The Juxtaglomerular Apparatus in Adrenalectomized Rats Light and Electron Microscopic Observations

The juxtaglomerular apparatus has been studied by light and electron microscopy in adrenalectomized rats at intervals of up to 75 days. Three-dimensional reconstructions of sections 1 to 2 µ thick show that the efferent arteriole of the superficial glomeruli forms a strikingly dilated sinusoidal channel. Granules increase greatly in number in cells in the arteriole as well as in the afferent arteriole and the juxtaglomerular cell mass. Dense cytoplasmic bodies appear increased in the macula densa. An increase of fluffy material in more dilated cavities of the endoplasmic reticulum, together with the appearance of granules with varying contents in the region of the Golgi complex, suggests the manufacture of a secretory substance. This evidence is compatible with the concept that the juxtaglomerular apparatus may respond to the blood volume or sodium metabolism of the body, and that hypergranulation is an indication of increased cellular synthesis of a secretory substance.

Harrison Latta
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Micropuncture Study of Ammonia Excretion in the Rat

Ammonia has been determined in blood and in samples of tubular fluid obtained by micropuncture at various sites along the nephron. Ammonia has been found in tubular fluid from all segments of the nephron, the concentrations being generally higher in those animals which were pretreated with ammonium chloride. In addition, there is a tendency for the concentration of ammonia to increase as the site of micropuncture progresses along the nephron. In the proximal tubule, concentrations of ammonia have been found which are greater than can be accounted for solely by the extraction of water in this segment. This is taken to indicate tubular addition of ammonia at this site. Since the increments of ammonia along the nephron generally exceed that which could be due to water reabsorption, it is concluded that all parts of the nephron contribute to urinary ammonia excretion.

% proximal
20 60
100

% DISTAL
0 50

URETERAL URINE
Fig. Ammonia concentration in tubular fluid at various sites in the nephron and in the ureteral urine.
Gerhard Giebisch
Department of Physiology, Cornell University Medical College, 1300 York Avenue, New York 21, N.Y. (USA).

Summaries – Resumes
251
Nephrotoxic Serum Renal Disease in the Taiwan Monkey
Chin Chiang Huang, Sheng Chein Chang, Yen Ching Lin, Kuang Hua Chen and Ing Ko Hsu
Experimental renal disease was produced in 5 Taiwan monkeys (Macaca cyclopsis) by the intravenous injection of anti-monkey-kidney serum obtained from rabbits. All developed proteinuria and statistically significant hypoproteinemia. Four monkeys revealed statistically significant reduction of the albumin fraction. Two monkeys had generalized edema, and 3 showed statistically significant hyper-cholesterolemia. These clinical abnormalities were associated with histopathologic renal lesions which closely simulated those of the nephrotic syndrome as observed in children. In 7 other monkeys receiving rabbit anti-monkey-kidney serum, the disease appeared to be intensified by the administration of ACTH or prednisolone before or during heteronephrotoxic serum injections. Obvious generalized edema associated with ascites and hydrothorax was observed in all animals. In addition to the foregoing changes, statistically significant increase in values of nonprotein nitrogen and urea nitrogen in the blood was observed in 6 of the 7 monkeys. Evident gross hematuria was noted in 2 young monkeys. Significantly increased serum α2-globulin fraction was observed in 4 monkeys. More prominent hyper-cholesterolemia was noted in 5. Attempts to produce experimental renal disease by the intravenous injection of anti-monkey-kidney serum obtained from ducks failed in 7 Taiwan monkeys. In all animals, neither evident proteinuria nor obvious abnormalities in the urinary sediment were observed throughout the entire course. No edema was noted in any case. The concentrations of total serum proteins were decreased in 5 monkeys, but a decrease in the albumin fraction was observed in only 1 monkey. Histologically, all 7 monkeys revealed no characteristic findings. In 4 other monkeys injected with anti-monkey-kidney duck serum, ACTH and prednisolone had no significant effect on the clinical and histologic response.
Chin-Chiang Huang
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252
Summaries – Resumes
Retrograde Proteus Pyelonephritis in rats
Localization of Antigen and Antibody in Treated Sterile Pyelonephritic Kidneys
Rats with retrograde proteus pyelonephritis were treated with antibiotics until their kidneys became sterile. Using fluorescent antibody techniques, specific P. mirabilis antigen was found in some sterile pyelonephritic kidneys 20 weeks after cessation of treatment and presumed renal sterilization. Persistent antigen was associated with interstitial chronic inflammation but not with
acute inflammation or progressive scarring. Rat gamma globulin and proteus antibody were localized in plasma cells of the renal inflammatory infiltrates. It is suggested that persistent antigen in chronic pyelonephritis may lead to the continued local appearance of antibody-producing cells.

