little ammonia is present and the CO2 buffer system is the predominant volatile buffer; for this reason (4), antidiuresis causes urine pH to rise as a result of H+-consumption according to reaction No. 2. The Pco2 of alkaline urine likewise rises with antidiuresis. The evidence indicates (4, 5) that the rise is due to continuing dehydration beyond the papilla of H2CO3 generated throughout the terminal nephron by reaction No. 2 and present in papillary urine at a concentration exceeding its equilibrium value for the system, since non-enzymatic dehydration of the H2CO3 being newly generated is outstripped by the rate of passive reabsorption of CO2. The rise of urinary pH
beyond the papilla which accompanies the dehydration of $\text{H}_2\text{CO}_3$ to equilibrium raises urinary $[\text{NH}_3]$ by increasing the urinary ratio $N/\text{total ammonia.}$

The $P_{\text{CO}_2}$ of markedly acid urine rises during water diuresis (4), apparently because the high flow rate sweeps into the pelves some of the undehydrated $\text{H}_2\text{CO}_3$ formed by reaction of $\text{HCG}$ with secreted $\text{H}^+$ (6). This mechanism appears also to account for the somewhat higher $P_{\text{CO}_2}$ of alkaline urine as compared with acid urine during maximal diuresis (4).

References
Author’s address: Dr. A. Gorman Hills, Section of Metabolism, Department of Medicine, University of Miami, School of Medicine, Miami, Flia. (USA).

Studies have been conducted in unanesthetized dogs during the acute transition from water diuresis to antidiuresis, induced by the rapid administration of lysine vasopressin. Attention has been directed primarily to the concentration patterns of urea and of nonurea solutes in the urine during this transitory state. The effect of variations in tubular permeability on these concentration patterns has been evaluated by administering graded doses of vasopressin, 10, 30, and 300 mU, in separate experiments.

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Following the highest dose of vasopressin, there occurs an initial rise in urinary nonurea solute concentration, which is not associated with a concomitant increase in urea concentration. This is interpreted as indicating a high degree of discrimination between these molecular species under conditions of maximal tubular permeability. Studies utilizing submaximal amounts of hormone suggest that the ability of the tubule to exercise this discrimination is directly related to the degree of tubular permeability, or the dosage of vasopressin. These observations suggest a method for the evaluation of membrane permeability in the distal nephron of the intact animal.

The apparent high degree of permeability to urea of the distal nephron in the presence of maximal amounts of vasopressin suggests that trapping of urea, by the vascular countercurrent exchanger in the medulla, may be the primary means by which a high concentration of urea is achieved within the distal collecting duct, and ultimately the medullary interstitium, in the antidiuretic state.

