Electron microscopic study of glomerular lesions resulting from intra-vascular fibrin formation
An electron microscopic study of glomerular alterations has been carried out in rabbits receiving
injections of Liquoid, thromboplastin or thrombin. The major acute lesions consisted of swelling
and proliferation of endothelial and intercapil-lary cells, heterophil infiltration, clumping of
platelets and deposits of fibrin and fibrinoid. The granular osmiophilic material identified as
fibrinoid was commonly seen between endothelium and the basement membrane. The
topographic relationship of fibrinoid to fibrin and the transitional forms between these two
substances indicated that fibrinoid was derived from fibrin. Phagocytosed fibrin was occasionally
observed in the swollen endothelial and intercapillary cells.
In addition to acute alterations, different stages in the development of progressive glomerular
obliteration were seen. These exhibited various degrees of proliferation of intercapillary cells,
accumulation of hyalin (basement membrane-like material) sometimes mixed with collagen
fibrils, and various basement membrane alterations usually in the form of thickening. Formation
of crescents was a less common feature. These changes sometimes ended in complete glomerular
obliteration.
The administration of epsilon-amino-caproic acid, a potent inhibitor of fibrino-lytic mechanism,
together with Liquoid resulted in marked intensification of the glomerular lesions, especially of
the fibrinoid deposits and the development of glomerular sclerosis.
It is proposed that the intravascular formation of fibrin was the essential mechanism in the
production of the glomerular abnormalities and could be an important mechanism of glomerular
damage in other instances.
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The mesangium of the renal glomerulus
By Suzuki, Y.; Churg, J.; Grishman, E.; Mautner, W. and Dachs, S.: Amer. J. Path. 43: 555-578
(1963).
The mesangium of the renal glomerulus is a branching stalk of tissue which extends from the
hilus into the peripheral lobules and provides support for the capillaries. The mesangium consists
of cells and intercellular substance. The cells are characterized by numerous cytoplasmic
processes and peripherally distributed fine fibrils 70-100 A in diameter. They have phagocytic
properties, they probably produce the intercellular substance and they bear some resemblance to
smooth muscle cells. The intercellular substance is designated as mesangial matrix; it consists of
fine fibrils embedded in a more homogeneous ground substance. It is similar to the basement
membrane but is looser in structure and reacts differently to certain stimuli.
The mesangium participates actively or passively in most of the diseases which affect the
glomerulus. Inflammatory response in the glomerulus consists, to a great extent, of proliferation
of mesangial cells. Glomerulosclerosis is due to increase in
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the mesangial matrix. Various substances, such as proteins, lipids as well as amyloid are deposited in the mesangium.

Pathological reactions in the mesangium were studied in man and experimental animals. In Masugi nephritis in rats, mesangial cell proliferation is accompanied by increase in mesangial matrix and focal collagen formation. In diabetes, there is only slight cell proliferation but marked increase in mesangial matrix to the point of formation of typical Kimmelstiel-Wilson nodules; collagen formation and deposition of protein and lipid is noted. In amyloidosis, deposition of amyloid substances appears to begin within the mesangial matrix and massive deposits in later stages are also localized in the mesangium. In Habu snake poisoning degeneration of both mesangial cells and matrix occurs.

The structure and the behavior of the mesangium is best explained by the assumption that it is a special type of mesenchymal tissue similar to pericapillary tissue.

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Glomerular and proximal tubular lesions due to inulin in rabbits, as seen by electron microscopy


Les doses d’inuline que nous avons injectées (1,5 à 2,5 g/kg en perfusion unique, ou 0,5 à 1,5 g/kg par jour pendant 14 jours) sont inférieures aux quantités maximaux qui furent administrées, soit à l’homme, soit à l’animal.

Ces alterations du néphron nous semblent presenter un certain rapport avec le stockage intrarénal de l’inuline que nous avions précédemment observés chez le lapin, même en diurèse osmotique (A. Falbriard; G. Schaller et R. Zender, à paraître). S’il fut signalé par certains auteurs, chez l’animal en oligurie, un tel phénomène n’est pas admis par la majorité des chercheurs. Ce stockage d’inuline est faible en valeur absolue, non décelable par les épreuves de clearance; mais il nous semble refléter un ‘transit’ intrarénal different de celui qui caractérise des cristalloïdes à plus faibles dimensions moléculaires. Sa localisation à telle ou telle structure n’est pas précisée par nos études fonctionnelles, encore qu’une precipitation dans la lumière tubulaire pourrait être favorisée par les processus de concentration urinaire.

Comme le stockage intrarénal, les alterations ultrastructurales sont à mettre en rapport avec les propriétés physico-chimiques de l’inuline. Le poids moléculaire moyen de ce polysaccharide est d’environ 5000, mais son coefficient de diffusion correspond à un poids moléculaire de 15000 et le rayon d’Einstein-Stokes atteint 15 Angstroms, vu la forme allongée de la molecule. C’est dire que les dimensions moléculaires de l’inuline se situent non loin des limites de filtrabilité compute;

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selon Wallenius, cette limite se trouve aux environs de 18 Å pour des particules non chargées. En outre l’inuline est relativement peu soluble et pourrait former des agrégats moléculaires dans certaines conditions.

Nos résultats indiquent que la filtrabilité plus ou moins complète d’une substance n’exclut pas la possibilité de réactions gloméralaires à cette substance, et de lésions tubulaires. L’étude plus approfondie citée plus haut (G. Simon; F. Chate-lanat et A. Falbriard, en préparation) a montré des altérations de la membrane basale gloméralaire suggérant une perméabilité accrue aux protéines produite par l’inuline; cette anomalie expliquerait les altérations de l’épithélium gloméralaire et tubulaire, mais il n’est pas possible d’exclure une action directe de l’inuline sur ces structures épithéliales.

Quels que soient la nature et le mécanisme des alterations du néphron produites par l’inuline, on peut se demander si l’emploi de cette substance reste indiqué dans l’exploration fonctionnelle du rein.

Adresse des auteurs: Dr. A. Falbriard, G. Schaller et G. Simon, CHnique Universitaire de Thérapeutique, Hôpital Cantonal et Départements d’Histologie et de Pathologie de l’Université, Genhe (Suisse).