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Inhibition of Distal Tubular Sodium Reabsorption by Angiotensin II

Angiotensin II or norepinephrine was infused directly into the left renal artery of anesthetized dogs undergoing mannitol diuresis, and the right and left kidneys were compared for GFR (Ccr or Qn), RPF (Cpah) &gt; sodium excretion, and distal stop-flow sodium and inulin patterns. Both angiotensin and norepinephrine caused similar reductions of GFR and RPF on the left, as compared with the right, but only angiotensin prevented normal lowering of left distal stop-flow sodium concentration, even when length of occlusion was 14 min. The minimum effective dose was 6-12 mµg/kg min, and maximal differences between left and right sodium minima occurred with 50 mµg/kg min. Distal inulin patterns were not altered by angiotension, nor were ‘postocclusive’ inulin patterns. Clearance data demonstrated that when GFR changes were taken into account angiotensin caused a relative increase in sodium excretion compared to control or norepinephrine-infused dogs. These stop-flow and clearance data support the hypothesis that angiotensin inhibits distal sodium reabsorption by a direct tubular effect. No attempt was made to evaluate possible effects of angiotensin on proximal tubular sodium reabsorption.

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Retrograde Proteus Pyelonephritis in Rats

Retrograde pyelonephritis has been produced in rats by the intra-vesical inoculation of P. mirabilis. The pathogenesis and course of pyelonephritis by this route has been studied in an attempt to correlate the morphologic and bacteriologic changes. It was found that organisms appeared in the kidneys by 24 to 48 hours after injection into the bladder, that they first invaded the pelvis and that the infection involved the medulla and the cortex by continuity through the inter-stitium and the tubules. The infection was usually bilateral but unequal in both kidneys. The surviving animals developed chronic active pyelonephritis with persistence of bacteria and of morphologic evidence of pyelonephritis for at least 13 months after initiation of infection. Chronic pyelonephritis was also bilateral and unequal and was associated with sufficiently widespread scarring to produce unilateral atrophy. In chronic infection there was often azotemia. Renal and vesical calculi were present in the majority of animals with chronic disease.

Fluorescent-antibody studies indicated that bacterial antigen persisted in the renal parenchyma following the initial bacterial proliferation. After the acute stage recognizable bacterial bodies were limited to the pelvis and occasional abscesses; however, variable amounts of amorphous bacterial antigen were present within some renal scars for periods up to 13 months.
After hematogenous infection the initial localization was in cortical and medullary blood vessels, followed by passage into the interstitium and production of scattered abscesses. The hematogenously induced lesions could not be differentiated from the retrograde lesions by the fourth day, presumably because rupture of bacteria into the pelvis, medulla and tubules was followed by intrarenal retrograde spread.

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Bio-Assay of Circulating Renin-Like Pressor Material by Isovolemic Cross Circulation
The renin-like pressor material present in blood under various experimental conditions was determined by isovolemic cross circulation using nephrectomized rats as assay animals and rats having different concentrations of renin in the kidney as ‘donor’ animals. Cross circulation was established by connecting the femoral arteries of both animals with the corresponding femoral veins and maintaining a constant flow. In intact anesthetized rats, a ‘basic’ concentration of renin-like pressor material is demonstrable in the blood which is not influenced by unilateral nephrectomy. In the rat made hypertensive by clamping one renal artery, leaving the other kidney untouched, an increase in circulating renin-like pressor material is found. In unilaterally nephrectomized rats in which the artery of the remaining kidney is clamped, the concentration of circulating pressor material is not elevated. In adrenalectomized rats, an increase of circulating pressor material coincides with an elevated concentration of renin in the kidneys. There is a good correlation between the concentration of renin in the kidney and of pressor material in the blood, while the level of circulating renin-like substance is not correlated with the height of blood pressure.