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Effects of cyanide, Qo and Dinitrophenol on renal sodium reabsorption and oxygen consumption
Effects on sodium reabsorption and oxygen consumption of the renal arterial injection of three
metabolic inhibitors were studied by unilateral clearance techniques in anesthetized dogs. In
control studies, 21.5 ± 2.3 mEq of sodium were reabsorbed per mM of oxygen consumed within
a spontaneous range of sodium reabsorption of from 2 to 9 mEq/min. A total dose of 10−4 M of
cyanide depressed both sodium reabsorption and oxygen consumption in the injected kidney.
Administration of 10−4 M of Q0, the quinone nucleus of coenzyme Q, reduced sodium
reabsorption and had a variable effect on C½ consumption. Dinitrophenol, in a total dose of 10−3
M, increased oxygen consumption without affecting the percent of filtered sodium that was
reabsorbed. The resultant Na:Ü2 ratios were 12:1. We conclude that the major fraction of O2
consumption energizes sodium reabsorption in the kidney. Energy from oxidation may energize
sodium reabsorption via the classic route of ATP synthesis and hydrolysis. However, all three
compounds used in this study would be predicted to decrease renal ATP concentrations. Only
cyanide and Q0, decreased sodium reabsorption. Energy for sodium movement may come
directly from oxidative metabolism by-passing synthesis and breakdown of ATP.
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Excretion of Krebs cycle acids in relation to the cycle’s activity in avian kidney
In the chicken, unilateral renal portal perfusion with certain intermediates of the Krebs cycle
(notably sodium α-ketoglutarate, succinate, and fumarate) increased excretion of other cycle
acids, particularly citrate and α-ketoglutarate. These were excreted at a much higher rate from
ipsilateral kidney. This phenomenon was even
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more striking during infusion of sodium pyruvate with one seventh the amount of sodium
fumarate, α-ketoglutarate, or oxaloacetate. This resembles the catalytic, or ‘sparking’ effect of
these same dicarboxylic acids on pyruvate oxidation by the Krebs cycle in certain tissues, a
resemblance strengthened by the fact that this sparked excretion of cycle acids is blocked by
sodium malonate or ammonium salts which also block the effect in tissues. These observations
are discussed in terms of (1) the possible renal tubular synthesis and secretion of these cycle
acids from their infused precursors, and (2) the increased excretion of citrate and α-ketoglutarate
in alkalosis.
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Experimental streptococcal infections. I. Production of renal disease in the white mouse
Several strains of group A streptococci induced renal disease in the Webster strain of white
mouse (Harvard colony substrain) when live organisms were injected subcutaneously. The strain
studied most intensively induced albuminuria in about 90% of animals receiving an appropriate
dose. Both sexes developed renal disease 2-5 days after the infection was established. Males
were more severely affected and frequently developed hypoalbuminemia and generalized edema
with ascites. Cultures made from kidneys after renal disease was well established rarely revealed
streptococci, although positive cultures were obtained from 1 or more of the viscera in almost
half the animals within 2 to 24 hours after subcutaneous injection of live organisms. Resistance
to renal disease developed in animals intensively immunized with live organisms. Attempts to isolate a nephrotoxic factor from broth culture filtrates were unsuccessful. Streptolysin S induced hemoglobinuria and methemoglobinuria but not albuminuria.

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Prolonged exposure to nephritogenic beta-hemolytic streptococcus in intra-peritoneal diffusion chambers

Diffusion chambers containing beta-hemolytic streptococci, nephritogenic in man implanted in the peritoneal cavity of rats and rabbits for intervals ranging from 2 to 42 days did not produce definite glomerular lesions and in particular the lesions characteristic of glomerulonephritis. Tubular damage was noted in all animals. There were no consistent urinary changes. The sera of experimental rats did not contain antibody with affinity for kidney as demonstrated by the fluorescent antibody technique. These results are somewhat at variance with previous reports of experiments performed with rats and mice, but similar to the results of others using mice.

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Nephrotoxic serum nephritis in thymectomized rats

Clinical, biochemical, morphological and immunohistochemical characteristics of renal disease induced in rats with injections of anti-rat kidney rabbit serum (NTS) were simular in adult rats which were thymectomized at birth and in intact members of comparable age. The development of chronic glomerular lesions in thymectomized, NTS-treated rats indicates that progression of the disease is not necessarily dependent upon those immunologic functions related to thymic function, at least during the time interval studied.

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Electron microscopy of renal coagulative necrosis due to d/-serine, with special reference to mitochondrial pyknosis

In the regularly induced coagulation necrosis occurring in the distal portion of the proximal renal tubule convolution in rats after administration of ¿/-serine (1), two types of cytoplasmic lesions were distinguished. These were ‘vacuolar’ and ‘coagulative’ and often co-existed in the same cell. The vacuolar lesion appeared in cyto-
Fig. 1. An electron micrograph showing part of two cells from a proximal convoluted tubule of a rat kidney one hour after the injection of dl-serine. Most mitochondria are pyknotic. A vacuolated mitochondrion is labeled vm. Conglomerations of dense mitochondria are marked by arrows. Towards the right edge of the picture several multivesicular bodies (mv) are seen × 18,000.

