ACTA MEDICA

ACADEMIAE SCIENTIARUM HUNGARICAE

SUPPLEMENTUM
TOMUS XIX

AKADÉMIAI KIADÓ, BUDAPEST
1963

ACTA MEDICA

A MAGYAR TUDOMÁNYOS AKADÉMIA ORVOSTUDOMÁNYI KÖZLEMÉNYEI

KIADÓHIVATAL: BUDAPEST V., ALKOTMÁNY UTCA 21.

Az *Acta Medica* német, angol, orosz és francia nyelven közöl tudományos értekezéseket az orvostudomány köréből.

Az *Acta Medica* változó terjedelmű füzetekben jelenik meg, több füzet alkot egy kötetet.

A közlésre szánt kéziratok a következő címre küldendők:

Acta Medica
Dr. Stark Ervin
Budapest VIII., Korányi S. u. 2/a, I. Belklinika

Ugyanerre a címre küldendő minden szerkesztőségi levelezés.

Az *Acta Medica* előfizetési ára kötetenként belföldre 80 forint, külföldre 110 forint. Megrendelhető a belföld számára az „Akadémiai Kiadó"-nál (Budapest V., Alkotmány utca 21. Bankszámla: 05-915-111-46), a külföld számára pedig a „*Kultúra*" Könyv és Hírlap Külkereskedelmi Vállalatnál (Budapest I., Fő utca 32. Bankszámla 43-790-057-181) vagy annak külföldi képviseleteinél, bizományosainál.

Die *Acta Medica* veröffentlichen Abhandlungen aus dem Bereiche der medizinischen Wissenschaften in deutscher, englischer, französischer und russischer Sprache.

Die *Acta Medica* erscheinen in Heften wechselnden Umfanges. Mehrere Hefte bilden einen Band.

Die zur Veröffentlichung bestimmten Manuskripte sind an folgende Adresse zu senden:

Acta Medica
Budapest VIII., Korányi S. u. 2/a, I. Belklinika

An die gleiche Anschrift ist auch jede für die Redaktion bestimmte Korrespondenz zu richten.

Abonnementspreis pro Band: 110 Forint. Bestellbar bei dem Buch- und Zeitungs-Außenhandels-Unternehmen »*Kultúra*« (Budapest I., Fő utca 32. Bankkonto Nr. 43-790-057-181) oder bei seinen Auslandsvertretungen und Kommissionären.

CONGRESS OF THE KORÁNYI SÁNDOR SOCIETY

BUDAPEST, 1961

INDEX

Rusznyák, I. : Opening Address 5
Bálint, P. : Advances in Renal Functional Diagnostics 9
Babics, A. : Modern Tests of Renal Function 21
Hámori, A. : Treatment of Nephritis, Pyelonephritis and Nephrosis 37
Földi, M. : Sodium Retention and Oedema 55
Kerpel-Fronius, E. : Paediatric Aspects of Renal Diseases 71
Horányi, B. : Neurological Aspects of Renal Diseases 77
Weinstein, P. : Ophthalmologic Aspects of Renal Diseases 89
Zsebők, Z. : Radiological Aspects of Renal Diseases 95
Kovács, A. : Gynaecologico-Obstetrical Aspects of Renal Diseases 103

REPORTS

Gömöri, P., Tu, S. H., Szalay, E. and *Zolnay, B.* : Functional, Morphological and Corrosion Studies in Masugi-Nephritis 109
Rényi-Vámos, F. and *Horváth, L.* : New Experimental Data Concerning the Development of Nephropyelitis 109
Egedy, E., Stekker, K., Füredi, E. and *Fonyódi, L.* : Signs of Renal Failure in Patients Operated for Diseases of the Liver, Bile Ducts or Pancreas 110
Rév, J. and *Solti, F.* : Sweat Excretion in Acute Renal Disease 110
Li, B. N., Kemény, T. and *Sós, J.* : Renal Injury due to p-N-oxyphenylglycine 111
Dési, I., Antal, M., Fehér, I. and *Simon, G.* : Nervous Factors in Experimental Uraemia 111
Tényi, M. : Enzyme Activity Changes in the Rat Following Unilateral Nephrectomy and Partial Hepatectomy 112
Beregi, E., Földes, I., Jankovics, D. and *Csötörtök, L.* : Renal Changes Caused by Serotonin in the Rabbit and Rat 112
Erneszt, J. : Significance in Pregnancy of Previous Nephritis 113
Láncos, F. : Juvenile Nephronophthisis 113
Erdős, Z., Cserháti, E. and *Hittner, I.* : Prognosis of Wilms' Tumour 114
Gál, G., Németh, A. and *Fazekas, S.* : Follow-up Studies in Patients Recovered from Acute Uraemia 115
Galambos, M. : Appraisal of Renal Regulation on the Basis of Electrolyte Excretion in Banal Infectious Diseases During Unrestricted Fluid Intake and During the Concentration Experiment 115
Gerő, S., Gergely, J., Dévényi, T., Jakab, L., Kocsár, L., Székely, J. and *Virág, S.* : The Significance of Intimal Mucopolysaccharides in Lipid Deposition 116
Juba, A. : Multiple Sclerosis and Disseminated Encephalomyelitis 116
Kubányi, E. : Intermedin Effect of Implanted Fish Pituitary in Cases of Pigment Degeneration 117
Kahán, A. : Transitory Retinal Response to Pituitary Implantation in Cases of Retinitis pigmentosa 117

Csillag, M. and *Morócz, K.* : Diagnostic Laparoscopy in Gonadal Disturbances of the Female 118
Köves, I. and *Kelemen, E.* : Restoration of Fluid and Electrolyte Balance in Intestinal Obstruction 119
Gelencsér, F., Gáti, T., Hideg, J. and *Selmeci, L.* : Duodenal Osmoregulation in the Rat... 119
Lányi, M. : Mycobacteriosis. Clinical and Experimental Data Concerning the Significance of the Mycobacterium Variants Arising in the Organism 120
Boda, D. and *Murányi, L.* : Estimation of the pH of Blood in the Diagnosis of the Disturbances of Acid-Base Balance 120
Dénes, Z. : Clinical and Laboratory Methods of Examination as Geriatrical Tests 121
Kelemen, E., Doctor, F., Lehoczky, D., Cserháti, I. and *Rák, K.* : A Humoral Sign Indicative of Hypersplenism 121
Csaba, G., Bodoky, M. and *Bernád, I.* : The Effects of Thymectomy and Thymic Substitution upon Experimental Arthritis 121
Aszódi, Z. and *Zombory, J.* : Biliary Acid Concentration in Blood Serum in Diabetes... 122
Szabó, G. and *Zoltán, Ö.* : Protein Absorption from Subcutaneous Tissues in Venous Congestion and in Hypoproteinaemia 124
Solti, F., Szabó, G., Iskum, M., Péter, Á., Rév, J. and *Földesy, K.* : The Effect of a Diminution of the Effective circulating Blood Volume on Cerebral Blood Flow and Cerebral Vascular Resistance in Man 124
Iskum., M, Solti, F., Komáromi, I., Simonyi, G. and *Réfi, Z.* : Effect of Hypoxia on Cerebral Venous Circulation 125
Sztankai, C. and *Csernohorszky, V.* : Artificial Hibernation in the Prevention of Postoperative Thyrolaxic Csisri 125

OPENING ADDRESS

delivered by

Professor I. RUSZNYÁK
CHAIRMAN OF THE SOCIETY

Before I declare open the First Congress of the *Korányi Sándor Society* I should like to say a few words of its coming into existence, its aspirations and functions, and of its office — imposed upon it by the times — of promoting growth and spread of modern scientific knowledge.

Quite a number of medical associations and specialists' groups have been active for many decades in this country, mostly to meet the claims of individual branches. Until last year, the Hungarian Physiological Society, a renowned association founded in 1931, was the only body of this type to be under the general supervision of the Hungarian Academy of Sciences. — "Physiological Society" is a designation that easily misleads; ever since its formation the society has been the home not only of physiology in the strict sense of the term, but also of biochemistry, pharmacology, and pathology; that is, essentially of all the work commonly referred to as basic medical research. Until quite recently, the so-called applied or clinical medical sciences have had no such organization. Clinicians could only apply to membership of the Hungarian Physiological Society on the merit of theoretical work. The few of us who were elected to this distinguished membership — let us admit it — have more than once, and notwithstanding all the gracefully courteous reception, felt ill at ease on hearing concern voiced at almost every annual general meeting that the participation of clinicians might set an undesired trend for the transactions of the society. This tendency to foment antagonism between the men of pure and applied research, is not of recent origin; it derives from the days when advocates of the view that the interests of research were autotelic interests, felt inclined to look down on workers devoting their efforts to the application of existing scientific knowledge to practical problems. Those days are gone of course, at least in this part of the world, but the weight of a dead past still obscures some minds.

It cannot reasonably be doubted that medicine is pre-eminently an applied science, nor is there room for doubt that like every other applied science, it is founded on basic research. To my mind, this implies that it would be wrong to force a sharp line of demarcation somewhere between the branches of basic and applied medical research. For, obviously, the so-called basic or theoretical

branches of medicine are to provide the sound foundation for the practical work, and applied or practical medicine must be thoroughly permeated by up-to-date theoretical knowledge; moreover, by genuine interest in the major theoretical problems of the day. Medical science as an interconnected whole is thus a fine illustration of the oneness of theory and practice. Nevertheless, every-day interests, the need to provide medical education and to co-ordinate scientific research, do compel us to fix certain dividing lines for purely organizational purposes between the basic or theoretical and applied or practical disciplines; moreover, to subdivide each into branches or specialties. Such artificial separation and distinction are liable to give rise to certain distortions and disproportions, which to avoid, one must never lose sight of the organic unity of medicine as a whole.

With these points in mind, it would be fair to say that it was right for the Hungarian Academy of Sciences to have organized, in 1950, in support of the so-called clinical sciences, the regularly held itinerant meetings named after KORÁNYI SÁNDOR, and to have, last year, pushed the idea to its logical conclusion by calling into life the *Korányi Sándor Society*. A society of members with permanent rights and duties is no doubt a more solid organizational base than are itinerant meetings with audiences of widely varying composition and coming together from time to time.

As laid down in the bye-laws, our Society's "objectives are to be achieved under the supervision of, and in concert with, the Hungarian Academy of Sciences, and include improvement of clinical medicine, aid to its activities, discussion of its results, and provision for their publication."

Before proceeding to discuss the means to the ends, I should like it to be clearly understood that the Society is not one of internal medicine. Its solemn adoption of the great Hungarian clinician's name is in no way to mean that it will represent but a single branch of medicine. KORÁNYI SÁNDOR's authority and the influence of his work go far beyond internal medicine in this country; and so I am expressing the wish of the Academy in saying that the Society is hoped, and expected, to develop into a forum for the synthesis of *all* the clinical sciences in Hungary. Already the program of the present Assembly has been designed so as to give expression to this tendency.

As the sciences grow at rates increasing from year to year so grows throughout the world the tendency to organize and hold ever more and ever larger congresses, conferences, and other scientific assemblies. The situation threatens to become as uncontrollable as the enormous and chaotic structure of the present system of scientific publication. The question has repeatedly been raised, even at international level, if there is much sense in organizing congresses of 5, 6 or 7 thousand participants whose very number practically frustrates serious discussion, if not attendance, at most of the lectures. Although, fortunately, no similar consternating giantism threatens our assemblies,

the point needs to be brought up whether it is rational comprehensively to discuss a question, possibly one of detail, in the presence of several hundred attendants, most of whom may be uninterested in the details. I think, it is not rational. A true discussion, if it is to be productive, must not be forced into the framework of a thesis advanced, one or two argumentative comments from the floor, and a summing up from the platform or the chair. The participants in a true discussion must be given the opportunity of speaking again and again, in a free conversational manner, for which, however, time is usually lacking in oversized assemblies. Once I attended a congress abroad where the chairman had to suggest that the parties in an animated controversion withdraw to the lobby and there try to settle their dispute. This one instance in itself shows that a profound debate is only possible when the attendance is limited in size. But the ensuing conclusion is not that a congress cannot be a place for debates. On the contrary, it must be one whenever momentous basic principles are at issue; yet the details should be relegated to smaller bodies for discussion. Conventions should only aspire to sketch out the situation in a branch of science, or make an analysis of the state of a weighty problem, compare this with the stock of recent knowledge, and point out the trend of future development. The wider the lecturer's knowledge of his subject and the more original his angle of approach to it, the greater will be the utility of his lecture; particularly, if he knows how to lay stress on unsolved points and problematic details suggestive of new ideas, principles and methods.

I have mentioned the necessity of smaller bodies for debating details outside the congress. Very wisely, our statutes emphatically point out that between the bi-annual congresses, conferences, symposia, and meetings may be held. I should say, must be held. Already two such meetings are planned to be organized in the coming year, and the members are invited to propound subjects which they deem to be timely and requiring discussion.

A word should be included here concerning this year's Congress. In our minds, KORÁNYI's name is linked up with fundamental knowledge acquired of renal function, both normal and pathologic, and so it seemed obvious to choose the problem of the kidney to form the principal subject of our first congress. In view of last year's very successful conference on renal pathology, concern was felt in some quarters if it was right to have selected this topic. Your presidium gave the point their close consideration and unanimously found that it was right, and on more than one ground. Apart from the tradition attaching to KORÁNYI's name, it was right, first, because of the extremely rapid advance in the physiology, the pathology, and the clinical treatment of renal disease; and secondly, because this country is known to possess internationally recognized specialists of the kidney in numbers unparalleled in almost any other field of medicine. I think, the list of the lecturers you are going to hear justifies full confidence in the success of our deliberations.

In declaring this Congress open I wish to express the hope that the *Korányi Sándor Society* will perform its noble office in the spirit which is expected from it not only by the Academy but the whole of the Hungarian medical profession. I feel, the times no longer favour disintegration into specialties but demand, instead, co-operation and synthesis. And so let our Society develop into a powerful tool of synthesis; let it be a forum, whence in the face of the precarious international situation the Hungarian world of science proclaims its fundamental faith in the progress of science, in a better future of labouring mankind, and in world peace. It is in such anticipation that we already consider inviting to our coming conferences scientists from abroad, primarily from the friendly states. In this manner, too, we wish to conduce to the coordination and furtherance of the efforts made by science in the socialist world in its struggle for the common goal. The critical importance of the part played by science in building socialism is steadily increasing, and the work that falls to the share of our Society is both earnest and substantial. I feel convinced that conscious of their responsibilities in the persistent efforts made for the benefit of our people and the whole of humanity, the clinicians of Hungary will be at one in devoting their undiminished energy and gifts to the tasks confronting them.

ADVANCES IN RENAL FUNCTIONAL DIAGNOSTICS

By

P. BÁLINT

INSTITUTE OF PHYSIOLOGY, MEDICAL UNIVERSITY, BUDAPEST

In endeavouring to fulfil the honourable task of delivering a lecture at this Congress I would first of all thank the Presidium for having given me a free hand in selecting my theme. This privilege, I am aware, imposes upon me increased responsibility.

I have chosen as my theme the subject of renal functional diagnostics, a field that I have always been particularly interested in, which however is far too wide to exhaust within the time at disposal. I shall therefore restrict myself to discussing some of the pertaining questions.

The tests of renal function may be classed in two groups. Those in the first group inform about the presence of active renal lesions, the intensity of disease processes, etc. They include the current procedure of urine analysis. Proteinuria, cylindruria, pyuria, etc., point to an active renal lesion, but yield no information about the kidney's functional capacity. For example, in acute nephritis the urine may be severely pathologic but renal functional capacity practically unimpaired.

The second group informs about the kidney's functional capacity, but fails to indicate activity, nature, etc., of the pathological process. My paper will be devoted to this second group of tests, especially those allowing bedside diagnosis of renal functional deficiency.

What served as the starting point for the progress in renal diagnostics, which has marked the last decades, was the introduction of the concept "clearance" and its widespread translation into practice. In its original sense the word clearance means the volume of plasma which is cleared in one minute of a certain component present in both the plasma and the urine. The clearance formula is $U \cdot V/P$, where U = the concentration of the substance in one ml of urine; P = the plasma concentration; V = the amount of urine passed in one minute. This quotient can be calculated for any substance which is present in the plasma and the urine. For instance, a carbamide clearance of 75 means that the quantity of carbamide excreted in the urine in one minute is the same as that contained in 75 ml of plasma.