Franz Gross
Research Laboratories, Pharmaceutical Department, Ciba Limited, Bask (Switzerland).

Diabetic Nephropathy: Clinicopathologic Correlation A Study based on Renal Biopsies
M.I. Salomon Metabolism 12: 687-703 (1963)
Fifty-one unselected diabetics underwent renal biopsy. They varied markedly in age, age at onset, modality of treatment and general clinical manifestations. In all, lesions were found in the kidney—at least under the electron microscope. In the majority of patients, the light microscope also revealed lesions, albeit of a minor degree in some. Essentially the lesions consisted of thickening of the basement membrane of the capillary walls and prominence of the mesangium. In the more severe cases, nodule formation was observed in the latter. The pathology of the lesions under light and electron microscopy is described and the data are correlated with the clinical findings. In several patients the histological nephropathy appears to have antedated the clinical onset of diabetes, i.e. the hyperglycemia and glyco-suria. Conversely, very mild changes have been observed in several cases of longstanding and clinically quite severe diabetes. There was no discernible ‘sparing’ of well controlled cases versus ‘poorly managed’ diabetics. There was no apparent parallelism between the severity of the nephropathy and that of other parameters of ‘complications’ of the malady, in particular the cardiovascular of ocular manifestations. Very little histologic evidence of renal infection was noted in this series, although it was carefully looked for.

Mardoqueo I. Salomon
New York Medical College, Metropolitan Medical Center, New York, N.Y. (USA).
Diagnosis of Significant Bacteriuria in Pregnancy
A study is reported of a simple biochemical method for detecting significant bacteriuria. It is based on the reduction of triphenyl tetra-zolium chloride (TTC) from a colourless solution to a red precipitate by actively respiring bacteria, and is quantitated so as to be sensitive to the critical 100,000 organism level in the urine.
The method was checked against full bacterial counts using 400 urine specimens sent to a routine laboratory. There was one false negative, and five false positives, this error being in the right direction for a screening test. The method was then applied to 100 unselected pregnant women, and a 7% incidence of bacteriuria found, all confirmed by full counts.
The TTC test can easily be applied to large numbers of urines, and requires only simple apparatus. It is suggested that it would make an excellent screening test for bacteriuria, especially in pregnant women.

Timothy Chard
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Fine Structure of Chronic Hypertensive Arteriopathy in the Human Kidney
The fine structural characteristics of 6 and 4 cases, respectively, of hyaline arteriolar sclerosis and of hyperplastic elastic arteriosclerosis in the kidneys of patients with chronic ‘benign’ hypertension were examined and compared with normal afferent arterioles and inter-lobular arteries.

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Hyponatremia and Bronchogenic Carcinoma Associated with Renal Excretion of Large Amounts of Antidiuretic Material
N.A. Thorn and I. Transbol
Amer. J. Med. 35: 257-268 (1963)
A patient is described who presented a typical syndrome of bronchogenic carcinoma, hyponatremia and excessive renal sodium loss during periods of high water intake. Schwartz et al., who called attention to this syndrome, have suggested continuous inappropriate secretion of antidiuretic hormone (ADH) as a cause of its manifestations. Considerable experimental support to this hypothesis is given in the present study. Biological assay of the patient’s urine revealed excretion of anti-

Summaries – Resumes
diuretic substances far in excess of what could be explained by physiological antidiuresis.

A detailed metabolic study was performed of the patient’s water and electrolyte metabolism and his reactions to loads of water, sodium and ethanol. In addition, an evaluation was undertaken of the function of the kidneys, adrenal glands and hypophysis. The possible mechanisms of the hypersecretion of ADH and the rapid excretion of sodium are discussed. It is stressed that the most likely explanation is that the tumor per se produced an antidiuretic substance.