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plasmic matrix with lessened electron density and was most frequently characterized by an increased number of vesicles. These could have originated from distended endoplasmic reticulum, in vacuolated, fragmented brush border micro-villi or from swollen mitochondria. There were also conglomerations of tubular and vesicular structures, possibly originating from the endoplasmic reticulum. Cyto-somes and particularly multivesicular bodies were markedly increased in number and size (Fig. 1). The majority of mitochondria appeared shrunken and exhibited increased matrix density.

In cytoplasmic coagulative necrosis, increased density was observed not only in mitochondria but in all other subcellular structures as well.

It was assumed that vacuolar changes, which may occur in a variety of states (e.g. anoxia) indicated a moderate degree of reversible cellular damage. The onset of mitochondrial pyknosis and cytoplasmic coagulative necrosis, however, signified an irreversible lesion.

Reference

Author’s address: Dr. Max Wachstein, Department of Pathology, Beth Israel Hospital, Passaic, N. J. and St. Catherine’s Hospital, Brooklyn, N.Y. (USA).

Dwarfed kidneys in children: The classification, etiology, and significance of bilateral small kidneys in 11 children
The radiologic demonstration of bilateral small kidneys in a child, usually presenting with signs of renal insufficiency, commonly results in the diagnosis of renal hypoplasia. However, in our experience, these kidneys are rarely truly hypoplastic, that is small in size but otherwise normal in gross and microscopic structure. The clinical course and gross and microscopic pathology of the kidney in eleven children in whom a diagnosis of ‘hypoplastic kidneys’ was made is presented.

Six were found to have a normal urinary collecting system, no evidence of urinary tract infection, and no dysplastic changes in the kidney at autopsy. The other group of five patients showed evidence of obstructive uropathy, had frequent urinary tract infections, and three had pathologic changes in the kidney, compatible with dysplasia of the renal elements. Clinically, all eleven patients were similar, with persistent proteinuria, marked inability to concentrate the urine, elevation of the erythrocyte sedimentation rate, very small kidneys, and the development of renal insufficiency and its sequellae characteristic of each course.

Microscopically, the kidneys in the first group of patients showed chronic inflammation compatible with a chronic non-bacterial inflammatory disease, primary either to the glomeruli or the interstitial tissues. We believe that this group represents a syndrome similar to chronic glomerulonephritis or chronic interstitial fibrosis of unknown etiology. The second group of patients clearly had dysplastic kidneys associated with frequent episodes of pyelonephritis. The term ‘hypoplastic kidneys’ is, therefore, not appropriate for description of either of these two groups. The literature regarding ‘dwarfed’ kidneys is reviewed, and the inter-relationships between the various forms of small kidneys is discussed.

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Association of nephrotic syndrome and nephroblastoma in siblings

The cases of a brother and sister aged less than one year who presented similar clinical pictures where Wilms’ nephroblastoma was associated with nephrotic syndrome are described. The exceptional nature of the case is emphasized and the appearance mechanism of the two phenomena, tumoural and nephrotic, is discussed in the light of the factor of familial appearance. At the present moment it is impossible to determine if one is a consequence of the other or if they arose contemporaneously. The familial nature, however, makes contemporaneous appearance more probable.

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Renal artery stenosis and the nephrotic syndrome

In this paper the authors describe three patients who had the combination of nephrotic syndrome and renal artery stenosis. In two of the patients, males aged 57 and 39 respectively, malignant hypertension preceded the onset of nephrotic syndrome, and was associated with a raised central venous pressure. Renal artery stenosis was diagnosed by aortography; the hypertension was treated with hypo-tensive drugs, resulting in reduction in proteinuria and cure of the nephrotic syndrome. In these two patients the cause of the development of the nephrotic syndrome was thought to be either severe hypertension or congestive heart failure, or both in combination. In a third case, a 13 year old girl, long standing nephrotic syndrome due to a lobular type of glomerulonephritis caused severe hyper-cholesterolaemia and led to the development of...
hypertension. At autopsy she was found to have multiple renal arteries the aortic mouths of which were occluded by severe atheroma of the aorta. It was considered that the prolonged hypercholester-olaemia associated with nephrotic syndrome was responsible for the atheroma of the aorta which caused renal artery ostial occlusion. From these three patients the following conclusions could be drawn:

That nephrotic syndrome could be a presenting feature of renal artery stenosis, responding to hypotensive therapy.