From the application of the clearance principle the obvious advantage accrues that the rates at which different substances are excreted can be stated

in the identical unit of measure, the quantity of plasma "cleared". A practica advantage is inherent in the fact that since the concentration of the same substance figures in both the numerator and the denominator, less care needs to be devoted to the determination of absolute concentration; essential is the ratio of concentrations.

In estimating the functional capacity of the kidney, the clearance principle has gained very much in importance since it had been established that, under certain conditions, it is possible to conclude from the clearance of some substances to the amount of ultrafiltrate forming in the glomeruli (glomerular filtration rate, GFR) and the amount of plasma (blood) flowing through the kidney (renal plasma flow, RPF; renal blood flow, RBF), namely, with substances neither reabsorbed nor secreted in the tubules, the clearance rate equals glomerular filtration; with substances fully extracted in the kidney from the blood, *i.e.* whose concentration in renal venous plasma is practically nil, clearance is a measure of renal plasma flow.

Without entering into details let me state that inulin clearance (C_{in}) and para-amino-hippuric acid clearance (C_{PAH}) have been universally accepted as measures of GFR and RPF, respectively. (But C_{PAH} = RPF only at very low plasma PAH levels.) [1, 2, 13, 15, etc.]

For some years doubts have been entertained about the value of the clearance methods. At the root of these doubts lies essentially the fact that in conditions accompanied by oliguria — *e.g.* hypotony, hypovolaemia, shock, post-traumatic states, dehydration, hypoxia, acute renal failure — the clearance points to almost complete renal ischaemia whereas considerable RBF is demonstrable in animal experiments by direct measurement and in humans by what is termed the foreign gas method. (For further details see my report at the 1960 Congress of Hungarian Internists [3].)

Whatever the position in regard to this question, in the human adult under physiological conditions GFR is approximately 125 ml, RBF 1000 to 1200 ml, and so RPF 600 to 650 ml/min. Normally, the glomerular filtrate is stable both in quantity and composition, from which it follows that the filtered amount of the various substances are likewise fairly constant; experiments of my own have convinced me that the direct methods show greater haemodynamic constancy than it had seemed on the basis of the clearances.

It is a fundamental fact in physiology that what maintains homeostasis (Claude Bernard's "milieu interieur") is that urine secreted by the kidney widely adapts itself in quantity and composition to the needs of the organism. In view of the considerable fluctuation in ingestion of substances, SMITH [15] was apparently right in saying that homeostasis depends not on what is ingested but on what is secreted by the kidneys.

The preconditions of homeostasis are a constant osmotic concentration, or isosmosis; constant ionic composition, or isoionia; hydrogen-ion concentra-

tion fluctuating within narrow limits, or isohydria; and volume constancy of body fluids, or isovolaemia.

The core of my present lecture will be the processes regulating osmosis; among others, for the reason thatKORÁNYI [11] was the first to direct attention to the variability in osmotic concentration of the urine secreted by the intact kidney. He established that in response to a water load the kidney of the "hydrated" organism excretes a large quantity of dilute urine, with readings down to 1.001 for specific gravity and —0.10° C for freezing point, and that after fluid deprivation there is reduced urine flow of high concentration, with specific gravity rising to 1.030 and freezing point to —2.2° C. SÁNDOR KORÁNYI was the first also to observe that the diseased kidney's ability to concentrate is within an inadequate range (hyposthenuria), and that in the terminal stage the kidney can only secrete urine isosmotic with blood, having a specific gravity around 1.010 and a freezing point near —0.58° C (asthenuria).

The role of the kidney in maintaining isosmosis may be summed up as follows. In a day approximately 180 l of fluid isosmotic with plasma is filtered, from which about one litre is excreted as urine of an osmotic concentration adapted to the needs of the organism. In the tubules the large quantity of ultrafiltrate is then transformed into hyposmotic or hyperosmotic urine.

The capacity of the tubules to reabsorb water can be measured from the amount of the filtrate and of the urine actually passed, $C_F = V + T_{H_2O}$, where C_F denotes glomerular filtration rate, V the urine volume per minute, and T_{H_2O} the quantity of water reabsorbed. Under physiological conditions, about 99 per cent of the filtered water load is reabsorbed. In dehydration this percentage may rise to 99.9, and after a water load sink to 80 to 85 per cent. In the organism loaded with hyperosmotic anelectrolyte or salt solutions (osmotic diuresis) the water excreted may amount to 50 or 60 per cent of the filtrate.

Sodium and the anions bound to it are known to give the bulk of the osmotic concentration of the body fluids. Accordingly, hyperosmotic and hyposmotic urine formation depends essentially on the ratio between reabsorbed sodium and water. If sodium and water were reabsorbed throughout the length of the tubule at the ratio of the plasma concentrations, the excreted urine would be largely isosmotic with plasma. The quantitative relationship between filtered, reabsorbed, and excreted sodium can be expressed numerically, $C_F P_{Na} = V U_{Na} + T_{Na}$ where the left side denotes the filtered, and the right the excreted and reabsorbed quantities of sodium.

Sodium and water reabsorption are within wide limits independent of each other. With the same intake of salt, urinary sodium excretion may be the same in the hydrated organism, passing large volumes of dilute urine, and in the dehydrated one, where small volumes of concentrated urine are discharged.

Processes taking place in the proximal tubule. (Cf. nephron diagram; Fig. 1.) First WALKER et al. (1920—1921) and more recently WIRZ [25, 26] have succeeded in puncturing the renal tubule. The results they obtained in cold-blooded animals (frog, Necturus) and in mammals

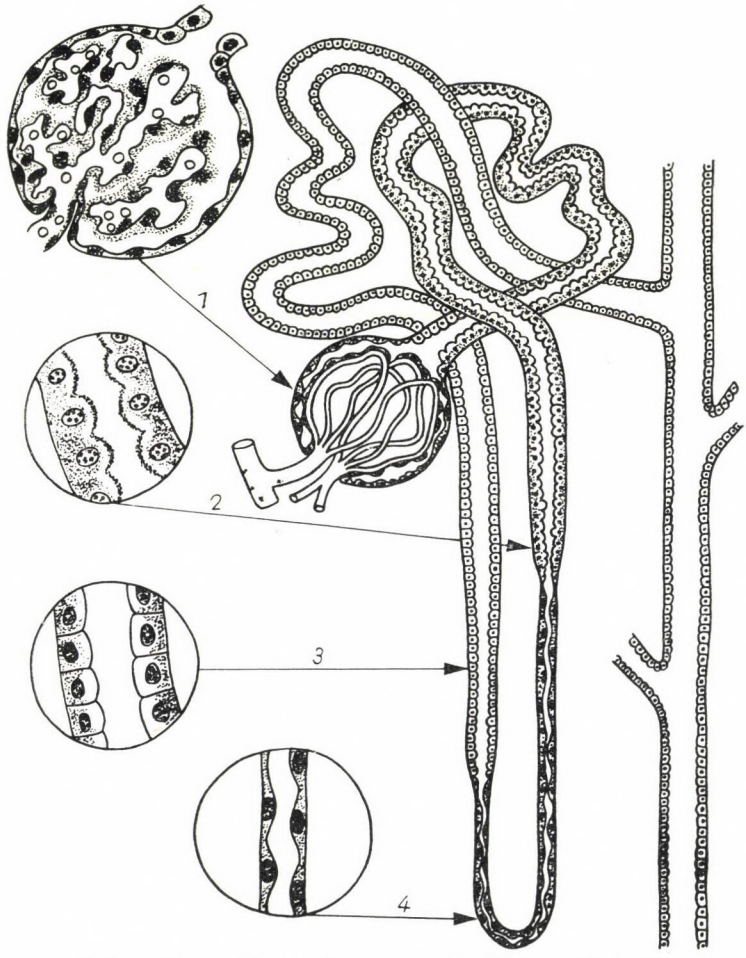


Fig. 1. Structure of the nephron. (SMITH, lectures on the Kidney, Univ. Extension Division, Univ. of Kansas 1943. Fig. 1, P. 28)

(guinea pig, rat, opossum, golden hamster) were as follows. (i) Proximal tubular fluid and plasma agree in sodium and osmotic concentration; (ii) glucose concentration is the lower the deeper the tubular loop lies from which the fluid to be analyzed has been removed; (iii) creatinine concentration, and in animals treated with phlorhizin also glucose concentration, rise in proportion to the depth of the tubular section from which the fluid has been

taken. (Phlorhizin inhibits tubular reabsorption of glucose.) The creatinine and (after phlorhizin) the glucose concentration rise to about five times their original value in fluid from the terminal end of the proximal tubule. I would emphasize that these data refer to hydrated and dehydrated animals alike (Figs 2 and 3).

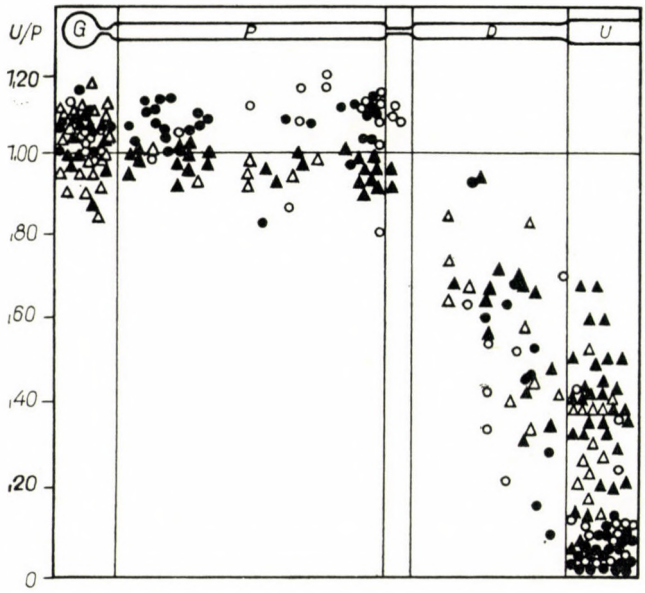


Fig. 2. Chloride (●: Necturus; ○: frog) and molar (▲: Necturus; △: frog) concentrations of different fluids obtained by tubular puncture. (WALKER, HUDSON, FINDLEY, RICHARDS: Amer. J. Physiol. **118,** 121, 1937.)

A reasonable interpretation of these results seems to be the following. Creatinine, and in the phlorhizin-treated animal glucose, are not reabsorbed. The fact that in the tubular fluid their concentrations increase fivefold without any change in osmotic concentration, is explained on the ground that about four fifths of the filtered amount of sodium and water are reabsorbed in the proximal tubule. The tubular fluid cannot remain isosmotic with plasma unless the ratio between reabsorbed sodium and water is identical with that of the plasma concentration.

Experiments carried out by WESSON and ANSLOW [22] in osmotic diuresis suggest the assumption that 80 to 85 per cent of the filtrated load of sodium is reabsorbed in the proximal tubule by active transport, and passively followed by a similar proportion of the filtered water, in accordance with its osmotic gradient. (The proximal phase of sodium reabsorption is denoted T^{P}_{Na} and that

of water $T^{P}_{H_2O}$.) On this assumption 15 to 20 per cent of the filtered amount of sodium and water reach the junction of the proximal tubule with Henle's loop.

By way of a fictitious numerical example, assuming 100 units of each sodium and water to undergo filtration, 80 units of each will be reabsorbed in the proximal tubule and 20 units pass into Henle's loop.

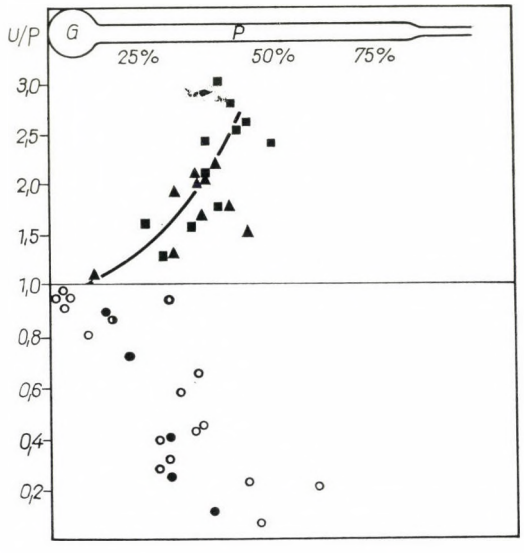


Fig. 3. Creatinine (▲: rat) and glucose concentrations in normal animals (○: guinea pig, ●: rat; ◑: opossum) and phlorhizin-treated rats (■). (WALKER, BOTT, OLIVER, MACDOWELL Amer. J. Physiol. **134,** 580, 1941, slightly modified.)

Processes in Henle's loop, the distal tubule, and the collecting tubule. In the foregoing it has been emphasized that proximal reabsorption is identical in hydrated and dehydrated animals, *i.e.* in those secreting a great volume of dilute, and a small volume of concentrated, urine. This means that the dilute as well as the concentrated urine is developed in the distal tubule.

The introduction of the concept free water clearance has greatly facilitated the quantitative evaluation of dilution and concentration [14, 23]. Knowing the osmotic concentrations of urine and plasma and the urine flow, osmotic clearance can be calculated from the formula $C_{osm} = U_{osm}\ V/P_{osm}$. By free water clearance is meant the mathematical difference between urine flow and osmotic clearance, $C_{H_2O} = V - C_{osm}$. If osmotic concentration of urine and plasma are identical, $C_{H_2O} = 0$. If the former is higher or lower than the latter, the C_{H_2O} value is a negative or positive number, respectively.

Accordingly, dilute urine means positive, and concentrated urine negative, free water clearance.

The kidney's ability to dilute urine. In principle, there are two possibilities for the dilution of fluid in the distal tubule, viz. water secretion and reabsorption of solutes. There is no reason to postulate water secretion, but distal sodium reabsorption, denoted T^{d}_{Na}, is an established phenomenon. The fluid obtained by tubular puncture from a hydrated animal, that is from one excreting dilute urine, will be of a concentration the lower the nearer the punctured tubular section lies to the terminal end of the tubular system, *i.e.* to the pelvis. The conclusion seems to be permissible that whereas there is sodium reabsorption, no water reabsorption follows it.

Continuing our fictitious example, in the hydrated animal, of the 20 units of each sodium and water that have passed into the distal tubule, 18 units are reabsorbed, leaving 2 units of sodium and 20 units of water to be excreted. Accordingly, of the 20 units of water none would come to be reabsorbed in the distal tubule.

It is an intriguing question in biology why in the distal tubule water fails to be reabsorbed after sodium, seeing that its concentration gradient permits reabsorption. Increased water diuresis is known to result from the absence of antidiuretic hormone (ADH) secretion; moreover, after a water load even the circulating ADH is destroyed [18]. Apparently, in the absence of ADH the distal tubule is impermeable to water, and this may furnish the answer to the question posed.

Numerous earlier experimental results appear to support this assumption. JANCSÓ [9] reported that in the presence of ADH preformed channels became visible in distal tubular cells of the frog, which were capable of taking up different substances. KOEFOED—JOHNSON and USSING [10] found that ADH considerably accelerated the migration of water through the frog's skin, corresponding to the concentration gradient. According to GINEZINSKY et al. [5, 6], ADH significantly increases hyaluronidase activity in the kidney and thereby facilitates water reabsorption.

ADH administered at the height of water diuresis, or stimulation of the organism to produce endogenous ADH, for example by an intracarotic injection of physiological saline, is promptly followed by a decrease in urine flow and an increase in urine concentration. Our explanation for this is that ADH restores the water permeability of the distal tubular cells, and so enables the water to follow the reabsorbed sodium in the direction of its osmotic gradient.

In further continuation of our fictitious example, eighteen units of sodium have been reabsorbed in the distal tubule, independently of ADH. In the presence of the hormone, this is followed by reabsorption of 18 water units, *i.e.* two units of each sodium and water are excreted, constituting isosmotic urine.

This latter phase of water reabsorption which depends on the presence of ADH in blood, is called facultative water reabsorption ($T^{d}_{H_2O}$). It may be

stated that after a water load free water clearance will have a positive value and that ADH will bring down that value to around zero.

