A method for exposing the rat renal medulla in vivo

A new method involving partial nephrectomy is described by which the distal portion of the rat renal medulla is made accessible to an investigation by the micro-puncture technique. Urinary flow was greater and osmolality less in the partially nephrectomized left kidney than the unoperated right kidney but the urine remained hypertonic. Micropuncture of the collecting duct revealed a rising osmotic gradient toward the papillary tip. Electrical potential differences across the collecting ducts were measured by microelectrode techniques. The lumen was electrically negative with respect to the interstitial fluid (mean – 11 mV). It is clear that medullary hypertonicity persists in the partially nephrectomized left kidney and the collecting ducts retain their ability to reabsorb water and maintain a transtubular potential difference. In these aspects of tubular activity, the exposed rat renal medulla appears to be similar to that of the hamster, but has the advantage of a greater exposure of its length to investigation by micropuncture.

Author’s address: Dr. Rex L. Jamison, Laboratory of Kidney and Electrolyte Metabolism, National Heart Institute, Bethesda, Md. 20014 (USA).

Effects of osmotic diuresis on sodium reabsorption and oxygen consumption of the kidney

Renal O₂ consumption and filtered and excreted sodium were measured in anesthetized dogs undergoing diuresis induced by water, Ringers solution, mannitol or ethacrynic acid. Renal O₂ consumption was calculated from measurements of renal blood flow and blood oxygen pressures. Mannitol diuresis decreased the percent of the filtered sodium load reabsorbed by 34% while no significant change in renal oxygen consumption was noted. This resulted in a decrease of Tna/C½ from a control value of 29 mEq Na⁺/mole O₂ to 20 mEq Na⁺/mole O₂. This decrement in Tna/C½ was thought due to ‘sodium cycling’ whereby net passive influx of sodium occurred in the terminal portion of the proximal tubule and/or the thin descending limb of Henle’s loop, moved around the loop and then was actively reabsorbed in the distal tubules, especially in the thick ascending limb of Henle’s loop in the outer medulla. Since the thick limb of Henle would be re-absorbing increasing amounts of sodium, it is predicted that the oxidative metabolism of the outer medulla must increase greatly.

Author’s address: Dr. D. W. Rennie, Department of Physiology, State University of New York at Buffalo, Buffalo, N.Y. (USA).

A micropuncture study of the relationship between flow-rate through the loop of Henle and sodium concentration in the early distal tubule

In the rat kidney, single loops of Henle were perfused with 0.9% NaCl at different perfusion rates after the single nephron filtrate was blocked by injection of oil into the proximal convolution proximal to the infusion site. Samples collected from an early distal segment had
higher sodium concentrations at high perfusion rates. This increased sodium concentration with increased perfusion rate is consistent with the hypothesis that sodium concentration at the macula densa site of the nephron provides a stimulus for a feedback mechanism regulating glomerular filtration rate through the renin containing juxtaglomerular cells in juxtaposition with the macula densa cells and the afferent glomerular arteriole.

Author’s address: Dr. K. Thurau, Physiologisches Institut der Universität, Pettenkoferstraße 12, München 15 (Germany).

Ammonium excretion during stopped flow: A hypothetical ammonium countercurrent mechanism


Successive ureteral occlusions were performed during mannitol diuresis on chronically acidotic animals first infused with HC1 and then with NaHCG. Peak ammonium concentrations developed in very distal samples of each occlusion were compared with urine pH. In successive occlusions on any one dog, the line relating peak ammonium concentration to urine pH closely followed the slope predicted by the theory of non-ionic diffusion when urine pH was above 6.0. When urine pH was below 6.0 in successive occlusions, the slope was significantly less than the theoretical. Glutamine infusions raised ammonium concentrations and tended to shift the slope towards the theoretical at urine pH's down to 5.6. In alkalotic animals, the ratio \[\frac{[NH_3]}{[\text{H}^+]_b}\] was much greater than predicted by theory, and urine concentrations of the free base, \(N\text{H}_3\), were as much as fourfold greater than renal venous blood concentrations. Gottschalk (1) and Glabman et al. (2) have proposed that \(N\text{H}_3\) in loop of Henle fluid may diffuse into acid, collecting duct urine. This suggestion is extended here by proposing a countercurrent mechanism that would allow the kidney to concentrate \(N\text{H}_3\) in alkaline urine. Owen and Robinson (3) have made a similar proposal as a result of a study of ammonium distribution in renal tissue.

References


Author’s address: Dr. L.P. Sullivan, Department of Physiology, University of Kansas Medical Center, Kansas City* Kansas 66103 (USA).

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Early distal sodium concentration in the rat kidney following renal ischemia and haemorrhagic hypotension. A study on the pathogenesis of decreased GFR following renal ischemia or arterial hypotension. Die frühdistale Natriumkonzentration in Ratten nach renaler Ischämie und hämorrhagischer Hypotension. Ein Beitrag zur Pathogenese der postischämischen und posthämorrhagischen Filtratsenkung


In micropuncture experiments on rat kidneys early distal sodium concentration, approximating that of the macula densa site, together with glomerular filtration rate and renal excretory function were determined before and after renal ischemia or hemorrhagic hypotension. In the ischemia experiments micropuncture samples were obtained using the same early distal puncture site of distal convolutions before and after ischemia.
Early distal [Na⁺] was found to be increased after ischemia or hypotension, in some experiments approaching plasma [Na⁺]. The degree of increased [Na⁺] was inversely related to GFR (Fig. 1). In order to eliminate the influence of reduced tubular flow rate which occurs after renal ischemia, single loops of Henle were perfused at a constant rate and the increase in early distal [Na⁺] was found to be in the same range of magnitude. U/P inulin was decreased after renal ischemia. Uns.V and urine volume were increased in most experiments. The results indicate that the ability of the ascending limb of Henle’s loop to establish a [Na+] gradient across the tubular wall is reduced after renal ischemia or hemorrhagic hypotension. According to the hypothesis that GFR is regulated by

\[
\text{GFR (ml/min/100g)}
\]

\[
1.2- \\
\bullet \text{ Controls} \\
1.0- \\
\times \text{ After Ischemia} \\
0.8- \\
\times \times \times \\
0.6- \\
\times \times \times \\
0.4- \\
\times \times \times \\
0.2- \\
\times \times \times \\
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\]
Fig. 1. The relationship between [Na⁺] in the early distal tubule and GFR before (.) and after (x) renal ischemia.