That severe hypertension associated with long standing and previously normotensive nephrotic syndrome may be due to renal artery stenosis caused by atheroma.

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Renal artery stenosis: A clinical-pathologic study in normotensive and hypertensive patients

Moderate or severe renal artery stenosis was found at necropsy in 53% of 295 un-selected patients (49% of 256 normotensive patients and 77% of 39 hypertensive patients). Severe stenosis of the renal arteries was uncommon in normotensive patients less than 50 years old; thereafter, the frequency increased with age. Afferent arteriolar sclerosis of moderate or severe degree was uncommon in normo-250

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tensive patients less than age 60. The demonstration of unilateral or bilateral renal artery stenosis does not appear to warrant the conclusion that the stenosis is responsible for the associated hypertension, particularly in patients more than age 50. Ancillary studies must be undertaken to determine the clinical significance, if any, of the renal artery stenosis before appropriate decisions regarding management can be reached.

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Renal homotransplantation in 24 patients

Between January 1963 and December 1964, 46 renal homotransplantations were performed on 39 patients. Nineteen patients have functioning homografts (8 from living donors and 11 from cadavers). Five recipients have lived for over one year, the longest period of function being 19 months. The longest period of survival of a cadaver kidney so far is 15 months. Two patients are being maintained by periodic dialysis after removal of the homograft.

Azathioprine and Prednisone were the main immunosuppressive agents used. Actinomycin C, local irradiation of the graft, splenectomy and thymectomy were used in many patients as adjunct therapy. Hemodialysis played an important part in the preparation of all recipients before transplantation and in the maintenance of recipients of cadaver kidneys during the period of renal shutdown.

After successful transplantation patients were able to lead a normal life. Recovery from anaemia, malignant hypertension, and pruritus was the rule. Clinical improvement of uraemic neuropathy was noted in four patients. Clinical episodes of rejection were uncommon when continuous and adequate immunosuppressive therapy was used. Vascular changes occurred in four patients and were probably a manifestation of rejection. Leakage from the ureterovesical anastomosis has
been successfully corrected in two patients but has caused a fatal septicaemia on two occasions. The diagnosis of postoperative anuria is difficult and ureteric obstruction must be excluded. Fever after transplantation may be due to infection or rejection; a therapeutic trial with Prednisone may be helpful, but it is unwise to increase the dose of azathioprine. The use of cadaver kidneys avoids many social and ethical problems. Our early results with cadaver transplants are encouraging and we believe that no cadaver kidney should go to waste. Author’s address: Dr. George Dunea, Dept. of Artificial Organs and Dept. of Urology, Cleveland Clinic Foundation, Cleveland, Ohio (USA).

Secretion gastrique des urémies chroniques

L’étude de la secretion gastrique a été entreprise chez 33 urémiques; les résultats sont comparés à ceux obtenus chez 26 sujets témoins. Contrairement à l’opinion couramment admise, l’acidité totale est augmentée et l’acidité libre conservée; la qualité de la secretion se trouve confirmée par la haute teneur en potassium du contenu gastrique des urémiques. La raison de cette modification de la secretion demeure inconnue.

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Le taux de l’ammoniac du liquide gastrique est très variable, inversement proportionnel à celui de l’urée. Le rapport de ces deux corps est indépendant de toutes circonstances extérieures apparentes, aussi bien chez les témoins que chez les urémiques. Cela suggère que le pouvoir uréasique de la paroi de l’estomac, variable d’un cas à l’autre, chez les témoins comme chez les urémiques, est conservée chez les insuffisants rénaux chroniques. L’ammoniac du liquide gastrique n’est jamais en quantité suffisante pour neutraliser l’acidité libre qui demeure élevée.