The kidney's ability to concentrate urine. It has been found empirically that water deprivation results in the excretion of a small amount of markedly hyperosmotic urine. The maximal value of U_{osm}/P_{osm} is also termed the osmotic ceiling. In value, it changes from species to species. In man it may be fourfold, but in the kangaroo rat living in the desert, twentyfold. Having established that the fluid reaching the terminal end of the proximal tubule is isosmotic with plasma, it seems that for maximal concentration to occur water must be reabsorbed somewhere in the more distal parts of the tubule in the direction opposite to its gradient.

The quantitative relations of the concentration process can be approximated by producing osmotic diuresis in an organism (human or animal) under dehydration, by infusing intravenously a copious amount of hyperosmotic anelectrolyte solution. It will be found that this markedly increases the volume of urine excreted and somewhat decreases its osmotic concentration. At the height of osmotic diuresis a large amount of urine is excreted of a concentration slightly higher than that of plasma. It has been established that in man the maximal negative free water clearance rate is 5 to 6 ml/min [12].

Not wishing to go into the details of the mechanism of osmotic diuresis, let us again take up our numerical example. In osmotic diuresis, owing to the osmotic agent, instead of 80 only 60 of the 100 units of each the filtered load of sodium and water are reabsorbed proximally, leaving 40 units to pass into the distal tubule. The latter is still unable to reabsorb more than 18 units of sodium, and since in osmotic diuresis there is ADH activity, the reabsorption of the 18 units of sodium is followed by that of 18 units of water conforming to its gradient. Thus 22 units are left of sodium and as many of water. There is good agreement between the experimental findings and the supposition that by some mechanism an additional 4 units of water are reabsorbed in the second part of the distal tubule, mainly the collecting tubule. This leaves 22 units of sodium and 18 units of water, *i.e.* a large volume of slightly hyperosmotic urine, to be excreted [14].

On the foregoing evidence two factors determine the kidney's concentrating capacity, *viz.* the osmotic ceiling, which in man is about 4, and the negative free water clearance with a maximum value around 5 ml/min in humans. The osmotic ceiling indicates only the rate at which the patient is capable of secreting urine; the negative free water clearance throws light on the quantitative aspects of the concentrating capacity.

For a better understanding of the situation in dehydration, we would refer for the last time to our numerical example. Of the 20 units of sodium reaching the distal tubule, 18 are reabsorbed and 2 excreted. As there is ample ADH secretion, sodium reabsorption is followed by the reabsorption of 18 units of water. Were it not for the osmotic ceiling the collecting tubule would be capable, in principle, of reabsorbing 4 ml of water; but actually only 1.5 units of water are reabsorbed and 2 units of sodium are excreted with 0.5 ml of water. This means urine is excreted in small volumes and is markedly hyperosmotic.

Most authors incline to the view that concentration is independent of ADH secretion, ADH making it possible for distal sodium reabsorption to be followed by the water in conformity with its gradient. The water reabsorption

occurring in the collecting tubules, and in the last analysis against the gradient, appears to be independent of ADH secretion; it is denoted $T^{c}_{H_2O}$, in distinction from $T^{d}_{H_2O}$ [4].

The mechanism of concentration. In the foregoing the quantitative aspects of dilution and concentration have been outlined. It remains to decide the

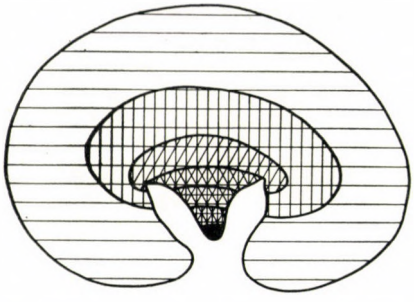


Fig. 4. Scheme illustrating kidney layers of identical osmotic concentration. Osmotic concentration increases from cortex towards papilla. (WIRZ, HARGITAY, KUHN, Helv. physiol. Acta **9**, 196, 1951.)

mechanism responsible for water migration against its concentration gradient during the concentrating process.

In this connection there are the following facts to guide us.

1. Only species with loops of Henle in their kidney (mammals, birds) are capable of secreting urine of higher osmolarity than the plasma concentration. The greater the length of Henle's loop the greater the ability to concentrate.

2. Fluid obtained by puncturing the first part of the distal tubule is hyposmotic also in the concentrating kidney (WIRZ; 27). Consequently, the isosmotic fluid that reaches the loop of Henle is diluted there, and in the second part of the distal tubule again undergoes concentration.

3. By direct measurements, the osmotic concentration of tubular fluid present in kidney slices was found to increase in proportion to the depth of the layer from which the slice had been removed. Obviously, fluid present in the bend of Henle's loop (GOTTSCHALK and MYLLE; 7) is as hyperosmotic as fluid obtained from equally deep-lying collecting tubules (WIRZ; 26). Not only tubular urine, but also blood obtained from the golden hamster by puncturing the medullary tissues and vasa recta, is of the same hyperosmotic character as the tubular fluid derived from the same layer. It would appear that in the concentrating kidney the layers of increasingly growing osmolarity follow one another in onion-structure fashion. Subcortical tissue is isosmotic with plasma; as the layers approach the renal papilla so increases their osmotic

concentration, until that of the innermost layers comes to agree in osmolarity with the concentrated urine excreted (Figs 4, 5, 6).

An explanation consistent with the facts set out above suggests itself in the assumption that sodium is reabsorbed throughout the distal parts of the tubule, including the loop of Henle, and is followed by water in conformity with its gradient. Another assumption, namely that the epithelium lining the ascending leg of Henle's loop is impermeable to water even in the presence of

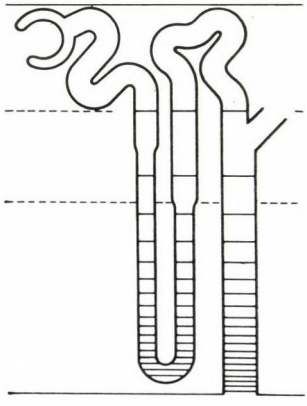


Fig. 5. Changes in osmotic concentration in Henle's loop and the collecting tubule of a nephron. Closer transverse lines indicate higher osmotic concentration. (WIRZ, HARGITAY, KUHN: Helv. physiol. Acta **9**, 196, 1951.)

ADH, might supply the explanation for the remarkable phenomenon that in the cortical distal tubules the urine is hyposmotic even in the concentrating kidney.

The only remaining question is that of the mechanism by which the renal medulla is rendered hyperosmotic in relation to plasma. The countercurrent theory ("Gegenstromprinzip") advanced by WIRZ [25, 26, 27] provides the explanation. It is common knowledge that in tubes turning back in a hairpin bend, hydrostatic pressure may produce a difference in concentration as water passes from the descending into the ascending and sodium from the ascending into the descending limb [8, 28]. Accordingly, the fluid becomes increasingly concentrated in places near the hairpin bend. This principle of countercurrent is widely applied in technology, and also encountered in biological systems, as for instance in the blood supply of the legs of birds trampling ice. In the structure of the kidney, the countercurrent system is given both in Henle's loop and the vasa recta.

According to the conception of WIRZ, concentration may therefore explained as follows. Isosmotic fluid finds its way into the descending limb of Henle's loop. The countercurrent principle comes into play; the fluid is con-

centrated, and the sodium (with its concentration increased in the tubular fluid) diffuses out and becomes evenly distributed over the interstitial space in the medulla, rendering the whole space hyperosmotic. Sodium reabsorption continues in the ascending limb of the loop, but there it is not followed by water, with the result that the interstitial space becomes further concentrated and the tubular fluid undergoes dilution. In the collecting tubules the fluid

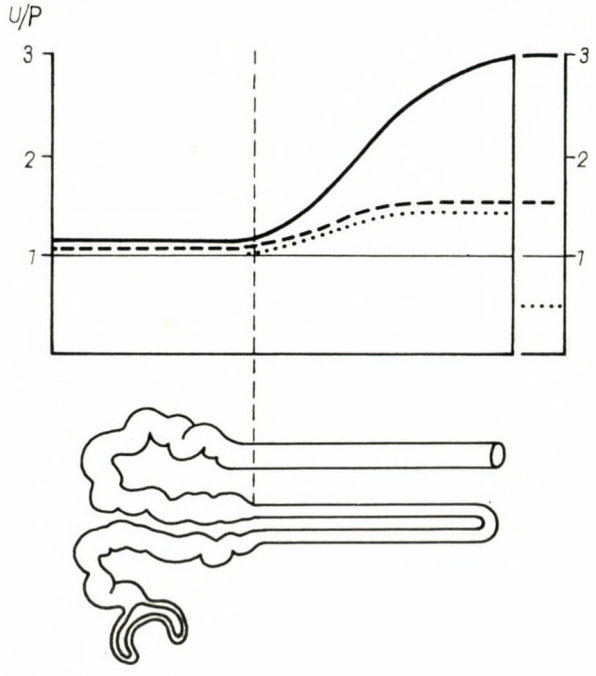


Fig. 6. Changes in the osmotic pressure in kidney slices: from thirsting animals (————); from animals with osmotic diuresis (— — — —); with water diuresis (. . . . .). On the ordinate: U_{osm}/P_{osm}; on the abscissa from left to right: distance from the renal surface. Column on the right indicates urine concentration. (Ullrich, Jarausch: Pflügers Arch. ges. Physiol. **267**, 491, 1958.)

is hyposmotic in relation to the interstitial space wherefore water migrates from them into that space, this time in the direction of its concentration gradient.

In the second part of the present report I have dealt with the processes of dilution and concentration, for two reasons. On the one hand I wished to show what achievements the genius of SÁNDOR KORÁNYI, and the technical improvements since his days, have produced; on the other hand I wished to underline the long-recognized paramount importance of impaired dilution-concentration capacity as a symptom of the highest prognostic value in renal functional disturbance.

REFERENCES

1. BÁLINT, P.: Aktuelle Probleme der Nierenphysiologie. Volk u. Gesundheit, Berlin 1961.
2. BÁLINT, P.: A veseműködés vizsgálata. (Klinikai laboratóriumi diagnosztika. Ed. Bálint, P.) 3rd ed. Medicina, Budapest 1962.
3. BÁLINT, P.: Über die Ermittlung der Nierendurchblutung (Kongreßbericht der Ungarischen Gesellschaft für innere Medizin 1961) Akadémiai Kiadó, Budapest 1962.
4. DE WARDENER, H. E., DEL GRECO, F.: Clin. Sci. **14,** 715 (1955).
5. GINEZINSKY, A. G., IVANOVA, L. N.: Isw. AN. SSSR **119,** 1043 (1958).
6. GINEZINSKY, A. G., SAKS, M. G., TITOWA, L. K.: Isw. AN. SSSR **120,** 216 (1958).
7. GOTTSCHALK, C. W., MYLLE, M.: Amer. J. Physiol. **196,** 927 (1959).
8. HARGITAY, B., KUHN, W.: Z. Elektrochem. **55,** 539 (1951).
9. JANCSÓ, N.: Speicherung, Stoffanreicherung im Retikuloendothel und in der Niere. Akademischer Verlag, Budapest 1955.
10. KOEFOED-JOHNSON, V., USSING, H. H.: Acta physiol. scand. **28,** 60 (1953).
11. KORÁNYI, S.: A vesebajok funkcionális pathológiája és therápiája. Magyar Orvosi Könyvkiadó Társulat, Budapest 1930.
12. RAPOPORT, S., BRODSKY, W. A., WEST, C. D., MACKLER, B.: Amer. J. Physiol. **156,** 433 (1949).
13. SMITH, H. W.: The kidney. Structure and Function in Health and Disease. Oxford Univ. Press, New York 1951.
14. SMITH, H. W.: Fed. Proc. **11,** 701 (1952).
15. SMITH, H. W.: Principles of Renal Physiology. Oxford Univ. Press, New York 1956.
16. ULLRICH, K. J.: Pflügers Arch. ges. Physiol. **266,** 55 (1957).
17. ULLRICH, K. J.: Pflügers Arch. ges. Physiol. **267,** 207 (1958).
18. VERNEY, E. B.: Lancet **2,** 1237 and 1295 (1957).
19. WALKER, A. M., BETT, P. A., OLIVER, J., MACDOWELL, M. C.: Amer. J. Physiol. **134,** 580 (1941).
20. WALKER, A. M., HUDSON, C. L., FINDLEY, T., RICHARDS, A. N.: Amer. J. Physiol. **118,** 121 (1937).
21. WALKER, A. M., OLIVER, J.: Amer. J. Physiol. **134,** 562 (1941).
22. WESSON, L. G., ANSLOW, P. W.: Amer. J. Physiol. **153,** 465 (1948).
23. WESSON, L. G., ANSLOW, P. W.: Amer. J. Physiol. **170,** 255 (1952).
24. WESSON, L. G., ANSLOW, P. W., SMITH, H. W.: Bull. N. Y. Acad. Med. **24,** 586 (1948).
25. WIRZ, H.: Heutige Ansichten der Nierenphysiologie, in: Pathologische Physiologie und Klinik der Nierensekretion, hgb. J. FREY, Part 1., Springer, Berlin—Göttingen—Heidelberg 1955.
26. WIRZ, H.: Helv. physiol. Acta **14,** 353 (1956).
27. WIRZ, H.: The Location of Antidiuretic Action in the Mammalian Kidney. In: The Neurohypophysis, H. HELLER, ed., Butterworth, London 1957, P. 157.
28. WIRZ, H., HARGITAY, B., KUHN, W.: Helv. physiol. Acta **9,** 196 (1951).

Prof. Dr. Péter BÁLINT, Budapest VIII. Puskin u. 9., Hungary

MODERN TESTS OF RENAL FUNCTION

By

A. Babics

DEPARTMENT OF UROLOGY (DIRECTOR: PROF. A. BABICS),
UNIVERSITY MEDICAL SCHOOL, BUDAPEST

Every medical testing method and procedure depends for its value on the extent to which it is capable of aiding diagnosis, the basis of all health restoration, or to which it is conducive, to basic research underlying applied medicine, provided, of course, it does in no way impair the patient's condition. This proviso is not out of place here inasmuch as there is no other organ in the human body which for testing purposes would be accessible from as many sides as is the kidney. Accordingly, the number of methods for establishing the condition and functional capacity of the kidneys at a given moment, is really vast. Some of the methods recorded in the literature have been abandoned, either because they proved technically difficult and unreliable even within wide limits, or because they involved hazards such as too great a strain, some associated disease, and perhaps loss of life; these hazards compare unfavourably with whatever diagnostic advantages such methods may have to offer.

The very number of the tests devised for renal function is a warning that none of them can be perfect. Each yields only information on one or some individual functional aspect, or on a single link in the chain of morphologic transformations occurring in the urine-conveying system at work. And even such information varies in accuracy, and therefore in value, depending on the visible contours' being dim or distinct.

Until quite recently it has been thought that the clearance tests would prove adequate and dependable for judging momentary, and predicting future, renal function. However, the reliability of these tests has come to hinge unconditionally on stable conditions of the organism and its environment for some time during testing, a condition not at all easy to fulfil. Another point is that in evaluating clearance tests our present knowledge no longer allows restricting our examinations to the kidney parenchyma, but makes it imperative to investigate the functional state of the collecting and excreting systems organically integrated with, and influencing the general and all the particular, functions.

So much to show that no matter how reliable some tests may be, each in itself can furnish information on but a small section of the whole range of

intricate renal function. Obviously, if a picture accurate in more than just one or a few respects is to be obtained, morphological, roentgenological isotopic, and other current and simple methods and procedures — unfortunately not always appraised with sufficiently discerning criticism — must be employed in addition to clearance tests. Naturally, every one of these tests, even though they be approved tests carried out in full knowledge of the situation and on the right considerations, will only represent a single effort in the complex endeavour of getting at the actual functional conditions or of diagnosing possible functional derangement. One of the most creditable achievements of the physician is the accurate construction of a coherent picture from the results produced by all the performed tests.