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[Na⁺] at the macula densa cells, it is suggested that persistent renal vasoconstriction and fall in GFR following renal damage is caused by the elevated [Na⁺] of the tubular fluid in the macula densa segment. It is concluded that reduction of RBF and GFR after renal damage is the response to decreased tubular Na⁺ reabsorption, and that the renin angiotensin system participates in this reaction at the level of the juxtaglomerular apparatus. The reaction is considered as a Na⁺-conserving mechanism.

Author’s address: Dr. K. Thurau, Physiologisches Institut der Universität, Pettenkoferstraße 12, München (Germany).

Effect of insulin on short-circuit current and sodium transport across toad urinary bladder

The effect of insulin on short-circuit current and on the sodium transport system of the toad bladder has been examined. The rate coefficients for sodium movements across the mucosal and serosal barriers of the bladder epithelium were studied by observing the approach to a steady value of the flux of ²²Na across the bladder. Insulin added to the solutions bathing both surfaces of the bladder increased short-circuit current from 54 µA/3.14 cm² to 83 µA/3.14 cm²; the mean insulin effect ± S.E.M. was 28 ± 5 µA/3.14 cm² (P < 0.001). A smaller effect may be elicited by adding the hormone to either the serosal or the mucosal bathing media. Insulin increases the rate coefficient for sodium movement from the cells towards the serosal solution from a mean of 2.9 to one of 5.4 h⁻¹; mean insulin effect ± S.E.M. was 2.5 ± 0.7 (P < 0.01). No change in the rate coefficients for sodium movement across the mucosal surface of the epithelial cells was found. The action of insulin appears to result from a stimulation of the active transport step at the serosal surface of the cells. Insulin does not seem to modify the permeability to sodium of the mucosal cell surface.

Author’s address: Dr. F.C. Herrera, Departamento de Biofísica, Instituto Venezolano de Investigaciones Científicas, Caracas (Venezuela).

Intrarenal distribution of ammonia during diuresis and antidiuresis

The intrarenal distribution of ammonia was evaluated in the dog during anti-diuresis and osmotic (mannitol) diuresis at various levels of urine pH. During antidiuresis, the concentration of ammonia in renal tissue water rose progressively from the cortex to the tip of the papilla. In contrast, the corticomedullary ammonia gradient was completely obliterated by osmotic diuresis. In both experimental groups, a close relationship was observed between urine pH and the logarithm of the ratio between the urine and papillary concentrations of ammonia. The data are compatible with a proposal that a medullary countercurrent exchange system is responsible for
medullary ammonia accumulation, and that diffusion equilibrium exists between the pN½ of loop of Henle fluid, vasa recta blood, and collecting duct fluid.

Author’s address: Dr. R. R. Robinson, Department of Medicine, Duke University Medical Center, Durham N. C. (USA).

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Effect of urinary pH on the renal concentrating mechanism


The influence of an alkaline urine on the maximum concentrating ability of the rat during antidiuresis and the T½ of dogs during osmotic diuresis was examined under conditions of alkali loading. In the rat, alkali loading induced an acute and reversible decrease in the maximum concentrating ability which could not be attributed to potassium deficiency or an associated increase in solute output. During osmotic diuresis in the dog, no change in the T½ accompanied alkalinization of the urine. It is suggested that the pCC½ of the urine plays an important role in determining the observed changes.

The lack of demonstrable effect of bicarbonate loading on T½ of the dog during osmotic diuresis may reflect a species difference. It is also likely that osmotic diuresis resulted in a reduction in the pCO2 of urine and medullary interstitium below the level which is present during antidiuresis. The pCC½ of fresh random urine samples from rats during antidiuresis which had received an alkaline load averaged 118 mm Hg, whereas the urinary pCO2 at the height of osmotic diuresis in the dog averaged less than half of this value. Further studies on concentrating capacity with alkali loads carried out during hydropenia and osmotic diuresis in more than one species are necessary to clarify the nature of the effect of alkali upon the concentrating mechanism.

Author’s address: Dr. A.I. Goodman, Grasslands Hospital, Valhalla, N.Y. (USA).

Effets des variations du pH urinaire sur la substance fondamentale inter-tubulaire médullaire du rein de rat albinos


Etude des affinités tinctoriales de la substance fondamentale intertubulaire chez le rat par la méthode de Pischinger ainsi que par les colorations au Bleu Alcian et à l’hydrate de fer colloidal. On a constaté un gradient de coloration cortico-papillaire dans la médullaire du rein du rat. Ce gradient n’est pas le même selon que les urines sécrétées sont alcalines ou acides. On en conclut que le point d’électricité de la substance fondamentale intertubulaire est différent dans ces deux circonstances. Cela suggère que les espaces intertubulaires de la médullaire subissent des modifications physico-chimiques variables selon le pH définitif de l’urine. On peut admettre l’hypothèse d’un gradient de pH cortico-papillaire, la papille étant plus alcaline que la corticale et la différence d’autant plus grande que l’urine est plus acide.

Adresse de l’auteur: Dr. G. Richet, Hôpital Tenon, 4, rue de la Chine, Paris XXe (France).

Comparison of creatinine and inulin clearances in male and female rats


Creatinine and inulin clearances were compared in anesthetized male and female rats.

Continuous intravenous infusion, mid-point arterial blood sampling, and ureteral catheterization aided accurate measurements. Average inulin clearances were 1.0 ml/min/100 mg. In the control male rat the creatinine clearance persistently exceeded that of inulin. The elevated cCr:cIn ratio could be reduced to 1 by
probenecid, PAH, mercury, or high plasma levels of creatinine. In females a single intramuscular
dose of testosterone elevated the ratio to that seen in male rats. This effect declined within 6 h.
Manipulations with steroids other than testosterone did not affect results in either sex. It is
suggested that male rats secrete creatinine under the influence of androgens and that inulin is
therefore a better measurement of the glomerular filtration rate in the male rat.
Authors’ address: Dr. Alice M. Harvey and Dr. L. Malvin, Department of Physiology, The
University of Michigan, Ann Arbor, Mich. 48104 (USA).