The kidney of the mouse at birth offers an interesting site for the study of effects of irradiation since active metanephrogenesis is present in the outer cortical zone, and all stages of development from primitive cells to well differentiated glomeruli can be studied. Mice, when irradiated (375-475 rads) shortly before or after birth, exhibit renal changes which can be classified as immediate, early delayed, and late delayed effects. These are dependent on the state of differentiation of the metanephron at the time of irradiation.

Immediate changes can be seen 12 hrs. after exposure and involve the primitive cells and early developing glomeruli of the neogenic zone. Injury is characterized by degenerative changes and destruction of many of the cellular elements, principally those forming the angioblastic anlage of the glomerulus. Anlagen of partially destroyed glomeruli show defects in vascularization in subsequent development and involute early. As a result, there is a permanent reduction in the number of nephron units, with compensatory hypertrophy of the remaining elements.

Early delayed changes, seen by 3 weeks, consist of marked increase in PAS-positive membranous material in the ground substance of the central avascular (mesangial) core of partially developed glomeruli in the outer cortex, progressing rapidly to hyalinization and loss of cellular structure.

Late delayed changes appear only in those glomeruli which were fully developed at the time of irradiation. In animals irradiated at birth, changes characteristic of progressive intercapillary glomerulosclerosis appear by 6 weeks; in animals irradiated at 12 or 24 days of age, they appear by 65 to 100 days. In the latter only the late delayed changes appear since the differentiation of the nephron is completed at the time of irradiation.

These studies illustrate the marked differences in the effect of irradiation on immature and differentiated cellular elements of the glomerulus. They also shed some light on the effect of irradiation of immature structures on the subsequent development of the adult organ.

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Glomerular lesions in aging rodents and their acceleration by X-irradiation
By Guttman, P.H. and Kohn, H.I.

A lesion termed progressive intercapillary glomerulosclerosis (IGS) has been described in the kidneys of normal aging mice, rats and Chinese hamsters. It is characterized by gradual thickening of the mesangial stalks due to increase in PAS-positive membranous material, enlargement, pleomorphism, clustering, increase in number of mesangial cells, and loss of acid mucopolysaccharides.

Progressive IGS fulfills some of the criteria of an aging process since it is consistently found in several strains of rodents, progresses with time and, in light of our present knowledge, it is unrelated to known causative agents. However, it is recognized that until more information is obtained, one cannot be certain that progressive IGS is an age dependent process or an intrinsic morphological expression of aging. A numerical system of grading based on the severity of the glomerular changes was developed to facilitate comparative studies.

IGS is accelerated by X-irradiation. When animals are exposed (whole-body) at 1 year of age or later, the development of IGS is accelerated after a latent period of about 1 year (1). When younger animals are exposed, the latent period is shorter (2). If exposure is at 12 days of age (475 rads), changes in IGS can be detected by 100 days, whereas animals irradiated at birth exhibit changes at 35 to 45 days. Studies employing partial-body exposure (3) showed that the effect of irradiation was direct, not abscopal. Small, continued, daily doses of Co60 y-rays (12 to 24 r) did not result in a significant increase in the degree of IGS compared to single doses of X-rays, despite the size of accumulated doses–up to 6000 r (4). In single or split exposures in the range 150-900 rads, the severity of the glomerular lesion was shown to be dose dependent.

Since the glomerular changes in normal, aging rodents and the accelerating effect of irradiation can be graded as to severity, these changes may be utilized as a morphological basis for evaluation of the effects of irradiation.

References


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The renal lesion of potassium deficiency in the rat*

When rats are fed a potassium deficient diet, eosinophilic granules appear in the cytoplasm of the collecting tubules cells of their kidneys. The granules which

* These studies have been supported by United States Public Health Service Grant No. A-6014.

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measure from 0.2 to 4.0 µ in diameter give a positive reaction with the Hale iron method for acid mucopolysaccharides and are also PAS positive (1). It has been possible to show by using the enzyme neuraminidase that a sialic acid-containing mucopolysaccharide is present in the granules (1). By injecting Evans blue dye (T-1824) to label the serum protein it has been demonstrated that serum protein enters into the composition of the granules (2). The way in which the serum protein gets into the granules is unknown, but it has been our impression that it enters from the tubular lumen. However, similar granules are found in interstitial and vascular endothelial cells of the renal papilla in the potassium-deficient rat, and it is quite possible that the serum protein enters from the vasa recta.

The origin of the granules has been the object of much study (3), and they have been considered by some investigators to represent damaged mitochondria (4). Recently, however, their similarity to lysosomes has been recognized on the basis of observations of the morphology of the granule by electron microscopy and the demonstration by electron microhistochemistry that acid phosphatase is present in the granules (5, 6, 7). These recent electron microscopic studies have also shown that lysosomes are sparingly present in normal collecting tubule cells. Thus we have available a method whereby one may induce lysosome formation in cells which are ordinarily free of these bodies, and this clearly offers a unique opportunity to study the origin and development of the lysosome.

References

Author’s address: A. B. Morrison, M.D., Department of Pathology, University of Rochester School of Medicine and Dentistry, Rochester, N.Y. (USA).

Pyelonephritis. II. Observations on the treatment of enterococcal infection in the nonobstructed kidney of the rat
Observations were made on the effects of treatment on the course of enterococcal pyelonephritis in the rat. The data obtained in these experiments indicated that it was possible to cure the acute renal infection if proper therapy was instituted early and given in sufficient quantity for a long enough period of time. The thera-

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peutic results were adversely affected if the initiation of treatment was delayed. It was felt that this impaired therapeutic outcome was related to the fact that at the time of beginning delayed treatment, the microbial population in the kidney had reached a plateau population and was then in a metabolically altered state which protected the bacteria from the maximum effects of antibiotics. When treatment failed, it was possible to demonstrate that the residual infection occurred in the medulla but not in the cortex of the kidney. This medullary microbial persistence was not related to the development of antibiotic resistance. It was incidentally noted that with the amounts of antibiotics employed, an in vivo chloramphenicol interference with the bactericidal action of penicillin occurred.