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Nephrogenic anemia and renal hemodynamics – Nephrogene Anämie und Nierenhämodynamik

The relation of anemia to atrophy of the renal parenchyma was investigated quantitatively under uniform test conditions in 132 patients, 89 with glomerulonephritis and 43 with chronic recurrent pyelonephritis. The findings were as follows: There is a highly significant (P < 0.001) hyperbolic correlation between inulin clearance and renal PAH clearance on the one hand, and the hemoglobin content of peripheral blood on the other. The correlation with inulin clearance is stronger than with PAH clearance. Chronic renal patients become anemic only when the glomerular filtration rate is reduced to 25-30% of the norm, a level corresponding to a rise in plasma creatinine to about 2-4 mg/100 ml. Pronounced anemia can be expected if the inulin clearance values are below 20 ml/min/1.73 m2 and the PAH clearance values far below 300 ml/min/1.73 m2.

Where the reduction in clearance values is the same, no difference in the degree of anemia in patients with chronic pyelonephritis and those with chronic glomerulonephritis can be detected from the hemoglobin content of peripheral blood. Nor is any difference in the anemia of patients with chronic glomerulonephritis and chronic recurrent pyelonephritis detectable on the basis of inflammatory activity. When the reduction of the renal parenchyma has reached a certain point, nephrogenic anemia appears to evolve regardless of the nature of the destructive process. Nephrogenic anemia is predominantly normochronic. The mean colour index is 0.978, with a range of variation between 0.77 and 1.11. No significant difference can be observed between glomerulo- and pyelonephritis.
The results are discussed in the light of other authors’ sometimes contradictory views on the pathogenesis of nephrogenic anemia. The results do not answer the question of how far the localisation of renal tissue destruction indicates the site of formation and role of renal erythropoietin in the genesis of nephrogenic anemia.

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On the glutathione (GSH) content of red cells in chronic renal failure – Über den Glutathion-(GSH)-Gehalt der Erythrocyten bei chronisch renaler Insuffizienz


In 26 patients with chronic glomerular, tubular and global insufficiency reduced glutathione content in the erythrocytes was determined by a new specific paper chromatographic technique [Wernze, H. and Koch, W.: Klin. Wschr. 43: 453-454 (1965)]. 38% of the values were in the normal range, the remaining were slightly or markedly elevated. Incubation with acetylphenylhydrazine did not show any GSH-instability. There is no definite correlation between the extent of anemia, azotemia, reticulocyte count and GSH-concentration.

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Interpretation of blood-sugar values and glucose tolerance in uremia


Investigations into carbohydrate metabolism in more than 150 patients, chiefly with advanced renal insufficiency, are reported. 60 uremic patients with a NPN of 209 mg% (SD 35) show hyperglycemic fasting values when measured with a ferricyanide method (total reduction Hagedorn): 154 mg% (SD 43), in comparison to a true glucose method with enzymatic determination (Boehringer): 111 mg% (SD 25). The true glucose method of Somogyi results in higher values: 140 mg% (SD 25) and is therefore not a true-glucose method in that NPN-range. There is a significant correlation (p < 0.001) between NPN and FBS as measured with the various methods. There seems to be a true fasting hyperglycemia in uremia and a more important pseudohyperglycemia. In vitro studies show that the latter is in part due to the increase in serum creatinine. Oral glucose and glucose-insulin tolerance tests indicate reduced glucose tolerance and insulin activity when the FBS is still within normal limits. I.v.-insulin (0.1 µ/kg) gives a retarded but prolonged decline in blood sugar. There is a moderate decline in blood sugar with i.v. tolbutamide. The fall is less marked with rising NPN. There is no correlation between elevated serum α-amylase and hyperglycemia. Elevated plasma ketone values (highest value 18.6 mg% in a series of 6 uremic patients) are found in some cases of uremia. For this reason it is necessary to differentiate a syndrome involving primary hyperazotemia and secondary hyperketonemia with slight genuine hyperglycemia from diabetic as well as hyperosmolar coma.

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