Shortly after the publication of this paper an article appeared (Amatruda et al., New Engl. J. Med. 269: 544 [1963]) in which a case of a very similar syndrome was described. No analysis of urinary excretion of antidiuretic material was performed, but antidiuretic hormone-like activity was demonstrated in extract from fresh oat-cell tumor tissue, obtained at autopsy.

These two studies, supplementing each other, seem to carry strong evidence that antidiuretic hormone-like substances may be produced in tumour tissue in large amounts. The substances can be released to the blood, exert constant antidiuretic action and be excreted in the urine.

This interesting phenomenon of hormone production in tumour tissue arising from non-endocrine organs can be compared with the recent demonstration of production in lung cancer tissue of corticotro-phin-like and parathyroid hormone-like substances. The mechanisms behind these abnormal syntheses of peptides or peptide conversions remain to be established.

Niels Thorn
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Current Interpretation of the Sodium Iodohippurate I131 Renocystogram

New terminology for the renogram’s three segments is recommended, namely, tracer appearance, blood flow, and drainage, to replace the

Summaries – Resumes
original terms, vascular, tubular, and excretion. The first or tracer appearance segment, is no longer considered a useful index of renal vascular volume because activity of blood within the kidney contributes in only a minor way to the height of the first segment. The slope of the second segment is a sensitive gauge of renal blood flow because tracer is retained in the kidney during this time and the extraction efficiency of the kidney for tracer quantities of ortho-iodo-hippurate 1-131 (OIH) is approximately 90%. The most important event in the third segment is urine drainage from the upper urinary passages. The term ‘renal transit time’ (time from tracer appearance to peak renal radioactivity) is added as another parameter of the renocystogram and is an index of individual urine flow.

The cystogram provides a separate measurement of renal transit time (time for tracer appearance to entrance of OIH into the bladder) and registers the delivery rate of tracer from both kidneys
into the bladder. In the absence of obstruction to urine outflow, the fraction of the administered dose recovered in voided urine in 15 minutes is an index of total renal blood flow. The clinical significance of the renocystogram is its ability to indicate abnormalities of individual renal blood flow, urine flow and urine drainage. A major application is the detection of unilateral renal ‘ischemia’ in hypertensive patients.

Earl K. Dore
Department of Radioisotope, Memorial Hospital, Long Beach, Calif. (USA).

Effects of Ethanol Administration on Urinary Excretion of Magnesium and Other Electrolytes in Alcoholic and Normal Subjects

Although clinical magnesium deficiency is now recognized frequently in chronic alcoholics, its cause or causes are not clear. It is unlikely that this magnesium deficiency results from dietary depletion alone.

260

Summaries – Resumes
as the kidneys are efficient in conserving magnesium and it is difficult to produce experimental magnesium deficiency in man by dietary restriction alone.

Recent studies have suggested that an increased urinary excretion of magnesium follows the ingestion of alcohol. The administration of ethanol (30 grams orally followed by a constant infusion of 5% ethanol at 5 cm³ per minute) to 7 normal and 4 alcoholic subjects in a steady-state water diuresis induced an acute urinary diuresis of magnesium (167% above control values) and calcium (89% above control values) and a decreased urinary excretion of potassium (44% below control values) (1). These changes were independent of alterations in glomerular filtration rate, renal blood flow or rate of urine flow.

Further studies were conducted in an attempt to define the mechanism responsible for these changes in urinary electrolyte excretion following ethanol. Previous studies had shown that (1) an increase in serum lactate followed ingestion of ethanol and (2) an increase in urinary magnesium excretion followed lactate infusion. It was postulated that the increase in magnesium excretion following ingestion of ethanol might result from increased lactate production and excretion. The observed increases in serum and urine lactate and urine total organic acids following ethanol, however, were small. Infusions of sodium lactate (3 subjects) which produced much greater increases in serum and urine lactate and urine total organic acids produced only small, transient increases in magnesium excretion. The increased urinary excretion of magnesium did not appear to result from an increase in cation-organic acid complexes.