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Experimental glomerulonephritis. III. Pathogenesis of glomerular ultra-structural lesions in nephrotoxic serum nephritis


An ultrastructural and immunologic study of nephrotoxic serum nephritis was made in normal untreated rats and rats tolerant to rabbit y-globulin. Rabbit nephrotoxic serum or y-globulin induced an immediate proteinuria in both groups of rats. In this primary phase glomerular basement membranes were diffusely thickened by fine deposits which were probably complexes of rabbit y-glo-bulin and host complement fixed to renal antigens of the basement membrane. There were also endothelial cell hyperplasia and swelling, and mesangial zone dilation. The primary phase was limited and reversible, since tolerant rats recovered morphologically and lost their proteinuria.

A secondary phase began 5 to 7 days after injection of nephrotoxin, in normal untreated rats only, and was signaled by persistence or increase of proteinuria. Between basement membranes and endothelial cells appeared dense, inhomoge-neous deposits which were probably complexes of host y-globulin, rabbit y-globu-lin, and complement. During the ensuing weeks the deposits were incorporated into the basement membranes, which became thickened and distorted. There were also progressive alterations of endothelial, mesangial, and epithelial cells, which, with the distorted basement membranes, resulted in glomerular destruction. Phase 2 changes did not occur in tolerant rats unable to make an antibody response to the rabbit y-globulin bound to basement membrane. There was, therefore, no evidence that an autoimmune antikidney antibody was a component of nephrotoxic serum nephritis.

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Altered permeability of the renal artery of the hypertensive rat: An electron microscopic study


The left renal artery of hypertensive rats with right nephrectomy was examined by electron microscopy. The vessels were fixed while distended in situ at controlled pressures in order to minimize distortion. Rats drinking 1% saline solution

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became hypertensive within 3 weeks after uninephrectomy and subcutaneous implantation of a deoxycorticosterone acetate pellet and were sacrificed at 8 weeks. Uninephrectomized rats and uninephrectomized rats drinking saline solution were not hypertensive at 8 weeks. The following lesions were abundant in the renal arteries of hypertensive rats: vacuolation and degeneration of endothelial cells; adhesion of blood cells to the endothelium; widening of the subendothelial
space; appearance of blood cells, macrophages, cell fragments and smooth muscle cells in the subendothelial space; vacuolation and degeneration of medial smooth muscle cells; and accumulation of extracellular osmiophilic material in the media. These findings suggest that hypertension or other hemodynamic changes may alter the permeability of the arterial wall. This may be one of the mechanisms by which hypertension enhances the development of atherosclerosis.

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The action of fursemide on intratubular electrolyte and water reabsorption studied by stop-flow-analysis. – Stop-flow-Untersuchungen zum Wirkungs-mechanismus von Fursemid


In six dogs the action of Fursemide1, a new anthranylic acid derivative with diuretic response, was studied by stop-flow-analysis. The i.v. injection of 1 mgm/kg body weight of Fursemide resulted within 20 min in a marked decrease in creatinine U/P quotient in all urinary fractions, indicating proximal and distal inhibition of water reabsorption. Urinary sodium concentration was doubled in proximal urinary fractions and almost 5 times higher in the urine, collected from the ascending limb of the loop of Henle. Maximal distal potassium secretion was also doubled. PAH-secretion was not inhibited by the drug.

In order to differentiate proximal Fursemide from proximal mercury action mercury-allyltheobromine was injected in a concentration of 1 mgm/kg body-weight first and this to be followed by additional Fursemide application. The stop-flow-pattern obtained following mercury application differed from that after additional Fursemide action in that mercury resulted after 40 min only in a decrease of proximal creatinine U/P ratio and an increase of proximal sodium rejection, whereas following Fursemide there was an allover further decrease in the creatinine U/P ratio as well as a further proximal and distal sodium rejection with mild distal potassium secretion being observed.

1 Lasix®, Farbwerke Hoechst, Frankfurt/Main, Germany.

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Serum factor in renal compensatory hyperplasia


The theory was tested that a specific humoral substance is partly responsible for renal compensatory hyperplasia. Male Sprague-Dawley rats aged 5 weeks were used. Serum from uninephrectomized rats (nephrectomy serum) was prepared from aortic blood 48 h after one kidney was removed. The time period was selected because the greatest mitotic activity of the remaining kidney was found to occur 48 to 60 h after nephrectomy. Control serum was obtained 48 h after a sham nephrectomy. Serum recipients were divided into three groups. The first group received an intraperitoneal injection of 0.5 ml of nephrectomy serum twice daily for 4 days. The second group received 0.5 ml of control serum according to the same schedule. The third group had one kidney removed and received saline according to the same schedule. Only those rats which had gained 8 to 12 g during the experimental period were selected. Tritiated thymidine was then injected intraperitoneally into each rat and the animals were killed one-half hour later. Autoradio-graphs of the kidneys and liver were prepared with stripping film. The number of labeled cells in 200 microscopic fields
from each kidney were counted. The final results were expressed as the number of radioactive cells per 1000 cells. In the cortex, the average number of labeled cells in each kidney of rats who received nephrectomy serum was 12.1 ± 0.92 (S.E.) per 1000 cells; in the case of the rats who received control serum it was 6.56 ± 0.57 per 1000 cells. These two results are significantly different from each other (p < 0.02). The average number of labeled cells in the kidney of rats who had a uninephrectomy was 20.33 ± 2.5 per 1000 cells. This figure is significantly different from that of the rats receiving nephrectomy serum (p < 0.05). This may mean the amount of serum was not large enough or injected often enough for maximum growth, or it may mean that factors other than a serum factor are implicated in renal compensatory hyperplasia. It may be related to the fact that the rats that received nephrectomy serum had two kidneys whereas the uninephrectomized rats had only one. The livers of the rats in all 3 groups contained between 1 and 2.4 labeled cells per 1000 cells, there being no significant differences between each pair of groups. The results indicate that a substance in the serum of uninephrectomized rats may be responsible for the increase in cell division during renal compensatory hyperplasia. The growth factor may be specific for the kidney and not a general growth factor since the liver showed no increase in cell division.

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Renal transport processes

By Fou%kes, E. C.