Influence of inorganic electrolytes and ouabain on uric acid transport
The importance of certain inorganic electrolytes in the transport of some organic acids by the
kidney has been demonstrated. The present study was undertaken to evaluate further the
transport characteristics for uric acid. Slices of rabbit kidney cortex were found to accumulate
urate with a dependency on the medium potassium concentration. At 5 mM potassium the urate
uptake was about 50% of maximum, with optimal accumulation above 10-40 mM potassium.
Rubidium or cesium were found to substitute successfully for potassium; both substances
permitted better uric acid accumulation than did potassium. Removal of sodium from the
medium to concentrations as low as 65 mM did not influence urate uptake. At 15 mM sodium the
urate accumulation was markedly depressed. Ouabain was found to depress urate uptake. The
inhibition produced by this substance could be reversed by elevation of the medium potassium.
Stopflow analysis on the rabbit indicated that ouabain increased the proximal secretory peak for
uric acid. On the basis of experiments where ouabain and probenecid were administered
together, it was possible to attribute the action of ouabain to blockade of urate reabsorption.
Author’s address: Dr. W.O. Berndt, Department of Pharmacology and Toxicology, Dartmouth
Medical School, Hanover, New Hampshire (USA).

Effect of hydrochlorothiazide and chlorthalidon on renal reabsorption of glucose
The maximal glucose reabsorption (T\textsubscript{g}) was determined before and after intravenous injection
of chlorthalidon and hydrochlorothiazide, and before and after oral administration of
hydrochlorothiazide over a period of 14 days. No changes in the inulin-clearance rate or in T\textsubscript{g}
were observed after intravenous infusion. After oral administration a significant (P < 0.001) fall
in inulin-clearance was seen, whereas the change in T\textsubscript{g} ranged between −17% and +20%. The
average variation is not significant. In all the patients treated orally, the serum potassium
decreased by 7-27%. The results are discussed and compared to previous data from the literature,
and it is concluded, that from investigations up to this time the assumption that thiazide exerts a
general influence on the glucose T\textsubscript{m} may be rejected.
Author’s address: Dr. P. Henningsen, Plantagevej 12, Gentofte (Denmark).

Micropuncture study of proximal renal tubular chloride transport during hypercapnea in the rat
The electrical potential difference and the concentration of chloride in tubular fluid and plasma
were measured in stopped-flow microp erfusion of the proximal tubule of rats breathing either air
or 12% CO\textsubscript{2} in air. Perfusion with 10% PVP completely stopped net transtubular fluid
movement. Chloride was not in electrochemical equilibrium under these conditions and
hypercapnea increased the concentration of chloride in tubular fluid relative to that in plasma. This suggests that the net reabsorption of chloride must overcome a force which moves chloride into the tubular lumen. An anion pump is postulated which secretes chloride into the tubular lumen and is linked to acidification of proximal tubular fluid.

Authors’ address: Dr. M. Kashgarian, Dr. Y. Warren and Dr. H. Levitin, Department of Pathology, Yale University School of Medicine, New Haven, Conn. (USA).

Nitrate, thiocyanate and perchlorate clearance in relation to chloride clearance

Simultaneous clearances of inulin, chloride, and nitrate, thiocyanate, or perchlorate were measured in salt-depleted dogs and/or dogs undergoing diuresis induced by mannitol, saline, or sulfate. A method for perchlorate determination in body fluids using methylene blue is given.

Plots of excreted/filtered NC\textsubscript{1/2}, SCN, or Cl\textsubscript{O4} against excreted/filtered Cl were made for the present data and for data taken from the literature. All of the available nitrate data conform to a power function between these two variables with an exponent of 0.36-0.38. Thiocyanate clearance was nearly equal to chloride clearance; during infusion of other foreign anions it was usually higher than chloride clearance. Perchlorate clearance was much higher than chloride clearance but varied with it.

In recent publications by the same authors, similar parallelism was noted between excreted/filtered chloride and iodide, bromide, and fluoride; at low chloride clearances, active transport of iodide and bromide became apparent. On the basis of kinetic considerations (1), this form of interdependence of clearances is consistent with the possibility that all seven anions are reabsorbed passively and co-extensively in the more proximal nephron, the sequence of tubular permeability being F < Cl\textsubscript{O4} < NC\textsubscript{1/2} = I < Cl < Br = SCN. Active distal processes modify the results at low clearances.

Reference

Antagonism of the inotropic action of ouabain by aldosterone

Aldosterone (3.3 \times 10^{-8} to 10^{-7} M) exerted a small positive inotropic effect on cat Langendorff heart preparations depressed by pentobarbital and on cat papillary muscles depressed by low calcium. Equimolar concentrations of ouabain exerted a much greater inotropic effect in both preparations compared to aldosterone. Aldosterone (3.3 \times 10^{-8} to 10^{-7} M) antagonized both the positive inotropic effect of cardiotonic concentrations and the bradycardia and cardiac arrest of toxic concentrations of ouabain. Cortisol (10^{-7} to 10^{-5} M) did not antagonize the effects of ouabain. Addition of aldosterone 20 min prior to the ouabain exerted maximal inhibition. Simultaneous aldosterone and ouabain addition resulted in a lesser degree of inhibition. Addition of aldosterone at the peak of the ouabain effect did not influence the subsequent course of the ouabain-induced inotropic effect.

Author’s address: Dr. A.M. Lefer, University of Virginia, School of Medicine, Charlottesville, VA (USA).

Effects of Na and Ca on the generation and conduction of excitation in the ureter
Effects of Na\(^+\) and Ca\(^{++}\) on the generation and the conduction of excitation were studied by using a pelvis ureter specimen of cat in which the renal pelvis and calyces were kept intact. Action potentials were recorded simultaneously from the renal pelvis and the various regions of the ureter, and they were used to indicate the arrival of excitation. In Na\(^+\)-deficient solutions, both the frequency of excitation and the conduction velocity decreased gradually, and finally a conduction block occurred at the border between the renal pelvis and ureter. In Na\(^+\)-free solution spontaneous excitation was not observed in most cases. When excess Ca\(^{++}\) was added to Na\(^+\)-free solution, spontaneous excitation was restored, but the concentration of Ca\(^{++}\) necessary for the restoration had to be at least twice that in normal Ringer-Krebs solution. The difference between the ureter and taenia coli was considered with regard to the role that Na\(^+\) and Ca\(^{++}\) play in the generation of spontaneous excitation.

Author’s address: Dr. M. Kobayashi, Department of Physiology and Biophysics, University of Illinois, Urbana, Ill. (USA).