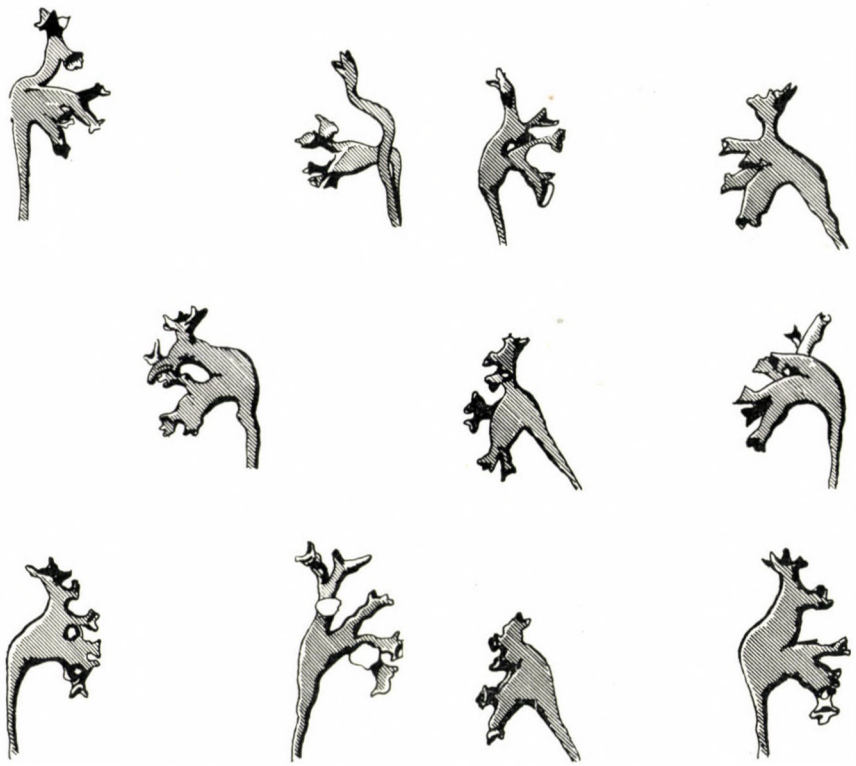
Needless to say, no exact picture of the renal state and function of a patient can even be approximated unless a whole series of tests, carefully planned on the basis of the patient's complaints and the result of the urine analysis, is systematically carried out, without any of them impairing his given condition of health.

I am afraid I would be wasting your time if I went into details about the orthodox urine examinations and water-load tests which, whether performed on a single occasion or carried out repeatedly for comparative purposes, are under certain circumstances undoubtedly of value and significance. I feel certain you are more interested in an informative account of methods to which, though currently used, there still attach problems of technique and evaluation that merit discussion.

One such method is chromocystoscopy. Though time-honoured and widely applied, when examined with the resources of a large experience, the procedure is not quite as superior as it is generally thought to be. Today it is performed not only by urologists, but in emergencies also by gynaecologists, surgeons, and physicians, because it is seemingly simple to carry out and suggests safe evaluation. All that is required for its performance is a good cystoscope, the right kind of indigo carmine, and some experience in visual control. Evaluation is based on long-established rules. The time is measured in which the dye begins to show itself in the urine, and the force of the jet and the colour intensity of the urine ejected, are determined. Failure of the blue dye to appear in the urine in four to five minutes from one or both of the ureters is interpreted as an indication of the functional impairment of one or both kidneys; a pale-blue colour of the dye is taken to point to tubular dysfunction, and so forth.

Since it affords the possibility of a simultaneous estimation of the functional state of the two kidneys, chromocystoscopy is capable of supplying quick information which is often urgently needed in impending abdominal surgery, and so in certain circumstances it may be invested with vital significance. Nevertheless I feel I should call attention to some reflections of mine concerned with the assessment of the value of this test of renal function.

Times with a stop-watch, the indigo carmine will be found not to appear through the two ureteral orifices at equal intervals, with equal jet force and grossly equal colour intensity, unless the parenchyma of both kidneys is uniformly intact, the capacity of the pelves is the same, and their transition to



Figs 1 and *2*. Differing intact pelves (original drawing)

the ureters is fairly regular; a further condition is that both renal pelves alike lie either inside or outside the renal sinus.

Always distinguishable from each other in their finer structural details, no man's kidneys fulfil all these conditions. Therefore, I suggest, no major significance should be attributed to slight differences (one-two minutes) in the time of the dye's appearance at the two ureteral orifices. Another point on which it is profitable to meditate is that not infrequently dye excretion satisfactory in every respect can be observed in patients with a localized tuberculous renal cavity, an isolated tumour, a circumscribed renal abscess controlled with antibiotics, and a moderate enlargement of the renal pelvis. With these and similar points in mind one cannot but admit that this wide-spread method,

though frequently considered of decisive importance, possesses only orientative value.

In one respect the indigo carmine tests does furnish dependable information. It is capable of showing whether in the presence of an intact mucosa of the bladder one of the kidneys is or is not occluded. But even here stress must be laid on the unimpaired condition of the bladder for if it happens to be highly irritable, ulcerated, inflamed, or of reduced capacity, the dye will be late in appearing or will not show itself at all during the time indispensable for cytoscopic observation. It will, however, at once appear as soon as cytoscopy is discontinued and the bladder allowed to empty unprompted; the same is usually seen in patients with a tuberculous bladder and if one kidney was intact.

The use of phenolsulphonephthalein is gradually going out of use. The benefits of this test are more than offset by the fact that even moderately impaired liver function invalidates the information it supplies of the kidney. In circulatory disturbances of cardiac origin it likewise yields a renal picture difficult to estimate with confidence.

Widely used and lending itself readily to estimation from many angles is *urography*, a procedure which can be recorded by cineroentgenography today. This method, known for 30 years, is achieved, in essence, by the slow intravenous administration of a substance containing iodine at high concentration which is then selectively secreted by the kidneys. The X-rays show the contrast material to fill the renal cavities, appear in the ureter, then in the bladder. In severe functional disorders the secretion of the contrast medium is retarded and protracted, or altogether indiscernible. This means that intravenous urography imparts more information concerning the functional state of the kidneys than any other type of renal testing. In addition, it informs about the configuration of the renal cavities, the position and shape of the pelvis, the functional condition of the ureter, and, depending on the situation, even about bladder capacity.

Just because intravenous urography offers so many sides of approach to renal problems, interpretation of the information it supplies requires a vast experience. Were it not that 16 different types of renal pelvis and calyces are classified, and that within each of these each individual system differs from the other in configuration, even though in but minor features, every doctor could use this procedure with confidence and success. As things are, even with a great experience it is sometimes difficult to decide whether or not an apparently irregular system is pathologic. Abnormal dilatation, deficient filling, the presence of calculi, are perceptible to everybody, but to distinguish a rugged calix from the sum of X-ray shadows cast, is always an intricate task.

Owing to the pharmaceutical industry's untiring efforts to supply us with ever better types of contrast material we cannot help working with many different types of differing concentration, but we must always bear in mind

that the type of medium used is not without influence on our careful evaluation of the functional state of the kidney tested. A 50 per cent iodine concentration is commonly regarded as the ideal. These substances are known to be secreted primarily by the tubules except if their plasma concentration is very high when they may find their way into the renal cavities by glomerular filtration. This knowledge is a warning that intravenous urography must not be made

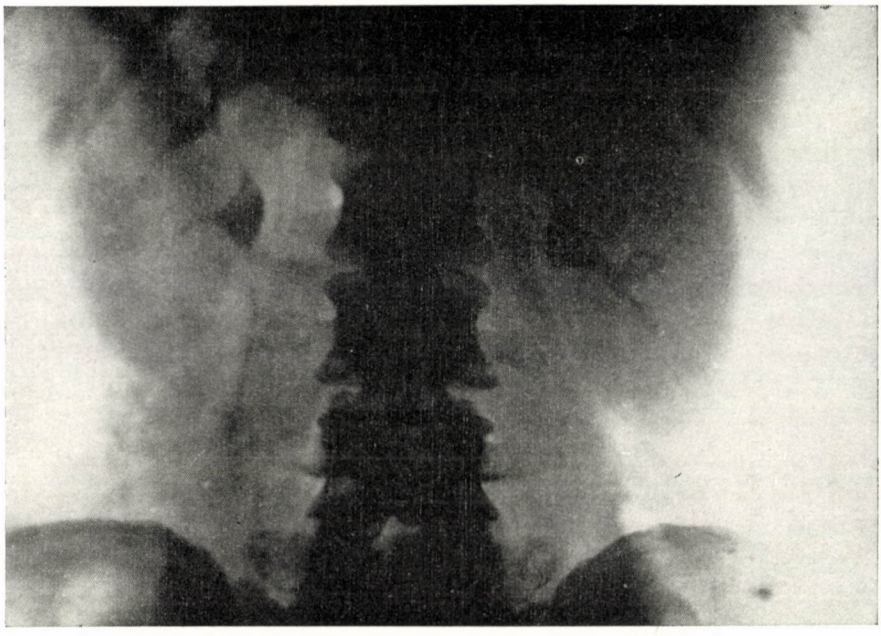


Fig. 3. Selective urography. Right side differs from the left

the foundation on which to build unreservedly all our considerations concerning renal function; the large statistical compilations show that in 20 to 25 per cent of the cases the information obtained is not wholly reliable.

To cite some examples, patients with hypertension and bilaterally impaired renal function may yield apparently normal urograms; moreover, the urogram may be unobjectionable when functional impairment is not of the same degree on both sides. Also, the contrast material may give a distinct shadow when in a solitary kidney there is failing function and definitely impaired ability to concentrate due to the presence of a calculus on the pyeloureteral junction which hardly gives a shadow and, being not yet wedged in tightly, is not causing complete occlusion.

On the whole it seems safe to state that intravenous urography is a well tolerated and practicable test, superior to most methods, provided its technique

is well mastered and the urologist's experience is sufficiently extensive to eliminate the sources of error.

Of course, with renal function unimpaired or a portion of the kidney capable of secreting it at a satisfactory rate, the contrast material fills the calyces and pelvis, the ureter, of the normal or abnormal configuration of which a series of X-rays will give reliable information. The serial pictures will of course all be different, because the conveying system while functioning undergoes constant changes in shape, position, tonicity, and dynamics.

During the three decades since its adoption as a test in humans, first proposed by the Hungarian urologist LICHTENBERG, intravenous urography has found wide recognition. Nevertheless, because of the unreliable results obtained in about a quarter of the cases and other obstacles in the way of its use (*e.g.* the patient's sensitivity to iodine), the test has not made other testing procedures dispensable.

With the group of indispensable methods must be classed the procedures which enable the separate collection and analysis of the urine of each kidney to be carried out simultaneously and under the same conditions, this being the only means for the reliable comparison of the urines from the two kidneys.

I have already mentioned that in a failing kidney the only fact registered by intravenous urography is the absence of secretion. However, though rarely, no secretion is noticeable although the kidneys are intact. These are the cases in which it is commonly assumed that the responsibility for the disappearance of the contrast medium injected into the circulation rests with the liver. The actual cause of this is unknown. The finding that there is no secretion on one side cannot in itself satisfy us. We must know the cause of its absence the failure, whether it is prolonged or permanent, and for therapeutical reasons we must be able to determine the site of the cause.

This is when tests involving the use of instruments, more precisely of the *ureteral catheter*, become unavoidable. It should be remembered that in accuracy these tests are in many cases superior to intravenous urography. The ureteral catheter enables us to obtain urine from either or both kidneys, it can be utilized for palpation, for estimating distance, and, if we are proficiently experienced, for determining the character of the palpable anomaly. Notwithstanding their remarkable diagnostic value, we are doing our best gradually to force these tests out of urological practice. We strongly recommend their abandonment. It is not the exacting and time-consuming technique that makes us prefer to these tests the costlier and often less satisfactory methods of intravenous urography, but the wish to avoid the hazard of injuries, particularly by hands of limited experience. We have in this connection the well-known types of prostatitis in mind, and the various injuries which we have shown to arise in the ureteral wall, and even the renal substance. Evidence has been produced that a few hours after ureteral catheterization reactive oedema forms

in the ureteral wall, and that even in the renal parenchyma with which it had no contact, pathological phenomena present themselves.

Taking all this into account, in certain conditions ureteral catheterization may yet be indispensable as the only diagnostic method which affords a possibility to compare the urines obtained from each kidney separately at one and

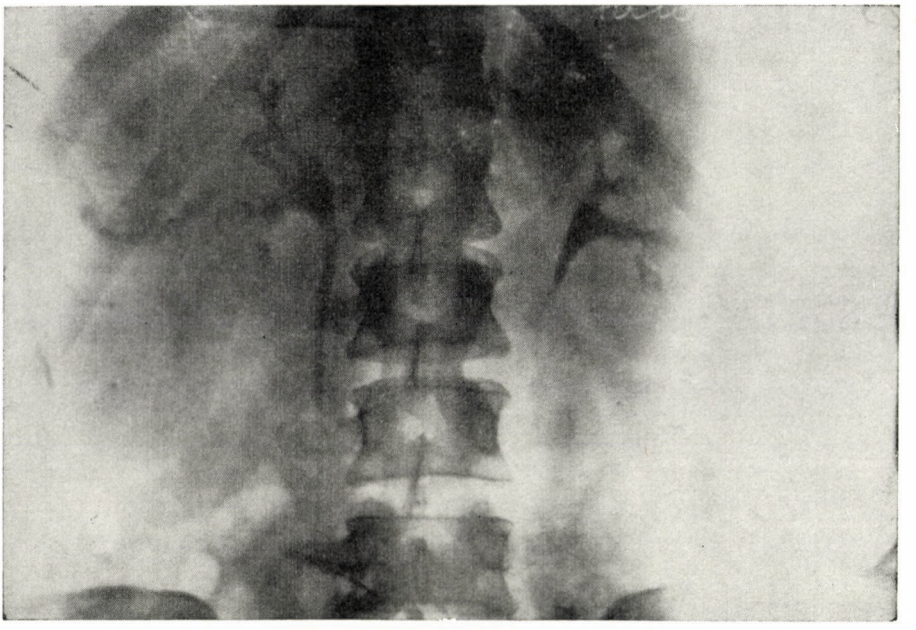


Fig. 4. Selective urography. Pelves differing from each other

the same time. In the hands of experts and an able laboratory staff it is an invaluable method yielding extremely comprehensive data. Being a time-consuming procedure, it has not become as wide-spread as SÁNDOR KORÁNYI had anticipated. In substance, the method enables the urines from the two kidneys, collected through ureteral catheters, to be examined for molecular concentration, indigo secretion, and the pathological elements they may contain (just think of how safe it is to reach the correct diagnosis in the presence of tubercle bacilli or leukocytes). In addition, wherever some suspicion arises during ureteral catheterization the method can be combined with *retrograde pyelography*. This is, for instance, the only means by which to obtain precise information of a prehydronephrotic state with failure of secretion of the contrast medium, and to detect the cause of extreme pelvic dilatation. I need not emphasize the value of such knowledge in the design and performance of corrective surgery.

Ureteral catheterization has now been utilized in this country for decades, and even our younger urologists have acquired the minute intricacies of its technique. They are often astonished at articles from abroad describing technical details in which they can see nothing new since they apply them daily. At the time I did not particularly stress the significance of these tests

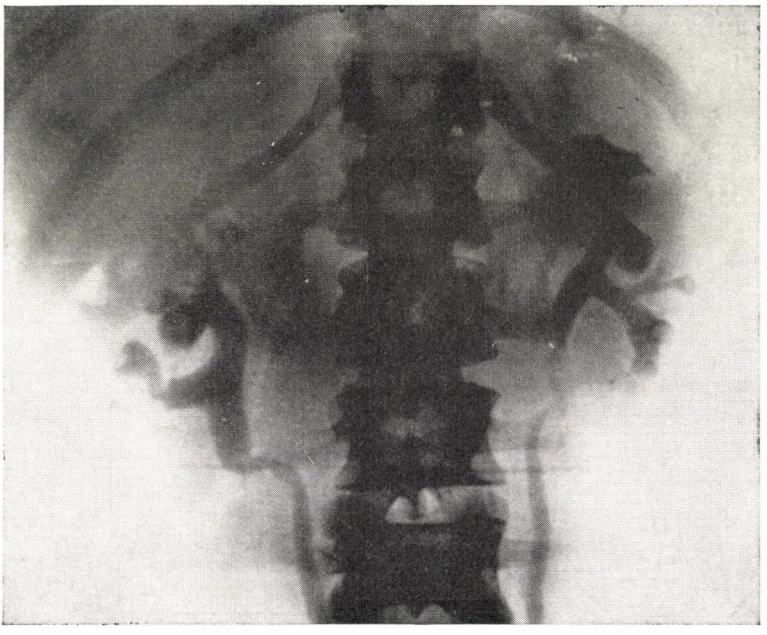


Fig. 5. Selective urography. Right kidney sunken but with intact pelvis

because of their being complicated and wanting in accuracy owing to the necessity practically to close with thick catheters the first 6 to 10 cm length of the lower part of the ureters.