Recent work from this laboratory has had as one of its aims the analysis of the nature and function of different intracellular solute pools in the kidney. Many workers in the field of electrolyte metabolism had previously observed the fact that in renal cortical slices and in other tissues the cellular K, for instance, does not behave as if it were all contained in one homogenous compartment. Operationally, one can distinguish at least two such compartments (Foulkes, Amer. J. Physiol. 203: 655-661, 1962): One of these, which has been referred to as the non-diffusible or Kd pool, fails to exchange in the cold with extracellular K or Na despite the high permeability of the outer membrane to both these ions. Only metabolically linked movement of ions appears to penetrate the Kd compartment, whereas both active and passive fluxes occur into the diffusible or Ka portion of the cell K. The distribution of K between Kd and Kd is altered by ouabain, cyanide, and other agents under conditions where the total cell K remains unaffected. The relative sizes of the two compartments can be altered also by acid-base changes in vitro and in vivo. This finding suggests that we are dealing here not with an in vitro artefact but with a phenomenon which can reflect the physiological state of the animal. As a corollary to this conclusion, it follows that the physiological behavior of various tissues may depend not only on the total electrolyte composition of the cells, but also on the distribution of these electrolytes between various cellular compartments. The inotropic action of ouabain, for instance, appears to bear little relationship to the total K content of the myocardium and may find at least partial explanation in the observed effect of this drug on K compartmentation. Direct evidence for functional differences between the compartments was found in an investigation of the role of K in the transport of PAH by kidney slices (Foulkes and Miller: in Symposium on Membrane Transport and Metabolism, p. 559 N.Y. Acad. Press, 1961). The observation was here reported that of the two K compartments, only Kd can support PAH
transport. In the presence of a high concentration of K\(\text{Pi}d\) but in the absence of Kd the cells of the renal cortex are indeed unable to accumulate PAH. Accumulation does begin at a maximal rate within seconds of the addition of K to the medium, before significant changes have taken place in the total tissue K.

Further differences in the participation of cellular ion compartments in transport processes were found in an investigation of the equilibration of cellular Na in the surviving turtle bladder with Na being transported across the cells from the mucosal to the serosal surface of the tissue (Paine and Foulkes: Biochim. bio-phys. Acta 78: 767-768, 1963). Only a portion of the total cell Na was here observed to be contained in the Na pool with which the transported Na is mixed. In this case the possibility can, of course, not be excluded that the different Na pools are contained in different cell types. Such an explanation seems not applicable, however, to the compartmentation of cell K observed in the mammalian kidney cortex where the same heterogeneity of cell solute remains apparent upon isolation of tubular fragments.

Little can be said at the moment about the nature of the various compartments. No evidence could be obtained to support the view that K\(\text{Pi}d\) consists of a portion of cell K bound to protein or other cell constituents. Measurement of the space occupied by Kd leaves open the possibility that the two compartments could represent, for instance, intra- and extramitochondrial solute. Centrifugal fractionation of the cell constituents and analysis of their K content provided no conclusive answers. Relevant to this problem is the conclusion drawn from an investigation of the properties of the secretory pool involved in PAH excretion by the kidney tubule (Foulkes, Amer. J. Physiol. 205:1019-1024,1963). This pool had previously been shown to consist primarily of intracellular PAH (Foulkes and Miller, Amer. J. Physiol. 196: 83-85, 1959) and to behave in some ways in a manner analogous to K\(\text{Pi}d\) (Foulkes and Miller, Amer. J. Physiol. 196: 86-92, 1959). The inference has now been drawn from a kinetic analysis of the passage of labelled PAH through its secretory pool in vivo that binding does not appreciably contribute to PAH accumulation. Whereas there are thus available strong indications of the physiological significance of solute pools within cells, the question of the nature of these compartments remains entirely open.

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The action of vasopressin, a vasopressin analogue (PLV2), oxytocin, angio-tensin, bradykinin, and theophylline ethylene diamine on renal blood flow in the anaesthetized cat


(1) In anaesthetized cats and rabbits synthetic lysine vasopressin, highly purified arginine vasopressin and PLV2 caused a large and prolonged increase in renal blood

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flow due to vasodilatation in the kidney, accompanied by increases in urine flow up to twentyfold. These changes took place whether there was a rise in blood pressure or not.

The changes in renal blood flow may explain early observations on the diuretic effect of pituitary hormones. The physiological significance cannot yet be assessed.

A brief period of vasoconstriction in the kidney preceded the vasodilatation in about half the tests.

PLV2 had a quantitatively similar effect on renal blood flow to LVP, although its antidiuretic activity is much less.
Angiotensin caused a profound decrease in renal blood flow, usually accompanied by a decrease in urine flow if the initial rate had been reasonably high. There was sometimes an increase in urine flow afterwards.

Bradykinin and theophylline ethylene diamine caused renal vasodilatation. Oxytocin sometimes led to increases in renal blood flow but these always followed the time course of a simultaneous rise in blood pressure. When renal blood flow was diminished during infusions of angiotensin, lysine vasopressin, bradykinin and theophylline ethylene diamine were all able partly or completely to restore it to normal.

Author’s address: G. R. Barer, M.B., B.S., Department of Medicine, Royal Hospital, Sheffield (England).

Changes in inorganic phosphate excretion induced by renal arterial infusion of calcium
Calcium chloride in varying concentrations was infused at a slow and constant rate into the renal artery of one kidney in the dog. The opposite kidney served as a control. In 20 experiments, the mean glomerular filtration rate and effective renal plasma flow diminished in the infused relative to noninfused kidneys. Mean phosphate excretion was decreased in the infused relative to the control kidneys by both a fall in filtered phosphate and a rise in the net tubular reabsorption of phosphate. Mean calcium, sodium, and water excretion did not change in the infused relative to the control kidneys during calcium infusion. The data indicate that hypercalcemia acts directly on the kidney to decrease phosphate excretion by decreasing glomerular filtration rate and increasing net tubular reabsorption of phosphate.

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Dissociation between filtered load of sodium and its rate of excretion in the urine
The relationship between filtered load of sodium and the rate of urinary sodium excretion ($\dot{V}_{Na}$) when plasma sodium concentration was increasing and filtered load decreasing was examined in anesthetized dogs.

No direct relationship between filtered load of sodium and UNaV was found. $\dot{V}_{Na}$ was markedly elevated over control values despite a depressed filtered load. Several explanations for the findings are presented.

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We concluded that factors other than filtered load influence $\dot{V}_{Na}$, and the data imply that plasma sodium concentration may be one of the regulating influences.