Disturbances of urine concentrating operation in chronic nephropathies / Störungen der Harnkonzentrierung bei chronischen Nephropathien


In 141 patients with various chronic nephropathies and impairment of renal function the urinary concentrating capacity was analysed quantitatively using osmotic diuresis with 10% mannitol. In the majority of cases a decrease of the concentrating capacity of the medullary countercurrent systems (phase I of the urinary concentration) was found as the cause of the observed hypo- or isosthenuria. Very pronounced in relation to the glomerular filtration rate was the concentrating defect (\(\Gamma_i > 3/4\) 100 ml GFR) in patients with predominantly interstitial nephropathies, less in patients with vascular nephropathies and the least in patients with glomerular diseases of the kidney. Patients with renal hypertension showed no evidence of a ‘pressure diuresis’ as a cause of diminished concentrating capacity. – 25% of the patients – mainly with pyelonephritis or malignant sclerosis – showed a hypotonic diuresis increment during osmotic diuresis which may be regarded as a decreased response of the distal nephron to ADH (impairment of the phase II of the urinary concentration). Between maximal specific gravity of the urine after a thirst period and 7\\% H20 during osmotic diuresis there was a statistically signifi-cant correlation (r = 0.60). However, in borderline cases with only discrete defects of renal concentrating capacity determination of the maximal specific gravity of the urine did not suffice for complete evaluation. Finally, the results are discussed in terms of their pathophysiological significance.

Author’s address: Dr. E. Buchborn, Medizinische Universitäts-Poliklinik und Medizinische Klinik, Ostmerheimer-straße 200, 5 Köln-Merborn (Germany).

Urine concentration in essential hypertension / Harnkonzentrierung bei essentieller Hypertonie


The purpose of this study was to determine whether urine-concentrating mechanisms are disturbed in even the early stages of essential hypertension. In a group of 13 normal subjects (4 women and 9 men) and 11 patients with various degrees of compensated essential hypertension (4 women, 7 men) without manifest signs of impaired renal function and normal or only slightly diminished inulin and PAH clearances, the following results were obtained under strictly standardised conditions: (1) in the early stage of essential hypertension there is a disorder of
urine concentration only, if at all, if there is osmotic diuresis. Maximal urine osmolality during hydropenia and oliguria, as well as so-called maximal removal of osmotically free water during osmotic diuresis produced by a hypertonic mannitol solution (7% d1%) are affected differently; (2) on withholding fluid, the maximal urine osmolality in patients with hypertension (916 \pm 98 mOsm/kg \%O) is not significantly different from that in normal subjects (934 \pm 78 mOsm/kg \%O); (3) during hypertonic mannitol diuresis the defect in urine concentrating capacity is often not apparent in all subjects. Often the value of T\%O is still within the physiologically very wide scatter of normal values. With comparable rates of osmolar clearance, the mean of T\%O in normal subjects is significantly greater than in hypertensives; (4) in patients with essential hypertension there is a functional disorder of sodium metabolism in the distal nephron segments which, however, does not affect the ionic exchange mechanism. This disturbance is expressed in a decreased removal of water, which during hypertonic sodium-chloride diuresis is osmotically bound in the tubules to the sodium chloride. It is assumed that the decrease in T\%O in patients with essential hypertension is the expression of a decreased transport rate and an decreased concentration of osmotically active material, particularly sodium chloride, in the renal medulla.

Author’s address: Dr. D. P. Mertz, Medizinische Poliklinik der Universität, Hermann-Herderstraße 6, 78 Freiburg i.Br. (Germany).

On the mechanism of an exaggerated natriuresis during intravenous loading of strongly hypertonic saline in patients with essential hypertension. I. Glomerular factors


The effects of a rapid intravenous hypertonic (5-6.7%) saline infusion, lasting between 30 and 120 min (infusion rate 5-15 ml/min), on water and electrolyte balance as well as on glomerular filtered load are examined both in compensated patients with differently graded essential hypertension and in normotensive healthy individuals. All the subjects studied were nonprehydrated, hydropenic and kept on a protein-low, salt-low diet several days before the examination. In respect to renal hemodynamics the group of patients with essential hypertension had normal or only slightly reduced clearance values. The following results were obtained:

If renal function in not markedly reduced, the compatibility of an intravenous loading with strongly hypertonic saline is partially determined by the level of the mean arterial blood pressure. Signs of cellular dehydration may be a limiting factor of infusion rate. Because of an exaggerated natriuresis the increment of plasma osmolality during saline infusion is significantly lower in patients with essential hypertension than in normal controls. During 60 min of saline infusion patients with elevated mean arterial blood pressure to more than 160 to 170 mm Hg generally will excrete more than 10 times as much of the infused sodium load as normal persons. In patients with essential hypertension the excretion rate of sodium averages 7% of the infused quantity during the first 30 min. It is 5 times as high as in normals within 60 min of infusion.

In both groups an increase of the fraction of filtered sodium excreted to more than 3% is accompanied by an increment of filtered sodium load. In single hypertonic cases an enhancement to more than 100% of the control value may be observed. A measurable increase of filtered...
sodium load occurs in normal subjects no sooner than 60 min after the beginning of saline infusion. On the other hand, patients with severe essential hypertension respond hardly without any delay. Changes of inulin clearance are more stable and more regular than those of PAH clearance. There is a rough correspondence between the changes described and the mean arterial blood pressure. The augmented natriuretic response to acute sodium infusion in essential hypertension is not related to an increase of the effective plasma osmolality. It is independent of the control levels of sodium excretion rate and of the infused quantity of sodium. The earlier appearance of an increase of filtered sodium load in essential hypertension may be considered as one factor for the development of the accelerated and augmented natriuresis. However, there is no consistent parallelism between the enhancement of filtered load and excretion rate of sodium.

Author’s address: Dr. D.P. Mertz, Medizinische Universitätsklinik, Hermann-Herderstraße 6, 78 Freiburg i. Br. (Germany).