Galactose ingestion (3 subjects) produced changes in urine electrolytes, lactate and organic acid excretion which closely paralleled those observed after ethanol ingestion (2). The oxidative metabolism of ethanol and galactose utilizes the electron transport system (DPN-flavoprotein-cytochrome enzymes). If the cation transport systems were dependent upon these same respiratory enzymes, a competitive inhibition of magnesium and calcium reabsorption and potassium secretion in distal tubular sites could explain the findings of these studies.

References

Summaries – Resumes

John M. Kalbfleisch
Department of Medicine, University of Oklahoma Medical Center, and the Medical Service, Veterans Administration Hospital, Oklahoma City, Okla. (USA).
Prolonged Survival of Human Kidney Homografts by Immunosuppressive Drug Therapy
J.E. Murray, J.P. Merrill, J.H. Harrison, R.E. Wilson and G.J. Dammin
This is a summary of 13 patients who have had kidney transplantation and have been treated with immunosuppressive drugs. Neither total body irradiation nor bone marrow has been used in any form. The experience is predicated on laboratory data using Imuran, an imidazo-yl derivative of 6-Mercaptopurine which was tested first in the Harvard Medical School Laboratories in the bilaterally nephrectomized dog receiving a renal homotransplant.
Additional drugs and combinations of drugs have been tested since the initial experience and have been used in the patients.
The clinical experience with the first 10 patients shows four with measurable and meaningful function. All had expendable kidneys either from cadavers or hydrocephalic children undergoing ureteral subarachnoid shunts. One patient has survived for over one year and is still living sustained by a homotransplant from a cadaver. The last three patients all had living volunteer donors and all have practically normal renal function 5, 4, and 3 months respectively following transplantation.
Unsolved problems are the duration for the need of the drug, the ultimate fate of the graft, and the mode of action of 'drug tolerance'. A note of cautious optimism has resulted from this experience with these 13 patients to be contrasted with the almost hopeless situation of 10 years ago.
Joseph E. Murray
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Varia
IIe Congrès International de Néphrologie
Le IIe Congrès International de Néphrologie se tiendra à Washington, D.C., USA, du 25 au 30 septembre 1966, dans les locaux du nouvel hotel Hilton International. Le president du congrès est le Dr Robert W. Berliner, du «National Institute of Health» et le secretaire general est le Dr George E. Schreiner, pro-fesseur à l'Université Georgetown.
Le programme préliminaire prévoit des sessions plénières consacrées à la physiologie rénale, aux pyélonéphrites, à l’urémie, à l’hémodialyse et aux homo-transplantations. En outre, des reunions spécialisées seront organisées sur les sujets suivants: l’anatomic pathologique du rein (comprenant l'étude des biopsies et les résultats des méthodes microscopiques spéciales); la physiologie du rein en y incluant les techniques de micropuncture, les transports d’électrolytes, l’équi-libre acido-basique, l’action des diurétiques, le flux sanguin renal, Faction des hormones
sur le rein, les transports à travers les membranes; les nephrites et pyélonéphrites expérimentales; les toxémies gravidiques; les déficits des fonctions tubulaires; le syndrome néphrotique; les néphropathies toxiques; l'hypertension d'origine rénale; les néphropathies congénitales et héréditaires; l'épidémiologie des maladies rénales; les techniques radiographiques et radioisotopiques; la dia-lyse pérétonéale et d'autres méthodes thérapeutiques. II est prévu le temps nécessaire pour de breves communications fibres. 

Dans les premiers mois de 1966, on fera connaître le programme scientifique détaillé et celui des autres activités et on distribuera les documents nécessaires pour la proposition des resumés de communications, ainsi que pour l'inscription et la réservation des places d'hôtel.

Pour tout renseignement, s'adresser au Secretariat du Hie Congrès International de Néphrologie, 9650 Wisconsin Avenue, Washington, D.C. 20014, USA. Adresse télégraphique: NEPHROCON, Washington, D.C.