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Diffusion of tritiated water into collecting duct urine in the dog
When tritiated water is infused during stopped flow in the dog the renal papilla is 8.7% as well labeled as is the cortex, when no urine is permitted to escape. With urine escape, the first urine from the collecting ducts is only 4.5% as well labeled as is the cortex, and the last urine (cumulative volume up to 4.5 ml) is considerably less labeled than are the papillae from which it has just emerged. We thus find that in our present series (kidneys frozen before sectioning), as
well as in our earlier series with nonfrozen kidneys, diffusion equilibration of tritiated water between papilla tissue water and collecting duct urine is incomplete in the dog.

Author’s address: Dr. H. L. White, Dept. of Physiology, Washington University School of Medicine, Saint Louis, Miss. (USA).

Interrelations of arsenate and phosphate transport in the dog kidney
The relation between arsenate and phosphate transport in the dog kidney was studied by measuring the renal clearance of arsenate labeled with its radioactive isotope As74. The experiments were performed during osmotic diuresis induced by mannitol. The results demonstrate certain similarities in the transport of these ions. Arsenate undergoes a net tubular reabsorption which is inhibited as the plasma phosphate concentration is raised. The inverse relationship between arsenate transport and the plasma As: P ratio suggests a competitive mechanism for the interaction between the two ions. Like phosphate, arsenate transport is inhibited by glucose and this effect is reversed by phlorizin. An important difference between arsenate and phosphate transport is the sensitivity of arsenate transport to urine flow. In vivo reduction of arsenate to arsenite and a net tubular secretion of arsenite has been observed. The results are discussed in terms of the known ability of arsenate to substitute for phosphate in biochemical reactions.

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Sustained depressor effect of renal medullary extract in the normotensive rat
The observation that hypertension develops in the bilaterally nephrectomized animal (renoprival) renewed interest in the possibility that certain forms of hypertension may represent a relative deficiency of a physiologically active renal depres-

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0.1ml. i.v. + 10|- .

mm Hg o " ^
-20 L i i i

5 10 15 20

minutes

1gm. medulla/10 ml. saline homogenate Fig. 1. Depression of rat blood pressure by rabbit medulla. sor material, rather than solely on overproduction of vasopressor agents. Since anti-hypertensive, but not vasodepressor factors have been observed in both renal cortex and medulla, we undertook the present study to determine the separate effects of rabbit kidney cortex and medulla on the blood pressure of normotensive rats. Crude homogenates of rabbit medulla produced sustained depression of blood pressure when injected intravenously into normotensive, anesthetized pen-tolinium-treated rats (Fig. 1). Similar activity was present in human, rat, and pig medulla, but not in extracts of renin-free cortex or certain non-renal tissues. The activity responsible for sustained vasodepression was a dializable, ethanol-soluble, low molecular weight (< 4500 Sephadex G-25) substance which was resistant to a mixture of peptide hydrolases. Recent studies (1, 2) of renomedullary vasodepressor substance, isolated by column and thin layer chromatography, have shown it to be an unsaturated, acidic (-COOH) hydroxylated lipid,
thus chemically as well as physiologically resembling the prostaglandin series of lipids. In
addition, the mechanism of action of vasodepression has recently been studied (2, 3). Intraarterial
administration of rabbit medullary extract resulted in a 35% increase in dog limb blood
flow and a 33% decrease in femoral arterial peripheral resistance. Intravenous administration
resulted in a 32% decrease in aortic diastolic pressure, an unchanged systolic pressure, and a
compensatory rise (30%) in cardiac output and heart rate. There was a 35% decrease in
calculated total peripheral resistance. No change in heart rate or contractile force was observed in
the isolated rabbit heart exposed to medullary extract. Renomedullary vasodepressor substance
therefore, appears to represent a physiologically active acidic lipid producing a sustained
decrease in blood pressure by direct peripheral arteriolar dilatation and without depression of
cardiac contractility. Whether this action represents a physiologically significant substance or a
non-specific depressor effect must await structural identification and evaluation of its regulatory
function in blood pressure control.

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Author’s address: Dr. James B. Lee, Department of Medicine, St. Vincent Hospital, Worcester,
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Albumin metabolism in aminonucleoside nephrotic rats
Aminonucleoside nephrotic and normal control rats were injected with biologically purified
homologous plasma albumin labeled with I131, and the decay of plasma albumin specific
activity and urinary excretion of protein and non-protein bound I131 were measured. The size of
the vascular and extravascular albumin pool and the rates of albumin breakdown and total loss
were obtained from these data. The rates of catabolism and loss were calculated by 4
independent methods: (1) by kinetic analysis based on the assumption of a system consisting of 1
vascular and 1 extravascular compartment; (2) and (3) by independent methods based on the
urinary I131 excretion and plasma specific activity after distribution equilibrium, and (4) from
the recoveries of urinary albumin and free and protein-bound I131 in the urine. In normal rats,
the mean catabolic rate obtained by method 1 was 3.2 mg/h/100 g of rat weight, and by methods
2 and 3 3.9 mg/h/100 g. In nephrotic rats, the values for total loss determined by methods 2, 3,
and 4 were in good agreement but differed greatly from that calculated by method 1 (kinetic
analysis). The value obtained by methods 2, 3, and 4 was from 1.5 to 2.5 times higher than that
obtained from 1. The values obtained by the latter procedure were less than the actual albumin
recovered in the urine, and it appears that the kinetic analysis is based on assumptions not valid
in nephrotics. Albuminuria in the nephrotic rats ranged from 5 to 12 mg/h/100 g and catabolism
from 1 to 4 mg/h/100 g. The fractional rates of catabolism ranged from 2.5 to 8% of the
circulating albumin per hour. There was a positive correlation between catabolism and
albuminuria. It is proposed that in animals with heavy albuminuria, albumin breakdown occurs
by 2 processes, one in the kidney and another in extrarenal tissues. The breakdown in kidneys is minor below an albuminuria threshold of about 5 mg/h/100 g, but above this threshold it increases with urinary albumin loss. In rats with extensive albuminuria, renal breakdown of albumin is the major catabolic process.

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Studies on activity and decay of factors that cause necrotizing arteritis induced in rabbits after experimental renal alterations


When the wrapping of one kidney in silk soaked with turpentine is followed in 7 days by contralateral nephrectomy, both hypertension and widely distributed necrotizing arterial lesions develop in rabbits. Neither hypertension nor necrotizing arterial lesions develop if contralateral nephrectomy is not performed. If, however, contralateral nephrectomy is delayed for several months after the production of silk-and-turpentine perinephritis, rapidly rising hypertension ensues, but no arterial lesions are found on extensive histological examination (1).