The acute effects of intravenous infusions of 5 or 6.7% sodium chloride solutions at rates between 5 and 15 ml/min on the pattern of renal tubular reabsorption of sodium and water were examined both in compensated patients with essential hypertension (but without clinical evidence of impaired renal function) and in normotensive healthy individuals. All the subjects studied were nonprehydrated, hydropenic and kept on a protein-low, sodium-low diet several days before the examination. The following results were obtained:

During the peak of natriuresis patients with essential hypertension may excrete up to 15% of the glomerular filtered sodium load. Even with comparable size of filtered load the fraction of filtered sodium excreted by normal individuals will reach at most 7%. In contrast to normal controls there is evidence of a reduction of the fractional sodium reabsorption in the proximal tubular segment of the nephron in patients with severe essential hypertension. Furthermore, our data indicate, that the reabsorption of sodium in patients with essential hypertension is disturbed too at a nephron site distal to the end of the proximal segment. Considering sodium alone, the tubular reabsorption of solute-free water is reduced and limited to a small range of saline diuresis in essential hypertension. Excluding, in hypothesis, other osmotic constituents than sodium, the elaboration of a hypertonic urine during saline diuresis under the experimental conditions described is effected by the removal of solute-free water, representing approximately 1.3% of the filtration rate in hypertensive and 2.0% in normotensive individuals respectively, from an isotonic urine. This portion of water is abstracted from a solution with a sodium concentration, which is osmotically equivalent to that of the plasma or of the glomerular filtrate. Beyond a saline diuresis of at least 12 ml/min and 1.73 m2 body surface patients with essential hypertension are no longer capable of removing solute-free water from an intra-tubular fluid, the sodium concentration of which is identical with that of the plasma.
Reduction of renal concentrating ability may be very small in single subjects. Thus, the derangement in concentrating process is sometimes not detected, when estimating ‘pseudomaximum’ of solute-free water, which is removed during hypertonic mannitol diuresis. There is no consistent dependence between the level of mean arterial blood pressure and the degree of disturbance of renal concentrating ability.

Because of the simultaneous occurrence of glomerular and tubular alterations in patients with essential hypertension an intrarenal mechanism may induce both changes. Possibly renin-angiotensin could be a transmitter system changing both glomerular filtration rate and reabsorption of sodium in various segments of the nephron. In this context, the known reversal of angiotensin II effect on sodium excretion in patients with essential hypertension should be assumed. It is suggested that extrarenal factors, as changes of pressure or volume in the central circulation, may be important.

Author’s address: Dr. D.P. Mrctz, Medizinische Poliklinik, Hermann-Herderstraße 6, 78 Freiburg i. Br. (Germany).

Measurement of renal artery pressures by catheterization in patients with and without renal artery stenosis


Fifteen patients with renal arterial stenosis and thirteen patients without renal arterial stenosis, 10 of them with hypertension, had pressure measurements made in the renal artery following catheterization of the femoral artery by Seldinger’s technique. A preliminary survey aortogram was deemed necessary. There were 6 failures in 34 passage attempts. One patient sustained a perforated renal artery without apparent clinical sequelae. A systolic pressure gradient exceeding 15 mm Hg was considered abnormal. There was poor correlation between the presence of such pressure gradients and casual evaluation of the stenosis by angiography. A better correlation was found when the stenosis noted on angiographic films was expressed as a function of its length (Ls) and the diameters of the stenosed segment (Ds) and non-stenosed vessel (Dn) according to the empirical formula Ls/(Ds/Dn)2. Some patients with documented renal arterial stenosis on angiography failed to have a significant pressure gradient across the lesion.

Author’s address: Dr. S. A. Carter, St. Boniface General Hospital, Winnipeg (Canada).

General and renal hemodynamic disorders in coarctation of the aorta


A simultaneous determination of renal blood flow (clearance of diodrast) and cardiac output (Stewart-Hamilton’s method) was carried out in 30 patients with coarctation of the aorta. The renal blood flow in patients (1091 ± 74.8 ml/min) did not significantly differ from the renal blood flow in normal people (1227 ± 102 ml/min). However, the renal fraction of cardiac output was lower in patients (16.8 ± 1.4%) than in normal people (20.1 ± 1.24%; p = 0.1). In cases with severe hypertension, cardiac output, renal blood flow and renal fraction of cardiac output (15.4 ± 1.7%; p = 0.05) were all significantly diminished. This latter could be due to prerenal or renal increase of vascular resistance.

Authors’ address: Dr. G.A. Glazer and Dr. G.L. Spivak, Institute of Therapy, Academy of Medical Sciences USSR, Petroverigsky per. 10, Moscow (USSR).

The effects of aldosterone and angiotensin on renal function

Several workers have investigated the effects of infusions of 1 or 2 µg/min of angiotensin in normal man; most have attributed the consequent antidiuresis to a fall in G.F.R. However in both the dog and man whilst small doses of angiotensin are antidiuretic, larger doses produce a diuretic response and both a rise in G.F.R. and possibly a tubular natriuretic effect contribute to this diuresis (1, 2). It was suggested by us that the sodium and water diuresis induced by small doses of angiotensin in hypertensive or cirrhotic patients might imply an increase in endogenous angiotensin production, the effects of the infused angiotensin summing with endogenous angiotensin to cause the diuretic response.

To examine this possibility further, the effects of aldosterone infusions on the renal response to angiotensin were studied in normal subjects, in patients with cirrhosis, and in the nephrotic syndrome. In normal subjects the antidiuretic response to small doses of angiotensin was unaffected by aldosterone administration. In patients with oedema and presumed secondary hyperaldosteronism, however, the diuretic response to small doses of angiotensin was converted by aldosterone to an antidiuretic response. By contrast, in normal subjects the antidiuretic response to angiotensin changed to a diuretic response after severe sodium depletion.

The suggestion is made that large doses of aldosterone depress the production of angiotensin by a feedback mechanism, and it is concluded that the diuretic response to angiotensin is probably at least in part due to tachyphylaxis of the renal vasculature to the constrictor effects of angiotensin. A less specific alteration in renal vascular sensitivity associated with disturbances of sodium regulation cannot be excluded, however.

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References
Author’s address: Dr. W.J. Louis and Dr. A.E. Doyle, University of Melbourne, Department of Medicine, Royal Melbourne Hospital, Melbourne (Australia).