I have already mentioned that the kidneys react with functional changes to stimuli that reach them from the ureters and are due to mechanical irritation of the mucosa or to the rise in intrarenal pressure which always follows interference with the ureter's own dynamism. I would now add that under normal conditions the pressure within the renal calyces and pelvis is very low, and immediately after voiding, near zero. A proof of the extreme sensitivity of the renal pelvis seems to come forth from the observations at our Department made by MERÉNYI and KOVÁCSI [2] which by now have found general acceptance. They have shown that the ureters and the pelves, respectively, respond to emotional stimuli with distinct rises in the curves produced by a self-

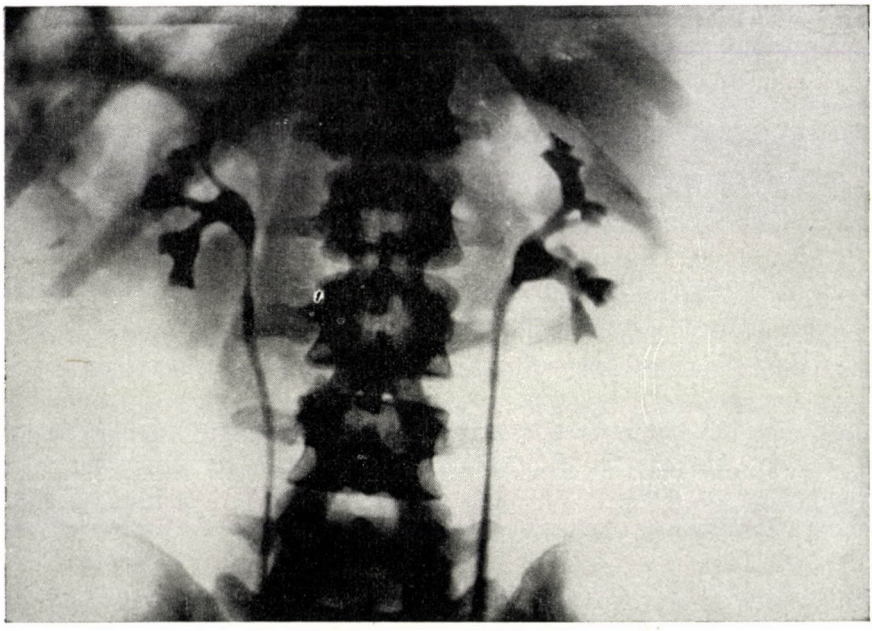


Fig. 6. Retrograde pyelography. Two sides intact but differing

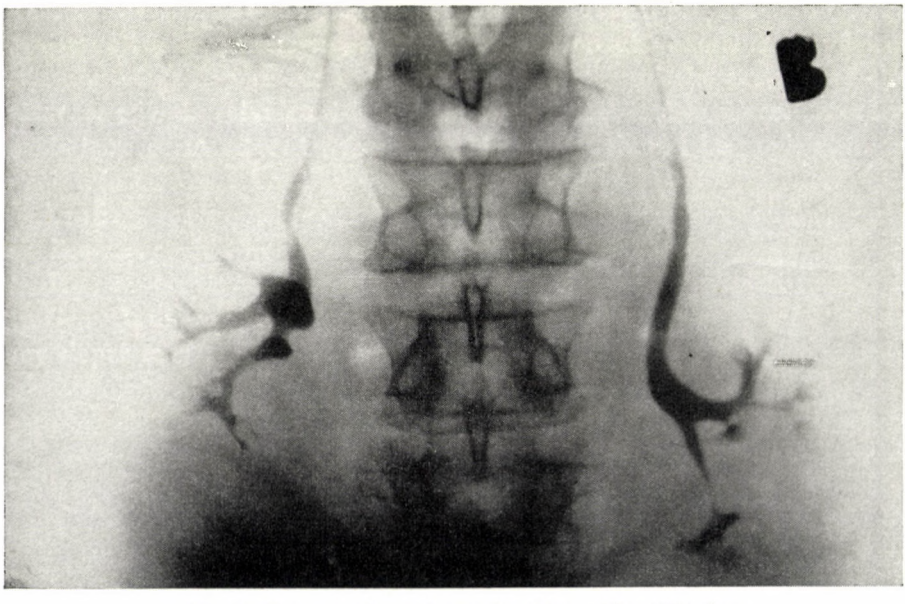


Fig. 7. Retrograde pyelography. Two sides differing

recording device; and that no response is gained from previously denervated ureters.

These observations have become the source of a novel method of examination which in certain cases is indispensable. The fate of the kidney being closely connected with ureteral function, an ureter which is, let us say, tuberculous, will sooner or later destroy the other whatever still intact kidney. In such cases it is obviously imperative to know the condition of the ureteral wall. The method is not easy to perform, yet it must be performed whenever information of the functional state of the musculature in the ureteral wall supplies the only basis on which to decide whether or not a kidney may be saved. Regrettably we have so far failed in bringing into general use the device designed for automatic recording of the curves. True, the test requires from two to three hours to carry out, skill must be acquired in handling the apparatus, and an aptitude for the evaluation of the data obtained; yet, no difficulty must be considered too much when a patient's only kidney, and that with a diseased ureter, is known to be at stake.

I have already pointed out the values of those modern tests which are combined with X-ray examinations. I feel I must once more urge the importance of a large experience in the evaluation of the data such tests supply. I propose to come back to this point later on in this paper. Here, I should like to mention the value of tomography in renal diagnostics. This, too, is a method wich requires the close co-operation of the urologist and the radiologist.

And now a few remarks on retrograde pyelography, particularly in relation to intravenous urography. Again I would emphasize the need for extraordinary caution in the use of this test. The method of tracing the outlines of the calyces and pelvis by means of a contrast material injected through a cannula introduced directly into the pelvis, is in most cases precarious and even risky. To find one's way into a hidden or small-sized pelvis is as difficult as it is easy to run the needle accidentally into some large blood vessel. Such an accident would in every case damage the kidney irrespectively of the nature of the contrast medium used. On the other hand, when the pelvis is known to be accurately dilated, or the hydronephrotic kidney is palpable, it will be relatively simple to make the needle reach the renal pelvis, inject the contrast material, and so obtain a dependable picture of the intrarenal conditions.

Knowledge of the shape of the kidneys is often of importance. In X-rays taken of slim individuals their outlines are mostly discernible. They will shown distinct shadow in the first two-three minutes after the intravenous injection of the contrast material, when this has not yet accumulated in the renal pelvis but fills the elements of the parenchyma. Pictures taken in this manner are termed *nephrograms*. Measures must be taken to ensure a systolic pressure of more than 70 mm Hg; no nephrogram is obtainable at blood pressures lower than that.

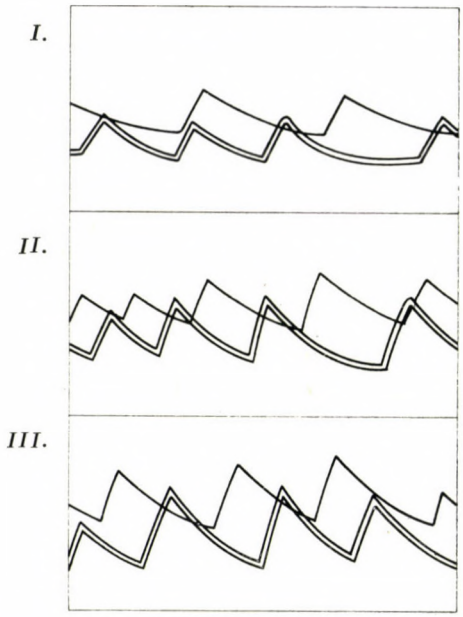


Fig. 8. Ureterograms. Right and left ureters I: normal; II: emotional stimulus; III: physical stimulus

Fig. 9. Combined perirenal insufflation and translumbar pyelography

Oxygen or air insufflated around it, will bring out the kidney's outlines unmistakably, particularly if the procedure is combined with nephrography at the right moment.

There are two ways of introducing air or, better, oxygen into the region around the kidney. One is *perirenal insufflation*, when 300 to 400 ml of the chosen gas are injected into the perirenal adipose tissue by means of a syringe. Performed carefully, this method will render the renal contours distinctly visible. The other way is *retroperitoneal insufflation* of air. This extends over a wider region and exposes wider relationships for clear evaluation. Its performance ist not without hazards wherefore certain precautionary measures must be strictly observed: an adequate amount of oxygen of the right pressure must be at hand, the pressure must be constant during insufflation, and the amount of oxygen introduced must be measured. The gas is blown in through a needle introduced under the coccy, and the position of the needle is controlled by rectal palpation. Oxygen is commonly insufflated at pressures between 120 and 250 mm Hg, depending on the patient's tolerance. Side effects — collapse, abdominal distension, discomfort — will be the less the slower the gas is introduced. The total of gas insufflated amounts to from 1800 to 2000 ml. The patient is then made to remain in a half-sitting posture for about one hour. The X-rays are taken 12 to 24 hours later. The method has the advantage that the needle being introduced in a poorly vascularized area remote from the kidneys, perirenal processes, *e.g.* perinephritis or perirenal abscesses, do not contraindicate its use. I have gone into details about this procedure because its use is spreading and so it seems timely to advocate strict observance of the precautions that safeguard us and the patient from untoward surprises.

Once I was called in to a case where the needle used for insufflation had passed through a hidden purulent atheroma in the coccygeal region. Two days later the patient was transferred to our department with sepsis accompanied by anuria. Obviously this useful method must not be used in the presence of perirectal inflammatory processes or abscesses.

We have been using both insufflation methods in many cases and on request have done them for other departments, without major complications; the worst was a passing inconvenience to the patient.

And now I should like to refer to *renal angiography*. This is a renal test which in the last decade has found ever wider acceptance, though I find the hazards inherent in it by far to exceed the value it yields.

Angiography is the X-ray representation of the renal vascular tree. It shows the renal artery, the branches into which it divides, the position and arrangement of the primary and secondary arteries in the renal substance, the thickness of the individual vessels, that is their pathologic dilatation and constriction, and in the case of an occlusion, the anomalous absence of arteries

in whole areas. It is from these observations that one has to conclude to the disease of the kidney.

Two techniques of renal angiography are current. In one the contrast material is injected directly into the abdominal aorta (Dos Santos). The other is an indirect method (Seldinger), in which the contrast medium is administered by way of an about 20 cm long polyvinyl catheter introduced through the femoral artery to reach the aorta. Given adequate X-ray equipment and competent examiners, the medium may be injected *via* the radial artery. Renal angiography is a test that has not been used in this department and I have a doubt if it will ever be used by us.

Why do I view renal arteriograms with such critical reservation?

Twenty years ago, together with Kádár from the Institute of Anatomy we studied in corrosion preparations the vessels of human kidneys removed at operation and of kidneys from experimental animals. In summarizing our findings I would first of all say that even intact kidneys differ from each other in their vascularization. Diseased kidneys naturally present differing pictures depending on the pathologic process. In renal tuberculosis some or all the vessels may be missing in the destroyed portion of the parenchyma. However, I am certain that we can just as reliably determine size and situation of a cavity without resorting to aortography. Or let us take prehydronephrosis. What benefit can be derived from making out that one or the other of the blood vessels pushed apart in the form of a spread fan traverses the ureter and is the cause of the condition? Still another example, how does the advantage to be gained from a representation of the pendulous vessels of a ptotic but readily palpable kidney, that would yield the typical X-ray picture, compare with such possible complications of angiography as, for instance, a collapse lasting for several hours?

In my opinion those are but rare instances in which the aim cannot be attained by other diagnostic means applied step by step, their failure forcing us to resort to angiography, so difficult to evaluate and often accompanied by hazards.

A method has recently been elaborated by Harris, Allen and Porch [1] to eliminate the hazards. The patient lies supine with the arms outstretched to form right angles to the trunk. Everything having been prepared to take X-rays at one-second intervals, a thick needle is inserted in each cubital vein, through which 5 mg of dehydrocholic acid, 1 ml of a 50 per cent methiodal sodium and 44 per cent saline solution is introduced to ascertain the circulation time and the degree of sensitivity to methiodal. Fifty ml of a 90 per cent methiodal sodium solution is then injected into both veins. The first X-ray is made two or three seconds before the ascertained circulation time, and is followed by 10 to 15 photographs taken one second apart.

Venography is another method difficult to evaluate; the more so as

the contrast medium introduced through the saphenous vein can only reach the renal vein if, at the given moment, the pressure in the inferior vena cava is on the rise. This can be achieved by the patient performing a *Valsalva* manoeuvre.

A more recent procedure is renal biopsy. It is a highly specialized but more rewarding technique than are most others. Biopsy has been used for a long

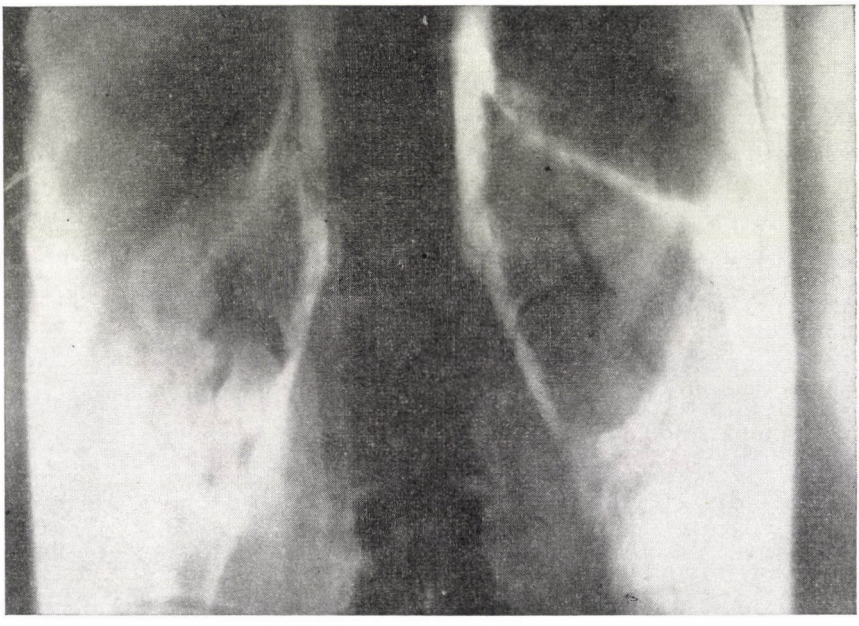


Fig. 10. Pneumoretroperitoneal examination

time in diagnosing diseases of the spleen and the liver, but in connection with the kidney was first studied in 1943. In the last ten years or so renal biopsy has gained gradual acceptance. In a few institutes it has been performed in numbers that permit statistical evaluation, showing its advantages over other methods in certain conditions. In Hungary, it has been studied especially in the 2nd Department of Medicine of the University Medical School in Debrecen.

Significant importance attaches to biopsy in institutes equipped with an artificial kidney, for there it affords a basis for prognosis, especially in intercapillary glomerulosclerosis and chronic glomerulonephritis.

Renal biopsy is performed by us with Silverman's needle. The first thing is to establish the exact position of the kidney in both the recumbent and the sitting position. Following local anaesthesia the needle is slowly inserted at the right height and at two fingers' breadth from the edge of the vertebrae. The experienced surgeon develops a feeling for the individual layers, and even

senses the needle's passage through the renal capsule. A haematoma, varying in size, is a possible complication. Yet, it is not for every doctor to handle a biopsy needle. In our department, during the last three years, about a hundred renal biopsies, including those done for other departments, have been performed, and all by the same experienced colleagues — still we had a case that ended fatally.

The latest renal test, developed about six years ago, is *radiorenography*. The first to describe isotopic nephrography was WINTER [3]. The essence of the method ist that a radioactive substance (^{131}I radiorenographin) is administered intravenously, and the amount collected by the kidney is estimated by a scintimeter placed above the organ. Under normal conditions, the instrument clearly distinguishes three separate phases. First, the increase in renal blood flow occuring four or five minutes after the injection (indicated by a steep rise of the curve); in another three to six minutes it measures the increase in tubular secretion (indicated by a less steep rise of the curve); in yet another six to eight minutes it registers a decreased activity due to the urine being transported.