Third International Congress of Nephrology

The Third International Congress of Nephrology will be held in the new Washington Hilton Hotel, Washington, D.C., U.S.A., September 25-30, 1966. Dr. Robert W. Berliner of the National Institutes of Health is President of the Congress, and Dr. George E. Schreiner, Professor of Medicine at Georgetown University, is Secretary General.

The Congress is under the general sponsorship of the International Society of Nephrology, and is being sponsored in the United States by the Renal Section of the Council on Circulation of the American Heart Association, together with a number of cooperating societies including, currently, the American Federation for Clinical Research, the American Urological Association, the American Medical Association, the American Society for Artificial Internal Organs, the Scientific Advisory Board of the National Kidney Foundation, and the Washington Heart Association, Inc.

Tentative plans for the program include general sessions devoted to renal physiology, pyelonephritis, uremia, hemodialysis, and homotransplantation. The program will also include sessions on the following topics: renal pathology including biopsy and special microscopy; renal physiology including micropuncture, electrolyte transport, acid base balance, diuretics, renal blood flow, hormones and the kidney, membrane transport; experimental nephritis and pyelonephritis; toxemia of pregnancy; renal tubular defects; nephrotic syndrome; toxic nephropathies; renal hypertension; congenital and hereditary renal disease; epidemiologic studies of renal disease; radiographic and isotopic techniques; peritoneal dialysis and other treatment techniques. Time will be available for the presentation of brief communications.

Details of the scientific program and social programs, and forms for the submission of abstracts, registration, and hotel reservations will be distributed early in 1966.

Address inquiries to: Secretariat, Third International Congress of Nephrology, 9650 Wisconsin Avenue, Washington, D.C. 20014, U.S.A. Cable address: NEPHROCON, Washington, D.C.

Actualités Néphrologiques de l'Hôpital Necker

3, 4 et 5 mai 1965

Le cours de perfectionnement sur la Néphrologie aura lieu, comme les années précédentes, à la Clinique des Maladies Métaboliques (Professeur J. Hamburger), Hôpital Necker, Paris.

Le programme est le suivant:


2) Autres sujets :

U excretion d’ammoniaque par le rein. R. Ardaillou, C. Amiel et G. Richet.
Méthodes nouvelles de me sure du debit sanguin renal. F. C. Reubi.
La reprise de la dïurèse des tubulopathies anuriques. M. Legrain.

264
Varia

La secretion inadequate a’hormone antidiurétique en clinique (syndrome de Schn &gt; artiç-Bartter). R. Mach et R.C. de Sousa.
Nouvelles données apportées par les biopsies rénales à la connaissance des néphropathies gravidiques. J.-M. Sue.
Le diagnostic de la thrombose veineuse rénale par les nouvelles techniques de phlébographie cave. C. Gillot, P. Milliez et G. Richet.
Pour tous renseignements s’adresser au Secretariat du Professeur Agrégé J. Cros-nier, Hôpital Necker, 149, rue de Sevres, Paris 15e.

Heinz Karger Memorial Prize

The Dr. Heinz Karger Memorial Foundation in Basle announced last year an international competition for outstanding medical-scientific papers, to be written on the subject ‘Enzymology of Leukemic Cells’. The Council of the Foundation— which comprises Professor H. Lüdin, Basle, Professor G. Mayor, Zurich, Dr. R. Richterich, Berne, Professor J.R. Rüttner, Zurich, and the publisher, Mr. T. Karger—has now awarded the sFr. 3,000.- prize to the two American research workers Dr. J. B. Block and Dr. S. L. Bonfond of the National Institutes of Health, Bethesda, Md., for their paper about ‘ATPase Transport in Normal and Leukemic Leucocytes’.

This paper will be published in the international journal Enzimologia Biologica et Clinica. Highly recommended were the papers submitted by Dr. W. Wilmanns from Tubingen (awarded the second prize) and Prof. D. Dioguardi of Cagliari and Prof. A. Agostini of Milano (awarded the third prize).

The Council of the Foundation has also announced that the subject of the second competition, to be held next year, will be ‘Microangiological Problems in Arteriosclerosis’.