Angiotensin II infusion in renal disease with hypertension
By del Greco, F.; Roguska, J. and Simon, N.: Amer. J. med. Sci. 251: 140–141 (1966). An intravenous infusion of angiotensin II sufficient to raise systolic blood pressure by 15-20 mm Hg was given to 4 normal subjects, 10 patients with hypertension secondary to renal disease and 11 patients with essential hypertension. The dose required ranged from 0.4 to 10 µg/kg body weight per min and the infusion was continued for a 6-8 h period. Both groups of hypertensive patients required less angiotensin II than did the normal group for a comparable pressor response. Anti-natriuresis occurred in all normals and in approximately one-half of both the renal hypertensive and the essential hypertensive patients. The increment in sodium excretion occurring in the remaining patients during the pressor angiotensin II infusion averaged 18 µEq/min in the renal (secondary) hypertensive group and 76 µEq/min in the essential (primary) hypertensive group.

It is suggested that angiotensin II may exert a direct tubular action, but the reason that bidirectional hypertensive group responses occurred is not known.
Author’s address: Dr. F. del Greco, Department of Medicine, Northwestern University Medical School, Passavant Memorial Hospital Chicago, Chicago, Ill. (USA).
The incidence of morbid-anatomical signs of ‘shock kidney’ and other renal disease in unselected post-mortem material / Über die Häufigkeit des patho-logisch-anatomischen Bildes der Schockniere und anderer Nierenerkrankungen in ausgewähltem Obduktionsgut
Among an unselected series of necropsies, judged by uniform criteria, there was an incidence of 4.3% of cases with the histological evidence of ‘shock kidney’ (147 cases among 3400 necropsies in the municipal hospitals of Stuttgart). This disease was the second most frequent cause of renal damage after interstitial inflammatory renal disease (6.9%) and more frequent than severe vascular (3.7%) and glomerular (3%) renal disease. In a second group of 747 necropsies performed at the University hospitals at Tübingen, 76 (10.2%) had histological evidence of shock kidney while inflammatory (6.0%), vascular (4.4%) and glomerular (2.14%) renal disease was less frequent. Clinical evidence of renal disorders of excretion was recorded in 33% among the first group of shock-kidney cases and in 53% of those in the second group.
Authors’ address: Dr. G.E. Schubert and Dr. H. Köberle, Pathologisches Institut der Universität Tübingen, Liebermeisterstraße 8, 74 Tübingen (Germany).

Summaries – Résumés
Unselective proteinuria in acute ischaemic renal failure
Studies of protein excretion in relation to the molecular weight of the proteins give information about the permeability of the glomerular basement membrane (1). There is considerable doubt about glomerular function and structure in acute ischaemic renal failure with tubular necrosis and proteinuria in this disease has been studied from the oliguric phase to recovery or death in 6 patients. Protein excretion patterns were studied by electrophoresis and immunoelectrophoresis and individual protein clearances of 5 proteins with a range of molecular weights were estimated by gel diffusion precipitin technique. The degree of proteinuria was greatest during the oliguric phase of the disease when large amounts of high molecular weight protein were detected in the urine by all techniques. This unselective pattern of protein excretion by the kidney persisted from the onset of illness to recovery. The source of the urinary proteins is uncertain but the most satisfactory explanation is that the proteinuria is due to a failure to reabsorb protein normally filtered by the glomeruli, possibly complicated by a leak of plasma proteins directly into the tubular lumen rather than to an alteration of glomerular permeability.

References
Author’s address: Dr. J.S. Robson, Department of Therapeutics, The Royal Infirmary, Edinburgh 3 (Scotland).

Renal-vein thrombosis in a newborn: report of a case / Die Nierenvenen-thrombose beim Neugeborenen
A case of unilateral renal-vein thrombosis in a 10-day-old girl is reported. The signs were haematuria and enlargement of the right kidney (thought to be an abdominal tumour). At operation an enlarged kidney was found with haemorrhagic infarction and extensive necrosis of the renal parenchyma, requiring nephrectomy. The child made an uneventful recovery and was discharged from hospital after eight weeks.
Haemolytic uraemic syndrome in children


Since 1959, 7 cases of haemolytic uraemic syndrome have been observed. The age group ranged from 5 months up to three years and 11 months. This syndrome is characterized by acute renal insufficiency, thrombopenia and haemolytic anaemia with marked morphological changes of the red cells. 4 Patients died as a result of acute renal insufficiency despite treatment with heparin in 2 cases and repeated peritoneal dialysis in 3 cases.

New reports on hereditary chronic nephropathy (Alport-Syndrome)


A family suffering from hereditary nephropathy, deafness and abnormalities of the eyes was examined. 6 persons (3 men and 3 women) out of 11 members (including 4 generations) suffered from an hereditary nephropathy, five of them (3 men and 2 women) had in addition an abnormality of the eyes and four (3 men and 1 woman) had also an inner ear deafness. All of them had the blood group 0.

Generally, the nephropathy appeared already in infancy. Occasionally it was discovered later by chance. The most important symptoms were as following:

- Proteinuria, erythrocyturia, leucocyturia, cylindrusia of alternating intensity, partly persisting for several decades;
- Reduced concentration power of the kidneys;
- An increase of the €½ fraction of the serum proteins;
- In most cases an hyperaminoaciduria consisting of alanin, glycine, serin and taurin.

The pathological findings were those of a chronic interstitial nephritis.

The disease of the examined persons seemed to be hardly progressive and the patients felt well without exception. But two male members had died from nephropathy before their 30th year of age.

An inner ear deafness appeared in several patients with renal involvement between their 17th and 20th year of age; the affected patients were almost always males, women were by far more seldom concerned. The inner ear deafness was a mediocochlear one of type B (Langenbecks). The observed abnormality of the eyes, shown by several men and women of the family, is described in this combination for the first time. Although scotomas were found, the acuity of the eyes was not reduced. By ophthalmoscopic examination, a ‘fundus albipunctatus’ could be observed in both sides.
The symptoms of the Alport syndrome were strongly preponderant in males. Only women with nephropathy transmitted the syndrome. It is not yet clear in which way the disease is inherited, but a dominant trait seems possible.

Author’s address: Dr. H. Sarre, Medizinische Universitätspoliklinik, Hermann-Herderstraße 6, 78 Freiburg i. Br. (Germany).

Acute transient hearing loss after ethacrynic acid therapy

Transient acute hearing loss is reported in 5 patients (ages 20 to 76 years) following administration of the diuretic ethacrynic acid [2,3 dichloro-4-(2 methylenebutyl) phenoxyacetic acid] for oliguria. Two patients received the oral form of the medication while intravenous medication was used in the remaining 3 patients. The total dose given during the 12 h preceding the deafness ranged from 150 to 700 mg. Tinnitus was seen in 3 patients but vertigo was absent in all patients. Audiometric testing in one patient revealed a 30 to 40 decibel sensory neural loss. The hearing loss subsided 3 to 48 h after discontinuing the therapy.