Should there be a decreased blood flow, the initial rise will be less sharp. Is the tubular function impaired, a moderate and slow rise will be registered in the second phase, which is the most valuable from the diagnostic point of view. Where there is disturbed excretion, *e.g.*, congestion and dilatation of the renal pelvis, the curve will assume the shape of a horseshoe, if the parenchyma is damaged as well.

Accordingly, the diagnostic value of the method lies in the fact that it enables us to observe each of the three phases, and to compare the separate curves obtained simultaneously for each kidney.

We have now been urging the acceptance of the method for three years because, although it is not indispensable, the many benefits that can be claimed for it, manifestly favour its introduction. The advantages are: 1. the patient is given a single injection; 2. a separate picture is obtained of each of the two kidneys; 3. the amount of ^{131}I to be introduced is so small as to cause no side effects at all; 4. no preliminary preparation of the patient being needed, the method can be performed in outpatients; 5. the radiant energy is only 1 per cent of that required in intravenous pyelography, and its adverse effect is proportionately less; 6. evaluation of the results takes not more than one half hour.

Naturally, the method does not supersede all others, but it can well replace some of those involving the use of instruments. This is a great benefit, particularly with critically ill patients.

There are numerous procedures that we have not mentioned, but not because we think we can do without them. On the contrary, urine output and specific gravity measurements, tests of the kidney's ability to concentrate

urine, or to produce a dilute urine, and a number of other simple tests, are certainly indispensable. More than this, the simple and harmless tests should always come first, the more intricate and hazardous ones following only if and when necessity requires.

REFERENCES

1. Harris, A. O., Allen, J. H., Porch, Ph. P.: J. Urol. (Baltimore) **85**, 377 (1961).
2. Merényi, I., Kovácsi, L.: Acta med. Acad. Sci. hung. **3**, 233 (1952).
3. Winter, Ch. C.: J. Urol. (Baltimore) **83**, 313 (1960).

Prof. Dr. Antal Babics Budapest, VIII, Üllői út 78/b. Urológiai Klinika, Hungary.

TREATMENT OF NEPHRITIS, PYELONEPHRITIS AND NEPHROSIS

By

A. HÁMORI

SECOND DEPARTMENT OF MEDICINE, UNIVERSITY MEDICAL SCHOOL, PÉCS

Vast, practically boundless, is the literature I am to survey. My lecture cannot possibly be exhaustive. It must be limited to the therapeutic recommendations made on the basis of modern knowledge. Nor can it extend to technical details. Instead, I shall endeavour to sketch out the theoretical background, in the spirit of S. KORÁNYI.

Glomerular nephritis

The progress in the etiology and pathogenesis of glomerular nephritis, which has marked the last ten years, has had its effect on the treatment of the disease. A critical evaluation of the new therepeutic methods is a task of extraordinary difficulty as the data so far accumulated are insufficient for reliably evaluating the results. Nevertheless, it is possible, to formulate a programme of management.

The acute stage

Diet. To begin with, the latest drugs have outdated neither bed rest nor dietary measures. On the contrary, in the light of recent research rules of diet seem to be assuming a new significance. VOLHARD [119], during World War I, prescribed fasting and withholding all fluids, to avoid cerebral oedema which proved fatal in one out of every ten cases of acute nephritis. SARRE [98], even today, holds that the VOLHARD cure is no kidney cure. We are unable to share his view: the results call for an immunological explanation.

Glomerular nephritis is an expression of an antigen-antibody reaction. On the other hand, a correlation is known to exist between antibody formation and protein intake. Unequivocal evidence particularly shows that increased protein intake is conducive to antibody formation. FARR and SMADEL [25], and later DUTZ [22], demonstrated that a diet rich in protein aggravates the MASUGI type nephritis, which has an indisputable immunologic background. Starting from clinical experience made during the blockade of Leningrad, TSHERVJAKOVSKI and KOVALJOV [114] established that fasting is of beneficial effect in MASUGI nephritis. On these grounds, and in the hope of inhibiting thereby pathogenic antibody formation, the patients with acute nephritis

are kept at our Department on a fruit diet as long as they can tolerate it. Usually, they start revolting against it after eight days or so. They are then placed on a strictly low-protein vegetarian diet which is to last, preferably, as long as clinical and immunological signs of the active character of the disease (hematuria, decrease in serum complement, etc.) persist. In uremic patients a fruit diet is of course contraindicated on account of the danger of hyperkalemia.

Penicillin. Glomerular nephritis is an allergic disease, and so it is in principle amenable to causal treatment by elimination of the antigen. RAMMELKAMP and WEAVER [88], in 1953, claimed the existence of "nephritogenic" streptococcus strains, viz. types 4, 12, 25, and the Red Lake [87]. The last one — labelled recently type 49 — which they were unable to identify with any of the known types, was incriminated to be the causative agent of the scarlet fever and nephritis epidemics experienced in an Indian Reservation at Red Lake, Minnesota. The view has since been confirmed bacteriologically in numerous areas geographically remote from one another [90, 94, 105, 120]. Outstanding among these from the point of view of therapeutic value are the results of WILMERS et al. [121] who could isolate the type 12 streptococci from the throat or nose of 28 out of 31 patients with clinically acute glomerular nephritis, in various hospitals of England and Wales. This would appear to form a basis for regarding acute nephritic patients as carriers of "nephritogenic" streptococci, and so it seems advisable to treat them with penicillin without delay, not awaiting the bacteriological results. Throat cultures from about half the acute cases in our clinical material needed to particular efforts to yield beta hemolytic streptococci.

In glomerular nephritis, more than in any other disease, it is indispensable that before initiating penicillin treatment the patient should be tested for hypersensitivity, for in addition to anaphylaxis, parallergy threatens. Instead of the simple intracutaneous, the modern scratch test should be employed [54, 75, 104]. An intracutaneous penicillin injection might bring forth fatal anaphylaxis. In established cases of hypersensitivity to penicillin, erythromycin should be administered, in full doses.

Removal of infective foci. Are we still justified in removing foci in the present antibacterial era?

Dental foci have lost much of the importance that had formerly been attributed to them as centres of infection. According to SEELEMANN [103], mostly *Str. salivarius* only can be cultivated from them, an organism devoid of antigenic function. In the available literature I have failed to find a single report of "nephritogenic" streptococcus having been cultured from a periapical abscess.

Tonsillectomy is seen in an entirely different light. In SARRE's [98] opinion, it is still in place; we too consider it indicated in view of the possible

residual hematuria or residual proteinuria. In our experience the operation, although performed under penicillin protection, often aggravates the symptoms. The reaction abates in a few days, but a dramatic improvement is seldom seen. It is as yet impossible to predict in an individual case what effect tonsillectomy will have on acute nephritis. The general view is that the tonsils should be removed because they might harbour hidden infective foci. However, the matter is not as simple as that; in our clinical material the inside of the tonsil was in each case found to be free from beta hemolytic streptococci and showing no sign of acute inflammation (RAUSS, ROMHÁNYI). At present we have nothing but suppositions to guide us in interpreting the effects of tonsillectomy. What we know for certain is that there are extrarenal antigens capable of starting immunologic processes that result in nephritis. Nephrotoxic serum was produced in animals of another species by SEEGAL and LOEB [102], using placenta; by HÁMORI and OLÁH [42, 43], using stomach; and by STREHLER [109], using aorta antigen. An autosensitization in human disease is conceivable not only within the kidney, but also at the site of the "first" disease, i.e. of direct contact between the bacteria and the capillary antigen, where the former interfere with the latter, or the two combine to form complete antigen [39].

Corticosteroids. Penicillin has failed to bring us the solution of how to treat nephritis, probably because the disease is the clinical manifestation of an intricate immunological mechanism. Studying the literature makes one feel convinced that each of the presently presupposed allergic mechanisms comes to play a part in the origin or in one or the other process of the disease (the slow progression of chronic nephritis, acute exacerbations, etc.). The chain of such allergic mechanisms comprises streptococcal sensitization, soluble antigen-antibody complex, inverse active anaphylaxis, and, as its last link, auto-immunization [37, 38, 39]. Penicillin exerts no influence on the autoimmune reactions wherefore it is advisable to apply general antiallergic therapy. Particularly, I am having in mind the corticoid hormones and the many variants which have been developed from them such as prednisone, prednisolone, dexamethasone, etc.

The most extensively debated question of the treatment of glomerular nephritis is that concerned with the use of corticosteroids. In our experiments carried out in collaboration with CZIRNER, BIBOR and GOFMAN [44], prednisone as well as prednisolone failed to bring about a sudden favourable change in acute nephritis running a protracted course or in immunologically active chronic nephritis. The results obtained in acute nephritis fluctuated widely; some were favourable, others unfavourable, yet others perhaps too good to be true, but — to all appearances — all conformed with the original dynamism of the pathologic process. Please note my emphasis on apparent conformity!

If interrupted before complete recovery from acute nephritis, prednisolone was found by us to enhance microhematuria as determined by ADDIS's method [1]; moreover, in one case visible hematuria was noted one day after discontinuance of the drug. This seems to prove its efficacy.

REUBI [93] considers corticosteroid therapy contraindicated in general. Among the American workers there is divergence of opinion. DANOWSKI and MATEER [20] assert that ACTH and cortisone, if administered in the proper doses (200 I. U. of ACTH, respectively 300 mg of cortisone, daily, divided in equal quantities, over a period of four weeks) inhibit transition from acute to chronic forms. Other authors are not enthusiastic about the use of corticosterone in the treatment of acute glomerular nephritis [15, 51, 62, 113]. Reports concerning prednisone and prednisolone treatment are remarkably scarce, and do not seem to have as yet been worked up statistically. To shape a definitive opinion would require the study of a large case material, in view of the marked tendency for spontaneous recovery of glomerular nephritis.

The following points emerge as main conclusions to be drawn from animal experiments.

The first indifferent findings [33, 65] were followed by reports of SPÜHLER et al. [106, 107, 123] that in rabbits injected with nephrotoxin huge doses of cortisone (25 mg/kg, daily) inhibited the formation of antibody against foreign protein, and practically prevented the development of MASUGI nephritis. ACTH was found to act similarly [118]. MOENCH and VOGT [80] advise great caution in the determination of doses, having found that MASUGI nephritis in rats is influenced favourably by small doses but adversely by large doses of prednisolone.

In our experiments carried out with CZIRNER and GOFMAN [46], prednisolone (Di-Adreson-F Aquosum, Organon, Oss), irrespective of dosage, neither prevented MASUGI nephritis nor inhibited antibody formation against foreign protein, but is apparently moderated the pathologic process.

According to LANGE et al. [71] triamcinolone (9-alpha-fluoro-16-alpha-hydroxy-prednisolone) is of value in avoiding uremia. In interesting experiments JULESZ et al. [56] showed that implantation of pituitary favourably affects MASUGI nephritis.

To summarize, we incline to the view that steroid therapy should be applied in all active cases of glomerular nephritis. We consider the disease active as long as routine ADDIS [1] counts reveal hematuria or the complement level is low. Steroid preparations that cause no sodium retention should be given preference. The medium dose is recommended as the dose of choice. Treatment should be continued, if necessary, for months, until the clinical and immunological signs of active disease have disappeared.

Steroid therapy is not without danger. Its prescription must be preceded by the same deliberations as go before a major surgical operation. Its risks

must be carefully weighed against the benefits to be expected. What dangers does entail prolonged treatment with steroid hormones? There are three occurrences to consider, *viz.*

1. Perforation of the stomach, gastric hemorrhage.
2. Adrenal atrophy.
3. Infection.

The greatest threat are gastric complications. To obtain direct information we studied the effect of cortisone and prednisolone on the gastric mucous membrane (HÁMORI, NEMES and HAL; 48). Cortisone did not enhance the ulcerogenic action of vagotomy in the rabbit; and prednisolone (Di-Adreson F, Organon, Oss), most interestingly, induced ulcers but exceptionally in the stomach of the dog. It did, however, greatly advance progression of cincophen ulcers. Prednisolone in combination with cincophen was found to give rise to extensive ulcers. In view of these observations all our patients are first subjected to an X-ray examination and those showing an ulcer are not treated with prednisolone. Responsable security might be attained by combining the administration of steroids with antacid drugs. Potassium deficiency must of course be prevented by adequate doses, provided the patient is not uremic. We recommend 40—50 mg of prednisolone daily, a sufficient quantity of sodium bicarbonate, and 1 g of potassium chlorate t.i.d.

Adrenal atrophy may be lethal, as in the cases reported by HAJÓS [34] and FARKAS [24]. But the feedback effect is perhaps not as dangerous as it was formerly thought to be. VECSEI and KEMÉNY [117] established that prednisolone, whether administered continuously or at intervals, reduced endogenous corticoid production in the rat, but the feedback effect began to wear off after some time. This means that prolonged steroid therapy does not enhance this untoward effect. Our method of shielding the patient against the carency syndrome is to discontinue prednisolone gradually, in the course of about two weeks. In our opinion ACTH does little, if anything, to reduce the feedback effect, and so its administration is unnecessary, and may even be harmful (parallergy).

Infection is extremely rare, but at times of epidemic influenza it may be a severe threat, as could be seen during the recent outbreak of "Asiatic" influenza in this country. In non-viral infections wide-spectrum antibiotics have proved beneficial in every one of our cases.

The evidence at hand strongly indicates that it is possible to diminish the side effects of steroid therapy. Hyperacidity and established peptic ulcer mentioned in the history contraindicate treatment with steroids, yet many other ways are known by which to depress antibody formation.

X-radiation. It has been known for more than 50 years that X-radiation inhibits antibody formation. BRAUN and MOELLER [11] attempted the treatment of glomerular nephritis with X-rays and reported favourable results

provided not more than two years had elapsed since the onset of the disease. X-radiation is capable of preventing the type of MASUGI nephritis which is supposedly caused by a biphasic mechanism [60, 61, 89].

Nitrogen mustard. In model experiments with bovine serum gamma globulin pathogenic antibody formation could be inhibited by nitrogen mustard [100]. Trials with the compound in humans were not convincing [6]; its use may cause dangerous complications.

Antihistamines. The intricate immunological mechanism of glomerular nephritis requires our efforts to stop the pathological process at every point. The antigen-antibody reaction releases diverse chemical mediators from the tissues. Little is known of these, though their neutralization might form a sound therapeutical approach. The most important of these mediators are histamine, serotonin, and what are termed the "wild" polypeptides. So far research has been concentrated mainly upon histamine. DIECKHOFF [21] found that nephrotoxin increased the histamine content of renal venous blood to from three to four times its normal. Using JANCSÓ's gelatine-India ink method, I demonstrated in collaboration with TOMPA [49] the release of histamine in the glomeruli of rabbits injected with nephrotoxic duck serum. REUBI [91, 92] observed the beneficial effect of antazoline in acute glomerular nephritis; however, HALPERN et al. [35] denied the value of antihistaminics because they found that promethazine was unable to prevent MASUGI nephritis. Artificial hibernation with chlorpromazine-promethazine-pethidine cocktail and physical cooling, contrary to expectation, was found to hasten the development of MASUGI nephritis [115]. In summing up the REUBI vs. HALPERN dispute one may say that promethazine is devoid of effect but certain antihistaminic substances can be conceived as being capable of producing beneficial results.

In collaboration with CZIRNER and GOFMAN [45] we have studied the effect the potent antihistaminic preparation chlorpheniramine maleate (Chlortrimeton SCHERING) in rabbits injected with nephrotoxic duck serum. The drug has been found to have no effect.

No definite conclusions can be drawn from clinical experience. Reports on the effects of the antihistaminic drugs are conflicting; some results have been said to be favourable [5, 10, 18, 66], others unfavourable [72, 112].

In sum, the true value of the antihistaminic drugs has still to be established; what seems to be certain is that the range of preparations exerting a favourable influence on nephritis cannot be particularly extensive.