Production of unilateral silk-and-turpentine perinephritis was then followed by removal of the contralateral kidney at intervals ranging from 7 to 62 days in rabbits of several groups. When the interval was 7 to 22 days, widely distributed necrotizing arterial lesions developed in 31 of 32 rabbits. As the interval was increased from 30 days, there was a progressive decrease in the percentage of rabbits that developed necrotizing arterial lesions. All rabbits of all groups developed hypertension. No relationship was demonstrated between the maximal rise in blood pressure and the presence or absence of arterial lesions in these rabbits (2).
As the interval between the two operative procedures was increased (2), the average maximum number of necrotizing arterial lesions per rabbit per interval-group decreased exponentially (Fig. 1).

Analysis of data from rabbits in a 7-day interval-group (1, 2) indicated that the occurrence of early arterial lesions with respect to time follows closely the form of a bi-exponential function (Fig. 2).

It was assumed that the number of arterial lesions was a direct indication of activity of undetermined factors with the capacity to cause arterial necrosis. Accordingly, findings of these experiments suggest that factors with the potential to cause necrotizing arterial lesions arose after the first operation and remained inactive until after the second operation when arterial lesions develop. The form of the expression in Fig. 1 would, therefore, describe the decay of the inactive factors in the presence of a normal kidney. On the other hand, the form of the bi-exponential expression in Fig. 2 describes the activity of factors that cause arterial necrosis after removal of the normal kidney.

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\[ N(t) = C_0 e^{\lambda_2 t} - C_1 e^{\lambda_1 t} \]

Fig. 2

References


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The mechanics of rejection of homotransplanted kidneys
By Dempster, W.J.

Evidence from electron microscopic studies. Biopsies subjected to electron microscopy reveal a progressive attack by immature plasma cells upon the intertubular blood vessels of the homotransplanted kidney (Kountz et al., 1963). The exact nature of the stem cell from which these plasma cells arise has not yet been defined. An attack is initiated well within 48 h of transplanting, and involves immature plasma cells coming into very close apposition with endothelial cells of the intertubular vessels. Endothelial cells are seen to shed cytoplasm, swell up and separate, disrupting the vessel. The process continues with leakage of red cells and debris
from the vessels. The vascular fields become progressively occupied by plasma cells, lymphocytes, swollen endothelial cells and cell debris. The process finally results in complete stasis of flow in the small blood vessels which initiates tubular necrosis and liquefaction by intense phagocytosis.

Slight shedding of tubular cytoplasmic elements is seen during the life history of the transplant. The initial shedding is probably secondary to the ischaemia of transfer and the continued loss is probably causal by focal ischaemia of tubule cells. There is also a progressive rise in urinary excretion during the functioning phase.

Evidence from tests of renal junction. Measurements of total renal blood flow and the clearance of 1133 hippuran and C14 inulin during the life history of homotransplanted kidneys indicate that the rejection of first-set renal homotransplants is an ischaemic process (Kountz et al., 1963). The surgical process of transfer results in a post-transplantation reduction in both renal blood flow and effective renal blood flow. Both return to normal within 24 h following which there is a progressive decline until oliguria.

Evidence from a histochemical and quantitative assessment of enzyme activity. Immediately after transplantation slight, but quickly recoverable, enzyme changes occur both in auto- and homotransplanted kidneys. These are likely to be due to the ischaemic and surgical effects of transplantation.

Following these initial transient changes, the quantitative levels of enzymes such as some dehydrogenases and glycosidases vary according to the time of survival of any given homotransplanted kidney. Homotransplants functioning well on the 5th day will, at this time, have normal enzyme levels, which, however, gradually fall throughout the remaining period of survival.

On the other hand, homotransplants becoming oliguric by the 5th day have low enzyme levels during their functioning period. An oliguric homotransplant is always characterized by a marked reduction in hydrogenase activity irrespective of the time of survival. The histochemical appearances at the oliguric stage indicate lysosomal damage, particularly in the straight and convoluted portions of the proximal tubule and reduced respiratory enzyme activity. Such changes are nonspecific and are consistent with the hypothesis that the kidney tubules are suffering ischaemic damage. The main enzyme changes appear, therefore, to be due to a progressive ischaemia of tubule cells; the rate at which these changes occur depend on the speed of the rejection process.

Evidence from metabolic studies (Tyler et al., 1964). Using similar techniques to those of Smith and Moses (1960) the ability of chopped kidney tissue to metabolise 14C-glucose, 14C-succinate, and 214C-acetate has been studied. It has been shown by chromatography of the soluble intermediates and autoradiography of the chromatograms, that such important pathways as glycolysis, the tricarboxylic acid cycle and transamination are intact in functioning homotransplanted kidneys. At oliguria, these pathways are still intact although there is less incorporation of 14C into the T.C.A. cycle. Such results again provide no evidence of a primary biochemical lesion but they do confirm the findings that at the onset of the oliguric crisis the nephron appears grossly intact (Darmady et al., 1955) and that functional impairment is due to
some intracellular metabolic upset. Hypoxia caused by disintegration of the intertubular capillaries appears to provide sufficient explanation of the disturbed metabolism.

References

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Physiological glucosuria in various states of diuresis. – Physiologische Glucosurie bei verschiedenen Diuresezuständen
Kidneys of normal persons continuously discharge small quantities of glucose. Fasting blood sugar, discharge and glucose concentration of urine were determined at the same time in various states of diuresis in 27 persons of normal metabolism. Physiological glucose excretion–tested with glucose-6-phosphate-dehydrogenase-hexokinase-reaction comes to 54.3 ± 22.6 × 10⁻⁴ g/min at blood glucose levels of 66-92 mg%. Increasing diuresis (up to the sevenfold of normal) has no significant influence in the quantity of glucose excretion. Also K⁺ excretion is not changed with increasing diuresis, whereas Na⁺ and Cl⁻ excretion increase according to urine flow. Only about 1/2300 of the filtered glucose normally is discharged in urine. This amount being unimportant for balances of metabolism, is of some physiological interest. The question arises whether this small amount of glucose escapes reabsorption in proximal tubules (being below the threshold of sensitivity of tubulocellular transport mechanism) or–contrary to existing conceptions– is excreted further distal. Since we know a physiological glucose excretion, the conception of ‘glucosuria’ should have been defined more exactly and a limit should be fixed against increased glucosuria. According to present knowledge this limit would be at about a urine concentration of 0.03 to 0.05 mg% in normal persons and normal urine flow.