Author’s address: Dr. E. Lovell Becker, 525 East 68th Street, New York, N.Y. 10021 (USA).

Allopurinol in the treatment of gout

Allopurinol [4-hydroxyprazolo-(3,4-d)-pyrimidine, abbreviated 4-HPP, trade-name-Zyloprim®] is an xanthine oxidase inhibitor which reduces the formation of uric acid by interfering with the oxidation of xanthine and hypoxanthine to uric acid. Forty-six patients with gout were studied for periods ranging between 3 to 28 months while being treated with this compound in an average daily dose of 500 mg. With 4-HPP therapy, serum uric acid levels began to fall in 2 days and maximal suppression with a given dose was usually seen in 7-10 days. Serum uric acid levels fell as low as 2-3 mg%. Concomittant with the decline in serum uric acid levels, there was a parallel decrease in urine uric acid excretion particularly in patients who were over-producers of urate. 4-HPP itself has no anti-inflammatory activity and was not immediately effective when used as the sole agent in the treatment of acute attacks. Disappearance of tophi may be enhanced by the addition of uricosuric agents to 4-HPP therapy.

The major adverse side effect noted was a reversible pruritic maculopapular rash which occurred in 5 patients with azotemia. The reaction was associated with fever in 2 patients. Two patients with chronic renal failure being with intermittent dialysis had hyperuricemia and arthritic symptoms. They were treated with 4-HPP without untoward side effects. None of the patients developed xanthine or pyra-zolopyrimidine renal calculi. 2 patients with advanced renal failure secondary to gouty nephropathy were treated without improvement in their renal function. Acute gouty attacks occurred despite moderate-to-marked reductions in serum uric acid levels, but gradually after a few weeks, became less frequent and less severe.

4-HPP therapy can be given with uricosuric agents (probenecid or sulfin-pyrazone) with good results, producing some additional reduction in serum uric acid levels and increase in urate excretion.

Allopurinol is recommended therapy at this time for patients with severe gout, poorly controlled by conventional therapy, for those with tophaceous deposits, those prone to form urate stones and for patients with early or incipient impairment of renal function. In many patients,
Allopurinol therapy should be combined with the use of colchicine to further reduce the liability to acute attacks.

Author’s address: Dr. R. Wayne Rundles, Department of Medicine, Duke University Medical Center, Durham, N.C. 27706 (USA).

Significance of asymptomatic bacteriuria detected during pregnancy


A study carried out 2 to 12 months after women discovered to have bacteriuria during pregnancy were delivered of their infants has shown the following: (1) bacteriuria persisted in 90 of 111 untreated women; (2) bacteria were present in urine obtained from one or both urethers in 17 of 23 patients; and (3) pyelographic abnormalities were detected in 61 of 131 patients. These findings suggest that in many instances asymptomatic bacteriuria first noted during pregnancy persists following delivery and is associated with active renal infection.

Author’s address: Dr. P. J. Whalley, The University of Texas, Southwestern Medical School, Department of Obstetrics and Gynecology, 5323 Harry Hines Boulevard, Dallas, Texas 75235 (USA).

Prevention of catheter-induced urinary tract infections by sterile closed drainage


A closed-drainage sterile collection system (Asept. Closed Sterile Drainage Set manufactured by Becton-Dickinson Company, Rutherford, New Jersey) was evaluated in all patients undergoing chronic catheterization during an 8 months interval. Some 12,200 patients were admitted to the hospital during this interval and of these, 1166 were treated with indwelling catheters. The junction of the catheter with the drainage tube is not broken after initial aseptic insertion. The initial urine culture was sterile in 676 patients. The catheter exposure time required to infect 50% of catheterized patients was 13½ and 11 days in males and females, respectively. Seventy-seven percent of patients retained a sterile urine at the time of the removal of the catheter or at the time of hospital discharge. Concomittant systemic antimicrobial therapy appeared to diminish the incidence of infection. Reflux of contaminated urine from the collection bag to the catheter was not a significant problem. The system used appeared practical and the results obtained compared favorably with systems employing antimicrobial rinses.

Author’s address: Dr. C. M. Kunin, Department of Medicine, University of Virginia School of Medicine, Charlottesville, Va. (USA).

Fixed and reproducible orthostatic proteinuria


A follow-up study was carried out on 57 of 64 young males previously evaluated 5 years earlier for ‘fixed’ orthostatic proteinuria. Urine protein was measured by a biuret method and orthostatic proteinuria was classified as ‘fixed’ if upright proteinuria was noted on serial testing on separate days and as ‘transient’ orthostatic proteinuria if not consistently present. Ages ranged between 21 to 29 years. 49% were now noted to have ‘fixed’ proteinuria, 29% ‘transient’ proteinuria and 19% had negative urine protein tests. The group as a whole enjoyed general good health during the 5 year interval. Whereas only 7 of 64 patients had ‘abnormal’ urine sediments 5 years earlier, at follow-up 24 out of 57 now had similar abnormalities. This suggested to the authors that fixed orthostatic proteinuria is not a transient condition and may well constitute an early manifestation of slowly progressive renal disease.

In nine patients with idiopathic nephrotic syndrome severe oliguric renal failure occurred soon after the onset of the disease. This relatively rare complication raised considerable problems of management and only two patients survived. One survivor made a complete recovery and the other was well apart from mild symptomless proteinuria a year later. Both patients had a minimal glomerular lesion but in only one was it responsive to steroid therapy. A third patient with a proliferative glomerulitis had recovered from oliguria when he died of secondary infection. This series of oliguric patients included cases with each of the three main histological lesions found in idiopathic nephrotic syndrome. Possible explanations for the oliguria are considered. A scheme of management is advocated for the nephrotic patient who becomes oliguric. This is based on the restoration and maintenance of normal plasma volume by intravenous albumin or other plasma expander and control of oedema and uraemia by daily peritoneal dialysis.

Vere, D.W.: Renal selective permeability for proteins during response to steroid drugs in the nephrotic syndrome.

Detailed estimations of renal selective permeability for proteins have been made using electrophoretic or gel diffusion methods in six adults with steroid-responsive nephrotic syndrome. No change in selective permeability was observed during the response to steroid, even to the point where proteinuria had almost ceased. A simple algebraic method has been used to represent renal selective permeability. The methods and results will be discussed.