Anticoagulants. An intriguing question is that of a correlation between blood clotting and inflammation. JANCSÓ and KOVÁCS [55] has recently reported that by the use of some new anticoagulants (quaternary polyammonium compounds of polypeptide structure) he mostly succeeded in preventing, in a number of experimentally induced inflammatory processes, the pathological phenomena which interfere with permeability. Other authors found that

heparin was capable of preventing the local [27, 85] as well as the generalized [27] SHWARTZMAN reaction. On the other hand, according to SARRE [97] heparin affords no protection against experimental glomerular nephritis.

Pathologists have long ago pointed to the presence, occasionally in vast numbers, of fibrin thrombi in the glomerular loops of humans with REICHEL type glomerular nephritis. Fibrin thrombi were also found to be present in renal glomerular lesions of rats [74] and dogs [101] injected with nephrotoxic serum. Working with nephrotoxin-treated rabbits, we produced indirect evidence of the clotting disturbance. Following nephrotoxin treatment, the animals were given an intravenous injection of India ink stabilized with gelatine according to JANCSÓ. Autopsy revealed India-ink thrombi in the renal arterioles, provided the nephrotoxic action had been violent. Precipitation of exogenous colloid was interpreted as a sign of latent clotting disturbance [41]. It is improbable that intravascular coagulation should be responsible for all inflammatory phenomena; nevertheless, one might conceive of it as a pointer in the direction of new therapeutic possibilities, i.e. of the right type of coagulant, applied at the right moment, and for the right period of time.

The chronic stage

As has already been stated, the treatment of chronic nephritis differs in dependence on whether the pathological process is in the active or inactive phase. The inactive phase requires strict observation of dietary rules and a mode of life that spares the kidneys. The active phase calls for steroid therapy.

Kidney denervation. Encouraged by favourable clinical results, BROD and ANTONIN [14] recommend denervation, but animal experiments show that it has no decisive effect on the immunological process in the kidney. HÁMORI and KORÁNYI [47] found that bilateral denervation fails to prevent the onset of MASUGI nephritis, and unilateral denervation involves the dysfunction of both kidneys. An explanation of the favourable clinical results reported is, perhaps, that spasm of the innervated arterioles adds itself to the glomerular lesions as a secondary factor in maintaining the nephritic symptoms. It is certainly not easy to determine the right time for surgery; performed prematurely it is unnecessary, and done too late it is unreasonable.

What can be done in the terminal stage? Uremia, though the fifth act of a Shakespearean tragedy, still leaves some room for hope, justified by two new promising methods, the artificial kidney, and kidney transplantation.

Artificial kidney. The problems of the artificial kidney have been discussed in detail at the Congress of Hungarian Internists in 1960. Here I would only emphasize that the artificial kidney must not be used unless there is reasonable hope that after uremia has been relieved there will be improvement in renal function.

The technical progress in this field is amazing. At the congress just mentioned we have learned from SARRE [99] that thin polyvinyl tubes are now inserted in the artery and the vein of the forearm, and left in them for days, and allow extracorporeal dialysis to be performed repeatedly and conveniently. A small receptacle, not unlike a tin for preserves, can hold the new-type artificial kidney which is discarded after use. However, even with the modern technique extracorporeal dialysis is of no avail in the terminal stage of patients with aglomerular kidneys.

Kidney transplantation. The idea of kidney transplantation had arisen more than 50 years ago. The technical details for its performance were soon elaborated, but biological incompatibility of the transplant with the recipient organism was for a long time an impediment. The experiments of MERILL et al. [76, 77, 82] are known to all of us; they have transplanted kidneys with success between identical twins. The results achieved in Boston have not been published in detail but at least one transplanted kidney is known to have retained its perfect functional capacity for three years. Unfortunately, it happens very rarely that one of a pair of uniovular twins should be perfectly healthy while the other suffers from chronic nephritis. The latest progress is to be credited to American [78] and French [36, 70] clinicians who achieved immunological tolerance in the recipient by subjecting him to sublethal whole-body irradiation with 400—460 r. This procedure has made kidney transplantation possible between twins who have not developed from a single ovum.

There is another impressive possibility. Kidney transplantation may be successful if the recipient suffers from agammaglobulinemia. To this at any rate points the experience acquired in skin transplantations [28].

SARRE [98] praises cortisone as the drug of choice in the terminal stage: it relieves the patients' anxiety and keeps them soothed to the end.

Prevention

Antibiotic treatment of coccogenous infections. Glomerular nephritis is a "second" disease, the "first" being usually some infection of the upper respiratory tract, or pyoderma. The "first" disease is the prelude to the tragedy. It is best prevented by competent antibiotic treatment. According to KERPEL-FRONIUS et al. [63], in children early treatment of scarlet fever with penicillin prevents involvement of the kidneys.

Epidemiological observations revealed that treatment with penicillin of carriers of type 12 streptococcus and type 12 streptococcal pharyngitis prevents spread of nephritis [86, 108]. On the other hand gamma globulin treatment of the patients with type 12 streptococcal infections not only valueless, but may even be harmful [108]. Let me point to bovine gamma globulin nephritis ! Prolonged penicillin treatment, as far the prevention of rheumatic

relapses, is in my opinion unnecessary in nephritis, where it involves certain risks (parallergy).

Detection of "nephritogenic" streptococcus carriers. For the prevention and control of epidemic outbreaks of nephritis the ideal solution would be a systematic detection of carriers of "nephritogenic" streptococcus strains. Unfortunately, typing is an intricate task. For the time being we can only suggest some practical measures. Persons in contact with acute nephritic patients should frequently be examined bacteriologically for the presence of beta hemolytic streptococci in the throat and the nose, and those found positive should be treated with penicillin. Each patient should be considered an infective source, and therefore be isolated and made to wear a face mask until residual infection has been controlled.

Pyelonephritis

Pyelonephritis has been known for over a hundred years, but it was only in the last decade that we became painfully aware of its frequency, gravity, and the deplorable insufficiency of its therapy.

The acute stage

The treatment of acute pyelonephritis apparently presents no challenging problems. According to COLBY's statistics [17], antibiotics are efficaceous in 90 per cent of the cases.

The chronic stage

Regrettably, the condition frequently develops into the chronic stage. Apparent recovery is followed after a few months by relapses or the infection remains latent for long periods, leading ultimately to a total destruction of the kidney. Chronic pyelonephritis proves curable in one third of the cases at the utmost. The cause of relapses or the persistence of an infection is not always obvious. It is at this point that we come into conflict with the weighty general problems of organ disposition and organ immunity.

Removal of foci and surgical correction of urological changes. The problem of organ disposition may lose some of its intricacy if it is contemplated in the light of the fact that, while inserted as a filter in the blood path, the kidney, by way of the urinary tract, communicates directly with the external world. What is strange is not that a person should have pyelonephritis, but why not everybody has it. In fact there is evidence that in one of every five autopsies changes are found which point to varying degrees of this disease [95]. The special position of the kidney in the organism explains the distinction of two types of pyelonephritis, viz. the ascending and the hematogenous type. In the

first type, some urologic change, such as developmental anomaly, calculus, prostatic hypertrophy, etc., is responsible for the persistence of the pathologic process; in the second, this is due to some active infective focus. It follows that recovery from pyelonephritis is inconceivable without the elimination of the underlying cause. Sucessful therapy imperatively requires the elimination of infective foci and the surgical correction of urologic changes.

Numerous authors have studied the relationship between pyelonephritis and hypertension. The question is whether nephrectomy is justified in chronic pyelonephritis when hypertension can be interpreted on the basis of the GOLDBLATT mechanism? Hypertension developing in pyelonephritis not infrequently reminds one of the malignant form. This underlines the significance of the question. Some authors regard nephrectomy as a lifesaver. Others, whose number is growing, keep pointing out that pyelonephritis is very exceptionally unilateral and that the functioning renal parenchyma is diminished by nephrectomy.

Evaluating the data on hand I cannot escape the impression that nephrectomy performed in order to lower blood pressure is in most cases a will-o'-the-wisp scheme. In COLBY's statistics [17], for instance, we see that only three of twenty such operations were successful. It would appear that nephrectomy in case of a GOLDBLATT type hypertension is unrewarding except in patients with stricture of the renal artery verified by lumbar aortography. GÖMÖRI and SZENDEI [30] recommended SMITHWICK's operation in several cases of hypertension supposed to be of pyelonephritic origin; the results were variable.

Patients with nothing for which to operate on them, constitute peculiar problems. These cases requiring medical treatment represent, according to BROD [13], at least one third of all the cases. The histories sometimes point to cystopyelitis, at other times they give no or not specific information. The prognosis of these non-obstructive forms is much poorer than that of the obstructive forms. I would once more refer to COLBY [17] whose statistics show that 28 per cent of the complicated forms of chronic pyelonephritis are curable against only 15 per cent of the non-complicated forms. To provide an explanation for this paradoxical observation, BROD [13] suggests that most patients suffering from one of these latent forms undergo treatment much too late. One may agree with those who say that the chance of curing chronic pyelonephritis is the greatest if it is acute.

Approaching the question from the Pavlovian standpoint, BROD [13] in his monograph underlines the possibility that some minor neurogenic functional disturbance imitates anatomical obstruction of the urinary system. The consequences of severe disturbances of nervous origin are well known. For instance, pyelonephritis following paraplegia leaves no hope of recovery, and is mostly lethal. Lesser disturbances of nervous origin acquire significance if there occurs some inflammatory process near the urinary system. Procain

block is known to have been recommended to relieve spasms of reflex origin, and injection of pituitrin, to regulate weakened dynamism [31]. In my view, etiological treatment of regional inflammations is to be preferred to such symptomatic treatment.

Control of bacteriuria. The chronic forms are usually treated by prolonged administration of sulphonamides relatively well soluble in the urine, of which doses of 1 to 2 g daily are prescribed intermittently for months, until the patient is symptomless and repeated analyses show the urine to be permanently sterile. In acid urine the acetylated sulphonamides assume a crystalline structure. To prevent crystallization, alkalies should be prescribed and it should be remembered that the combination of hexamine and sulphonamides forms a formaldehyde compound and the mass of precipitate obstructs the renal tubules; the result is anuria and uremia. The alternative is a prolonged course of some tetracycline preparation in 100-mg doses b.i.d. The choice of the antibiotic may be a subject of dispute; not so the ultimate end, which is to control bacteriuria by some means or other, irrespective of whether or not it is accompanied by pyuria. Subclinical infections may likewise cause irreversible renal damage [59, 69]. Bacterial counts prove the etiologic significance of the bacteria discharged [57, 58, 73, 81]. They afford the best indication of the presence of an infection in the urinary tract [19].

In view of the above, we cannot possibly be satisfied with the current methods of treating chronic pyelonephritis. Obviously some new ways must be found to approach the problem.

Electrolyte balance. There are several therapeutical possibilities that have not yet been put to the full proof. Foremost among them stands a careful control of the electrolyte balance, and the immediate restoriation of its changes. Until recently, the problem had been the "retaining" kidney; now, the concept of the "losing" kidney is being much expounded. Perhaps the most frequent loss is that of salt, particularly in pyelonephritis, where potassium deficiency may also occur, though less frequently. KERPEL-FRONIUS et al. [64] found tubular dilatation in rabbits kept on a potassium-free diet. From the therapeutical point of view this finding is not without interest in pyelonephritis. Tubular dilatation due to potassium deficiency intensifies the infectious process, and a vicious circle may develop. Correction of the deficiency might, on the other hand, start a benignant circle. The vicious circle is reversible, as S. KORÁNYI [67, 68] had frequently pointed out in other connexions.

Antihistamines. Another therapeutical possibility seems to be the use of antihistamine drugs. On the basis of the convincing experimental evidence produced by BABICS and RÉNYI-VÁMOS [3, 4] there seems every reason to assume that in the chronic forms urine is absorbed by the adipose tissue around the renal pelvis, whence it finds its way into the interstitial space, causing vast release of histamine. Another therapeutical result of the work of these

authors is the removal of the scarred adipose tissue in the renal sinus. Occlusion of the lymph ducts automatically causes the lymph flow to fall short of normal; the adverse effect of this on protein transport is heavily responsible for renal destruction and contraction.

Exogenous and endogenous poisons. Organ immunity would certainly afford full protection from pyelonephritis. Unfortunately, its mechanism is still imperfectly known. Perhaps local antibody formation plays a part in it. Observance of general hygienic and sanitary rules, rest and administration of vitamins, are undoubtedly beneficial measures, but most important is to eliminate every factor that might interfere with renal immunity. This equally includes exogenous and endogenous poisons. A commonplace example is the extremelly severe clinical manifestation of pyelonephritis in diabetics, developing not infrequently into necrotizing renal papillitis.

It is certain that exogenous poisons also impair renal immunity. In the first place, I am thinking of chronic damage due to acetophenetidin. Although the pathologic findings are the same as those seen in interstitial nephritis, animal experiments supply unequivocal evidence that the compound only destroys the kidney in association with an infection [79, 110].

Corticosteroids. ZOLLINGER [122] states that flooding of the kidney with foreign protein may produce interstitial nephritis. In his view the lesion can be interpreted on the basis of an allergic mechanism.

It may be assumed that the lesion can be induced by various mechanisms, and should this prove true, the treatment of pyelonephritis would have to be placed on a wider than its present basis; in this case the corticosteroids might become one of the components of a complex therapy.

Prevention

The urologist's responsibility. Growing emphasis is now being layed upon the urologist's responsibility in reference to iatrogenic infection. There has been considerable discussion about the question whether catheterization had not better be abandoned. In the initial portion of the male, and the outer two thirds of the female, urethra, bacteria are present, which the catheter is likely to transport into the bladder. The risk incurred is still more serious in ureteric catheterization because the delicate instruments used in this manoeuvre are difficult to sterilize. Urological departments are habitats of antibiotic-resistent pathogenic agents, of which the most dreaded are the *B. proteus* and *B. pyocyaneus* strains. COLBY [17] discards the ureteral catheters used in patients found to be infected with these strains. BABICS and RÉNYI-VÁMOS [3, 4] describe with dramatic force the catastrophe which may occur during manipulations involving the use of internal instruments in ureteric occlusion due to a calculus. The urologist inserts the ureteral catheter past the stone. He want

to obtain information by retrograde pyelography. He injects the contrast medium. This gives rise to considerable overpressure in the dilated pelvis and so enables the infected urine to enter the interstitial space through the cracked calyces, causing foudroyant renal inflammation. I think that the right treatment of calculus obstruction is one of the most provocative questions in clinical practice. Whether he takes his time or is in a hurry, the urologist in any case may make a mistake.

The pediatrician's responsibility. The responsibility the pediatrician has to bear is not small either. In childhood the incidence of pyelonephritis is known to be high and to account for 2 per cent of all deaths, primarily because of developmental anomalies [16]. In the presence of the latter particular care must be taken in eliminating infectious foci.

The gynecologist's responsibility. Recent research has revealed the special problem of pyelonephritis in pregnancy and puerperium. During pregnancy there is physiological ureteral dilatation, but functional disturbances of the urinary tract are known to equal an obstructive disorder. Pregnant women often harbour microorganisms in their urine [52, 59]); the bacterial counts should decide their significance, and antibiotics must be prescribed accordingly.

The internist's responsibility. He must know that asymptomatic bacteriuria, too, can be of consequence, that its absence is to be preferred, and that he must keep his patient under careful observation for it. We subscribe to GÖMÖRI's [30] demand for early diagnosis and treatment. Prompt and energetic treatment of infections of the urinary system must go beyond the control of pyuria, and must aim at the eradication of the organisms. Even this is not enough. In consultation with the urologist, all structural and functional changes must be corrected. If nevertheless there are recurrent attacks, the points of entry of the invasive bacteria must be found, especially in women.

The nephrotic syndrome

Since it has been introduced by MÜLLER [83], the term "nephrosis" has undergone many conceptual changes. The term accepted at present is the "nephrotic syndrome". The nephrotic syndrome may occur in any of a variety of conditions, such as lipoid nephrosis, nephritis with traits of nephrosis, amyloidosis, systemic lupus erythematosus, KIMMELSTIEL—WILSON's disease, renal vein thrombosis, constrictive pericarditis, etc. These conditions cannot be amenable to the same treatment.