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Glycosuric renal tubular dysplasia
Diffused marked flattening of the proximal tubular epithelium and resulting ectasia of proximal tubular lumens were reported in renal diabetes for the first time in 1939 (1). 7 cases were functionally studied in 1953 (4) and defective reabsorption of sugar at proximal tubular level was confirmed. In 3 cases the histological findings (needle biopsy) were similar, though less marked, to those previously described. Recently, 2 new cases have been functionally and morphologically thoroughly studied. The same structural lesions were found in both cases, though TmG was normal in one case and very low in the other (5, 6, 7). The proximal tubular lumens appear large and ectatic while the proximal tubular epithelium appears flattened. The glomeruli are normal.

The distribution of the lesions throughout the cortex is irregular and in some areas the normal configuration of the cross sections through the proximal convolutions is preserved. The
mitochondria of the flattened epithelial cells are more or less markedly altered. The histochemical reaction for alkaline phosphatase is positive in both cases, though very faint in dilated tubules. The lesion can be localized specifically to the proximal convolutions by microdissection of the nephron.

Electron microscopy (7) fully confirms these findings, revealing obvious cyto-logical tubular changes. The appearance of this widespread cellular change producing disturbances involving all the cytoplasmic elements of the proximal tubular cells seems to indicate that a dynamic degenerative change is occurring in these kidneys. In correlating the structural lesion with the functional abnormality of glycosuria it must be assumed that the structural lesion is reversible as the functional abnormality is typically variable. These considerations justify the term of Glycosuric Tubular Dysplasia (Monasterio et al.).

The nature of the causal relationship between the structural and functional aspects of the disease remains entirely obscure.

References

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The intrarenal arterial pattern in the normal and diseased human kidney

An investigation has been performed of the arterial tree of the normal and diseased human kidney using a combination of stereomicro-angiographic and histologic techniques. This provided the following advantages over earlier investigations, none of which have included histologic examination of these tissue: (i) the state of the normal material was verified histologically; (ii) the type of pathologic tissue changes was diagnosed; (iii) the vessels studied in the microangiograms were followed in the histologic sections through the renal tissue and their positional relationship to the other structures thus determined; (iv) it was possible to decide if filling defects observed in the injection specimens were artefacts resulting from incomplete filling of normal vessels or whether they were due to structural changes; (v) it could be decided whether the contrast medium seen in the microangiograms represented vessels or leakage into the tissue through ruptured vessels.

The material consisted of 135 normal kidneys ranging in age from the beginning of the fourth fetal month to 79 years, 15 kidneys from cases of benign and 3 from cases of malignant
hypertension, and 30 kidneys from cases of chronic pyelonephritis with and without renal papillary necrosis and with and without hypertension.

In normal ageing kidneys and in hypertensive and pyelonephritic kidneys the preglomerular cortical vessels were spiralled. Possible causes of this were (i) interstitial fibrosis with shortening of the distance between the terminal points and (ii) elongation of the vessels between the stationary points, representing a collateral reaction due to obstruction or depletion of other vessels. In the renal pelvis spiralling vessels occurred normally.

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In the pyelonephritic kidneys with renal papillary necrosis vascular changes were observed in the medulla: dilatation, spiralling and thickening of the walls of the arteriolar rectae–evidence of collateral adaptation. This suggested that the inflammatory exudate and/or the periglomerular fibrosis in the juxtamedullary zone constricted efferent vessels leading to the medulla, so that collateral adaptation tended to develop. If this adaptation was inadequate papillary necrosis occurred.

In the youngest of the kidneys examined there were well developed arteriole-glomerular units in the connective tissue of the renal pelvis and in the juxtamedullary zone. At the end of the fourth fetal month there was a typical medullary vascular pattern with arteriolar rectae spuriae given off by efferent arterioles of pelvic and juxtamedullary glomeruli. Postglomerular vessels in the cortex did not appear until the eighth fetal months. These conditions were considered as evidence that the intrarenal circulation up to about the eighth fetal month took place via the medulla. During the seventh fetal month arteriolar rectae verae were seen; these developed as a result of contact being established between the afferent and efferent arterioles through degenerated glomeruli in the pelvic connective tissue and the juxtamedullary zone. From the afferent pelvic arterioles branches were given off to the pelvic connective tissue. In the cortex the glomerular degeneration led to atrophy also of the afferent and efferent vessels.

The fact that the cortical on the one hand and the pelvic and juxtamedullary arteriole-glomerular units on the other undergo different changes in glomerular degeneration suggests that there is an anatomic difference between the glomeruli of these areas. The latter type of glomerulus probably has a connection between the afferent and efferent arterioles which the cortical one lacks, and which, in the degeneration of the glomerular tuft itself, does not degenerate but gives rise to a direct continuity between the afferent and efferent vessels.

The increasing frequency of degenerated glomeruli with age and the pathologically high number in hypertension and pyelonephritis led to an increase in the number of atrophied arteriole-glomerular units in the cortex and arteriolar rectae verae to the medulla. This implies anatomically less favourable conditions for the cortical circulation and better conditions for the medullary one. The development of hypertension would then be ascribable to the cortical ischaemia accompanying the vascular changes. In cases of chronic pyelonephritis, however, postglomerular vessels from the juxtamedullary zone are also lost, so that the otherwise favourable conditions for the medullary circulation are impaired. This would explain the less regular occurrence of hypertension in these cases. A contributory cause of cortical ischaemia, and hence hypertension, might be found in the often marked thickening of the walls of the cortical vessels.