In 1960, preliminary studies of the treatment and prognosis of 36 adults patients with the nephrotic syndrome related to functional and renal biopsy findings were published from this Department. This work has now been expanded to report more detailed findings on renal biopsy of 313 patients with glomerulonephritis, followed for periods of 2 to 10 years. The nephrotic syndrome was present in 136 patients and the remaining 177 patients suffered from persistent and prolonged proteinuria, acute nephritis or recurrent haematuria. The histological findings show no clear distinction between those patients with the nephrotic syndrome and those with milder proteinuria, although the functional and histological correlations previously observed in the nephrotic syndrome have been fully confirmed. Twenty-eight patients showing minimal histological changes in the glomerulus have had excellent responses to steroid therapy and made a complete recovery irrespective of the severity of the proteinuria. Severe thickening of the basement membrane (membranous glomerulonephritis) has been associated in 35 patients with heavy proteinuria and with negligible responses to steroid therapy, although the deterioration of
renal function has been slow in many cases. Fifty-seven patients with glomeruli showing severe proliferation of epithelial cells and crescent formation have mostly shown a relatively rapid deterioration of function with a high mortality. Endothelial cell proliferation or focal increase in either epithelial or endothelial cells has been associated with the nephrotic syndrome in 45 cases but more commonly milder proteinuria occurs and the long term prognosis is good.

Cameron, J.S.; White, R.H.R. and Trounce, J.R.: The treatment of severe steroid-resistant proliferative nephritis with immunosuppressive drugs.

Twenty-one patients (13 children and 8 adults) with severe proliferative glomerulo-nephritis were treated with immunosuppressive drugs, 16 with azathioprine (‘Imuran’) and 5 with cyclophosphamide (‘Endoxana’). Two patients who were critically ill and died within 2 days of starting treatment with cyclophosphamide are excluded from analysis. Of the remaining 19, 17 had the nephrotic syndrome at some time in their course and 5 had haemorrhagic nephritis; 7 had anaphylactoid purpura in addition. Fourteen patients had previously failed to respond to treatment with corticosteroids but 7 patients were given immunosuppressive agents as the treatment of choice, and the selection of such patients was discussed.

Investigations carried out included creatinine clearances, serum and urine protein estimations, examination of the urinary sediment and immunochemically determined protein clearances in the nephrotic patients. Renal biopsy was performed in all cases initially and in seven, to date, since treatment. Ten patients showed severe crescents. Most of the children have benefited considerably from treatment, 2 losing proteinuria.

None of the adults showed response to the agent alone, 2 improving on azathioprine and steroids together. At the dosage employed (azathioprine 4-8 mg/ kg/day, cyclophosphamide 5-7.5 mg/kg/day) leucopaenia and anaemia were seen in 6 patients reversing on stopping the drug. In view of the grave prognosis of this type of patient, controlled studies in both adults and children are beginning.

Renal Association (April, 27, 1966)


It is usually assumed that the cessation of urine flow implies the cessation of glomerular filtration. It is conceivable, however, that under certain conditions filtration may continue, but that all the filtrate is reabsorbed so that no urine is passed. This possibility is supported by the fact that changes in the reabsorption of water and electrolytes are not proportional to changes in the filtered load.

Evidence in favour of the concept was adduced from 2 types of experiments. In the first, dogs were bled until their systemic blood pressure was reduced well below the level at which urine flow ceased. The addition of mannitol at this stage could produce urine flow at blood pressures as low as 20-30 mm Hg provided a sufficient pressure had existed at the glomeruli. This was achieved by the previous injection of hexamethonium bromide, which in itself failed to restore urine flow. If THAM were employed it would replace both substances owing to its dual vasodilator and diuretic action.

In other experiments urine flow was stopped by the infusion of nor-adrenaline. On restarting flow by the injection of mannitol the first urine to appear contained a quantity of vitamin B12 (used here to measure the filtration rate) that could only be accounted for by the continuance of filtration after the cessation of urine flow.

Varia – New Book

Sodium transport was measured in the isolated toad bladder by means of the short-circuit current technique and isotopic labelling at different potassium and calcium concentrations before and after stimulation by oxytocin. At a low potassium concentration on the serosal side there was a decrease in active sodium transport and no response with oxytocin. At a low calcium concentration there was a decrease in active sodium transport but the bladder responded in a normal manner on the addition of oxytocin. A high potassium or calcium concentration had no effect on the active sodium transport either before or after the addition of oxytocin. It is thought that the effect of oxytocin and vasopressin on sodium transport may involve a different mechanism from their effect on water movement.


Resonium A is a sodium-containing resin from which at least 2 mEq of sodium per gram of resin are liberated in the bowel.

Three patients were found to have gone into right and/or left ventricular failure as a result of Resonium A therapy. A new resin in the calcium cycle is described which has the advantage of not liberating a dangerous ion. It is as efficient as Resonium A in removing potassium from the body.

Book Review – Livre nouveau

Club international sur l'hypertension artérielle (première réunion, Hôpital Broussais, Paris, 5-7 juillet 1965)

Par P. Milliez et P. Tcherdakoff. 524 pages (Expansion Scientifique Française, 1966). Cette réunion a été la première du Club International sur l'Hypertension Artérielle. Les comptes rendus comportent d'une part les textes et présentations, d'autre part toutes les discussions qui ont eu lieu entre la centaine des plus éminents spécialistes du monde réunis à cette occasion. Cinq grands sujets ont été envisagés: les facteurs hypertenseurs du rein, les facteurs hypotenseurs du rein, l'alodstéron et l'hypertension artérielle, l'hypertension artérielle par lésion des artères rénales, l'hémo-dynamique au cours de l'hypertension artérielle et de son traitement. L'ensemble constitue un document remarquable, cohérent, qui reflète non seulement les travaux déjà publiés, mais aussi ceux en cours d'élaboration qui, un an après, n'ont pas encore fait l'objet d'une rédaction définitive. Au moment où se renouvellent sans arrêt toutes nos conceptions sur l'hypertension artérielle, de telles publications sont indispensables pour que ceux qui se consacrent à son étude évitent de se fourvoyer dans une voie de recherche stérile et déterminent à temps les champs d'action pouvant aboutir à de véritables progrès. G. Richet