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A study of urinary and serum lysozyme in patients with renal disease
Lysozyme, a bacteriolytic enzyme discovered in 1922 by Sir Alexander Fleming (2), is found in a number of biologic fluids. The enzyme is a basic protein of low molecular weight that lyses susceptible bacteria by a reaction with cell-wall muco-polysaccharides releasing N-acetyl amino sugars and N-acetyl amino sugar-peptide complexes (3). Kidney contains more lysozyme activity than any other mammalian tissue (4), but little, if any, lysozyme activity is found in normal urine (5, 6). Lysozymuria has been reported in some children with nephrotic syndrome (7) and in some adults with renal disease (6), but no definitive evidence of the source of urinary lysozyme is available. Urinary and serum levels of lysozyme activity were measured in 100 normal subjects and in 109 patients with and without renal disease. All the subjects who excreted 5 µg of lysozyme or more per ml of urine had unequivocal evidence of renal disease as judged by other criteria. No direct relation was found between lysozymuria and pyuria or proteinuria, and several patients thought to have azotemia on a nonrenal basis did not excrete the enzyme. Little increase in lysozyme excretion was observed when the nephrotic syndrome was produced in rats, but marked lysozymuria was observed after the administration of mercuric chloride. These observations suggest that lysozymuria may be a relatively specific indication of renal tubular damage and that assay for this enzyme may become an important tool for establishing the diagnosis and prognosis of renal lesions in man.

References


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Renal effects of angiotensin II infusion in pregnant women


Normotensive women in the latter half of pregnancy are resistant to infusions of Angiotensin II in that they show smaller pressor responses and less inhibition of urine flow and electrolyte excretion than do normotensive nonpregnant subjects. Renal function was studied in 3 control clearance periods followed by 2 clearance periods during the infusion of 5 µg/min of
Angiotensin II. In nonpregnant women the maximal rises in blood pressure averaged 31 mm Hg in the systolic and 27 mm Hg in the diastolic pressures and the response was sustained throughout the infusion (45 to 90 min). In contrast, the maximal pressor responses of the pregnant women averaged about half those in nonpregnant subjects and the pressures often fell toward, or even back to, control levels while the infusion continued. The urinary excretion of water, sodium, and chloride was strongly inhibited in nonpregnant women; in pregnant women the decreases were significantly smaller and actual increases were found occasionally. The changes induced in the inulin and para-aminohippurate (PAH) clearances were similar in the 2 groups.

In later experiments (2), the infusion rates of Angiotensin II were adjusted so as to give equipressor responses in pregnant and nonpregnant women. Characteristically, the pregnant subjects required infusion rates that were 2 to 4 times as great as those eliciting comparable blood pressure changes in nonpregnant women. Angiotensin II, in equipressor doses, had far less effect upon the renal excretion of water, sodium, and chloride by pregnant women. When women in late pregnancy lie on their backs, their inulin and PAH clearances and renal excretion of water, sodium, and chloride all drop significantly, the changes closely resembling those elicited by Angiotensin II. Inasmuch as the studies described above were made with the pregnant women lying supine, it seemed possible that the infusion of Angiotensin II had had small effects because renal excretion was already greatly inhibited by body position. Ten pregnant women were studied, with each patient lying on her back one day and on her side the preceding or following day. The effects of Angiotensin II infusions on inulin and PAH clearances and renal excretion of water, sodium, potassium, and chloride averaged the same for both positions (3).

References

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Incidence of renal lesions in polycythaemia
By Brandt, P.W.T.; Dacie, J.V.; Steiner, R.E. and Szur, L.: Brit. med. J. i: 468-472 (1963). Ninety-one patients, previously diagnosed as suffering from polycythaemia vera, were investigated by intravenous pyelograph, and when necessary, tomography at a second I.V.P. or renal aortography were also performed. The various deformities of the left kidney caused by an enlarged spleen are described, occasionally these can be very marked. Renal lesions were found in 19 cases, i.e. 21%. 8 patients had ‘significant’ lesions, i.e. lesions which have been described as causing polycythaemia. The other 11 were considered to have incidental lesions, and these included pyelonephritis, infarcts, calculus, etc. Of the 8 significant lesions, 2 were due to carcinoma, 2 to bilateral polycystic disease, and 4 showed appearances compatible with unilateral cysts or neoplasm. All these 8 patients were males, although the whole group of 91
consisted of almost equal numbers of males and females. At least one of the following features—leucocytosis, thrombocytosis or splenomegaly—was present in 7 of the 8 patients. Nephrectomy was performed in one of the patients with carcinoma of the kidney, but it was too early to assess its effect. The other had widespread metastases when the tumor was diagnosed.

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The article reviews the previous literature on the relationship of polycythæmia and renal lesions and notes that a few patients, in whom nephrectomy induced a remission, had high platelet or leucocyte counts. On the other hand 15-20% of patients with apparently incontrovertible polycythaemia vera have both normal leucocyte and platelet counts. It is concluded that at the present time it is difficult to separate clearly polycythaemia due to renal lesions from polycythaemia vera with an incidental renal lesion, by the presence or absence of splenomegaly, leucocytosis or thrombocytosis. It is felt therefore that until further information is available, investigation of the kidney should be included in the routine examination of all patients suspected of having polycythaemia vera.

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Renal toxicity of oral cholecystographic media. Bunamiodyl sodium and iopanoic acid

Endogenous creatinine clearances were performed before and after the administration of bunamiodyl sodium and iopanoic acid in 31 subjects. Bunamiodyl sodium caused significant depression of endogenous clearances for two consecutive periods when given in a single 4.5 g dose in 4 of 7 patients. One of these patients who had an indwelling Foley catheter became transiently oliguric. A single patient who was studied following a multiple dose of bunamiodyl became oliguric and azotemic. Clearances in this patient dropped from a control value of 105 ml/min to 7 ml/min. Her urea nitrogen rose to a maximum of 87 mg/100 ml on the third day. Subsequently, it returned to normal values.

Patients given multiple doses of iopanoic acid appeared to show some depression in endogenous creatinine clearances; however, changes were not as frequent nor as profound as those seen following a single exposure to bunamiodyl sodium. An additional fatal case of acute renal failure following bunamiodyl sodium is described. Preexisting hepatic or renal disease was not a dominant feature in this group of patients.

It is our conclusion that bunamiodyl sodium is significantly more toxic than iopanoic acid and that it should not be used in human beings. Published or in press case reports of renal failure following bunamiodyl number at least forty three. 19 have been fatal, 6 have occurred following a single dose. Four of the published series contain five cases or more coming from single institutions. The drug is no longer permitted to be used in the United States or Canada.