Experimental and clinical data suggest an allergic mechanism of lipoid nephrosis, and that it is possibly a form of chronic glomerular nephritis. In its treatment a decisive role is played by adrenal cortical hormones. Ultimately,

lipoid nephrosis is as much a clinical manifestation of vascular allergy as is a systemic lupus erythematosus, and this consideration prompts and encourages intensive and consistant application of steroid treatment [40]. Steroid preparations, mainly prednisone and prednisolone, can now be administered for months [2, 8, 9, 23, 26, 29, 32, 50, 53, 84, 111, 116). Formerly short-term steroid therapy was applied generally, but today prolonged either continuous or intermittent treatment is preferred. The results are statictically valid [96].

Amyloidosis is reversible, provided the chronic infection has been eliminated in time, if necessary by surgery, as for instance by amputation of a limb in osteomyelitis, or by lobectomy in bronchiectasis.

The problem of treating the KIMMELSTIEL—WILSON syndrome still awaits solution. There are several reasons for assuming that nodular hyalinosis, which in the rabbit appears after a 3-week course of cortisone, is in humans the result of endogenous hypercorticism. In Hungary, this has been pointed out by BRETÁN [12]. Accordingly, the administration of corticosteroids is inadvisable. Nor does it seem to be of value in conditions with symptoms due to renal congestion. Thrombosis of the renal vein calls for nephrectomy, and anticoagulant treatment has been recommended for bilateral thrombosis [7]. Perhaps antialdosterone preparations should also be given, since there is experimental evidence pointing to the important role of aldosterone in renal oedema formation — or else kidney transplantation should be performed. In patients with chronic constrictive pericarditis surgery is the only promising intervention.

Conclusion

Glomerular nephritis, nephrosis, and pyelonephritis have the feature in common that all issue from infections. On this ground, it may be reasonably hoped that with the general progress of man's struggle against infectious diseases, they will be wiped off.

Summary

I. Nephritis

Modern drugs have outdated neither bed rest nor rules of diet. Patients should be kept on strictly vegetarian diets, preferably as long as the pathologic process is active.

Patients with acute nephritis should be treated with penicillin immediately, without waiting for the bacteriological result, but not without scratch testing for hypersensitivity. If the test yields a positive reaction, erythromycin should be administered in full doses.

Tonsillectomy is justifiable if residual proteinuria or residual hematuria has been diagnosed.

Corticosteroid therapy is indicated in every clinically or immunologically active case, provided there are no complaints pointing to hyperacidity, and no established signs of peptic ulcer. Steroid preparations that cause no sodium retention should be given preference over others. The medium dose is recommended as the dose of choice. The most important signs of activity are microhematuria and a low complement level.

The true value of the synthetic antihistamines has still to be established. The use of anticoagulants has not yet passed the experimental stage.

Kidney denervation, recommended by some authors in chronic nephritis, involves the difficult problem of determining the right time for its performance, because if it is performed prematurely it is unnecessary, and done too late it is unreasonable.

The use of the artificial kidney is only justifiable in cases where there is hope of an improvement in renal function.

Kidney transplantation is now possible between twins who have not developed from a single ovum, if immunological tolerance has been ensured by sublethal whole-body irradiation.

Early treatment of coccogenous infections with antibiotics is most effective in prevention of nephritis. The patient with acute nephritis is an infective source; he should be isolated and made to wear a face mask. To prevent epidemic outbreaks the ideal solution is a systematic detection of carriers of "nephritogenic" streptococcus strains.

II. Pyelonephritis

The principles of treatment are (i) the administration of suitable antibiotics; (ii) the removal of the infective foci; (iii) the surgical correction of urological deformities; (iv) the control of exogenous and endogenous poisons; (v) the correction of the electrolyte balance; (vi) the general observance of hygienic rules.

The use of antihistaminic drugs and corticosteroids is still in the experimental stage.

With regard to prevention, the responsibility rests with the urologist, the pediatrician, and the gynecologist. Catheterization, and manipulations involving the use of instruments, must be preceded by grave deliberation and performed under antibiotic protection. On recognizing some developmental anomaly, eventual infective foci must be eliminated at once. Urinary bacterial counts are the best indicator of urinary infection. If the number of coliform organisms exceeds 1000 per ml, antibiotic treatment is advisable in pregnancy and the puerperium.

III. The nephrotic syndrome

Treatment of the nephrotic syndrome varies with the cause eliciting it. An allergic mechanism calls for prolonged corticosteroid treatment. The latest development in symptomatic treatment is the administration of antialdosterone preparations.

In unilateral renal vein thrombosis nephrectomy is indicated; in bilateral thrombosis anticoagulants should be prescribed.

REFERENCES

1. Addis, T.: Glomerular Nephritis, Diagnosis and Treatment. Macmillan, New York 1949.
2. Arneil, G. C.: Lancet **1,** 409 (1956).
3. Babics, A. and Rényi-Vámos, F.: A vesepusztulás elmélete és klinikuma. Akadémiai Kiadó, Budapest 1952.
4. Babics, A. and Rényi-Vámos, F.: Das Lymphgefäßsystem der Niere. Verlag der Ung. Akademie der Wissenschaften, Budapest 1957.
5. Baffi, V.: Pediatria (Napoli) **58,** 198 (1950).
6. Baldwin, D. S., McLean, P. G., Chasis, H. and Goldring, W.: Arch. intern. Med. **92,** 162 (1953).
7. Barclay, G. P. T., Cameron, H. MacD. and Loughridge, L. W.: Quart. J. Med. N. S. **29,** 137 (1960).
8. Barnett, H. L. and Eder, H. A.: J. chron. Dis. **5,** 108 (1957).
9. Bickel, G.: Schweiz. med. Wschr. **85,** 859 (1955).
10. Biró, L.: Wien. med. Wschr. **98,** 193 (1948).
11. Braun, H. and Moeller, J.: Strahlentherapie **96,** 408 (1955).
12. Bretán, M.: Az angiopathia diabetica klinikuma és pathogenesise. Dissertation. 1961.
13. Brod, J.: Chronische Pyelonephritis. Volk und Gesundheit, Berlin 1957.
14. Brod, J. and Antonin, V.: Čas. Lék. čes. **93,** 1082 (1954).
15. Burnett, C. H., Greer, M. A., Burrows, B. A., Sisson, J. H., Relman, A. S., Weistein, L. A. and Colburn, C. G.: New Engl. J. Med. **243,** 1028 (1950).
16. Butler, A. M. and Lanman, T. H.: New Engl. J. Med. **217,** 725 (1937).
17. Colby, F. H.: Pyelonephritis. Williams & Wilkins, Baltimore 1959.
18. Craig, J., Clark, N. S. and Chalmers, J. D.: Brit. med. J. **1,** 6 (1949).
19. Csokonay, L. and Kirchknopf, M.: Orv. Hetil. **102,** 1838 (1961).
20. Danowski, T. S. and Mateer, F. M.: J. chron. Dis. **5,** 122 (1957).
21. Dieckhoff, J.: Kinderärztl. Prax. Sonderheft 141 (1953).
22. Dutz, H.: Verh. dtsch. Ges. inn. Med. **62,** 619 (1956).
23. Fabre, J.: Helv. med. Acta Ser. A, **23,** 381 (1956).
24. Farkas, K. and Molnár, I.: A leggyakoribb diagnosztikus tévedések. Medicina, Budapest 1961.
25. Farr, L. E. and Smadel, J. E.: J. exp. Med. **70,** 615 (1939).
26. Friederiszick, F. K. and Hoffecker, E.: Med. Klin. **51,** 1260 (1956).
27. Good, R. A. and Thomas, L.: J. exp. Med. **97,** 871 (1953).
28. Good, R. A. and Varco, R. L.: J. Amer. med. Ass. **157,** 713 (1955).
29. Goodman, H. C. and Baxter, J. H.: J. Amer. med. Ass. **165,** 1798 (1957).
30. Gömöri, P. and Szendei, Á.: Acta med. Acad. Sci. hung. **12,** 329 (1958).
31. Gregoir, W.: Les troubles moteurs de l'arbre urinaire supérieur. Bruxelles, 1951. cited by Brod (13).
32. Grégoire, F., Malmendier, C. and Lambert, P. P.: J. d'Urol. méd. et chir. **62,** 140 (1956).
33. Hackel, D. B., Portfolio, A. G. and Kinney, T. D.: Proc. Soc. exp. Biol. (N. Y.) **74,** 458 (1950).
34. Hajós, K.: Allergie u. Asthma **1,** 183 (1956).
35. Halpern, B. N., Trolliet, J. and Martin, J.: Acta allerg. (Kbh.) **2,** 150 (1949).
36. Hamburger, J., Vaysse, J., Crosnier, J., Tubiana, M., Lalanne, C. M., Antoine, B.,

AUVERT, J., SOULIER, J.-P., DORMONT, J., SALMON, CH., MAISONNET, M. and AMIEL, J.-L.: Presse méd. **67,** 1771 (1959).
37. HÁMORI, A.: Orv. Hetil. **100,** 1317 (1959).
38. HÁMORI, A.: Allergische Krankheiten der Niere. In Rajka, E.: Allergie und allergische Erkrankungen. Akadémiai Kiadó, Budapest 1959. Vol. 2, chap. 5.
39. HÁMORI, A.: Magy. belorv. Arch. **13,** 161 (1960).
40. HÁMORI, A.: Rheum. Balneol. Allerg. (Budapest) **1,** 237 (1960).
41. HÁMORI, A.: Unpublished data.
42. HÁMORI, A. and OLÁH, F.: Orv. Hetil. **91,** 1455 (1950).
43. HÁMORI, A. and OLÁH, F.: Lancet **1,** 586 (1951).
44. HÁMORI, A., CZIRNER, J., BIBOR, Z. and GOFMAN, L.: In preparation.
45. HÁMORI, A., CZIRNER, J. and GOFMAN, L.: In preparation.
46. HÁMORI, A., CZIRNER, J. and GOFMAN, L.: In preparation.
47. HÁMORI, A. and KORÁNYI, A.: Z. klin. Med. **133,** 722 (1938).
48. HÁMORI, A., NEMES, T. and HAL, T.: In preparation.
49. HÁMORI, A. and TOMPA, S.: cited by HÁMORI [38].
50. HEIDORN, G. H. and SCHEMM, F. R.: Amer. J. med. Sci. **229,** 621 (1955).
51. HELLER, B. I., JACOBSON, W. E. and HAMMARSTEN, J. F.: J. Lab. clin. Med. **37,** 133 (1951).
52. HIRSHFELD, J. W., LEARY, D. C. and FOOTE, W. R.: Yale J. Biol. Med. **14,** 297 (1942).
53. HOOFT, C. and EECKELS, R.: Acta paediat. belg. **14,** 105 (1960).
54. IRWIN, J. W., GRAHAM, M. J., JACOBSON, B. M. and BURRAGE, W. S.: New Engl. J. Med. **245,** 246 (1951).
55. JANCSÓ, M. and KOVÁCS, K.: Acta physiol. Acad. Sci. hung. Suppl. **20,** 40 (1962).
56. JULESZ, M., SZATMÁRI, É., HOLLÓ, I., ROMHÁNYI, GY. and SZUSZEKÁR, J.: Magy. belorv. Arch. **9,** 82 (1956).
57. KASS, E. H.: Trans. Ass. Amer. Physicians **69,** 59 (1956).
58. KASS, E. H.: Arch. intern. Med. **100,** 709 (1957).
59. KASS, E. H.: Trans. Ass. Amer. Physicians **72,** 257 (1959).
60. KAY, C.: J. exp. Med. **72,** 559 (1940).
61. KAY, C.: Amer. J. med. Sci. **204,** 483 (1942).
62. KEITH, N. M., POWER, M. H. and DAUGHERTY, G. W.: Proc. Mayo Clin. **25,** 491 (1950).
63. KERPEL-FRONIUS, Ö., KOVÁCH, I. and HORVÁTH, M.: Acta med. Acad. Sci. hung. **3,** 83 (1952).
64. KERPEL-FRONIUS, E., ROMHÁNYI, G., GÁTI, B. and DOBÁK, E.: Pediatrics **26,** 939 (1960).
65. KNOWLTON, A. I., LOEB, E. N., STOERK, H. C. and SEEGAL, B. C.: Proc. Soc. exp. Biol. (N. Y.) **72,** 722 (1949).
66. KOCH, M.: Med. Klin. **45,** 1001 (1950).
67. KORÁNYI, A. v.: Nierenkrankheiten. Springer, Berlin 1929.
68. KORÁNYI, S.: A vesebajok. Magyar Orvosi Könyvkiadó Társulat, Budapest 1930.
69. KUNIN, C. M., SOUTHALL, I. and PAQUIN, A. J.: New Engl. J. Med. **263,** 817 (1960).
70. KÜSS, R., LEGRAIN, M., MATHÉ, G., NEDEY, R., TUBIANA, M., LALANNE, C.-M., CAMEY, M., LARRIEU, M.-J., SCHWARZENBERG, L., VOURC'H, C., DESARMENIEN, J., MAISONNET, M., ATALLAH, F.: Presse méd. **68,** 755 (1960).
71. LANGE, K., DEMOLEAS, P. N. and WENK, E. J.: Amer. J. med. Sci. N. S. **240,** 458 (1960).
72. LAWSON, D.: Brit. med. J. 1951. I. 1423.
73. MARPLE, C. D.: Ann. intern. Med. **14,** 2220 (1941).
74. MASUGI, M.: Beitr. path. Anat. **91,** 82 (1933).
75. MAYER, P. S., MOSKO, M. M., SCHUTZ, P. J., OSTERMAN, F. A., STEEN, L. H. and BAKER, L. A.: J. Amer. med. Ass. **151,** 351 (1953).
76. MERRILL, J. P.: J. chron. Dis. **5,** 149 (1957).
77. MERRILL, J. P., MURRAY, J. E., HARRISON, J. H. and GUILD, W. R.: J. Amer. med. Ass. **160,** 277 (1956).
78. MERRILL, J. P. et al.: cited by HAMBURGER [36].
79. MIESCHER, P., SCHNYDER, U. and KRECH, U.: Schweiz. med. Wschr. **88,** 432 (1958).
80. MOENCH, A. and VOGT, A.: Verh. dtsch. Ges. inn. Med. **64,** 527 (1958).
81. MONZON, O. T., ORY, E. M., DOBSON, H. L., CARTER, E. and YOW, E. M.: New Engl. J. Med. **259,** 764 (1958).
82. MURRAY, J. E., MERRILL, J. P. and HARRISON, J. H.: Ann. Surg. **148,** 343 (1958).
83. MÜLLER, F.: Verh. dtsch. path. Ges. **9,** 64 (1905).
84. POST, R. S. and ECKEL, R. E.: J. chron. Dis. **12,** 211 (1960).
85. RALL, D. P., SMITH, N. H. and KELLY, M. G.: Proc. Soc. exp. Biol. (N. Y.) **88,** 241 (1955).
86. RAMMELKAMP, C. H. JR.: Ann. intern. Med. **43,** 511 (1955).
87. RAMMELKAMP, C. H. JR.: J. chron. Dis. **5,** 28 (1957).

88. RAMMELKAMP, C. H. JR. and WEAVER, R. S.: J. clin. Invest. **32,** 345 (1953).
89. RATHE, I.: Helv. med. Acta, Ser. A, **22,** 133 (1955).
90. REED, R. W.: Canad. med. Ass. J. **68,** 448 (1953).
91. REUBI, F.: Helv. med. Acta, Ser. A, **12,** 547 (1945).
92. REUBI, F.: Helv. med. Acta, Suppl. 18 (1946).
93. REUBI, F.: Nierenkrankheiten. Huber, Bern, 1960.
94. REUBI, F. and LÖFFLER, H.: Schweiz. med. Wschr. **84,** 1239 (1954).
95. RHOADS, P. S., BILLINGS, C. E. and O'CONOR, V. J.: J. Amer. med. Ass. **148,** 165 (1952).
96. RILEY, C. M., DAVIS, R. A., FERTIG, J. W. and BERGER, A. P.: J. chron. Dis. **3,** 640 (1956).
97. SARRE, H.: Dtsch. med. Wschr. **79,** 1713 (1954).
98. SARRE, H.: Nierenkrankheiten. Thieme, Stuttgart 1959.
99. SARRE: H.: Congress of Hungarian Internists, Budapest 1960.
100. SCHWAB, L., MOLL, F. C., HALL, T., BREAN, H., KIRK, M., HAWN, C. V. Z. and JANEWAY, C. A.: J. exp. Med. **91,** 505 (1950).
101. SEEGAL, B. C. and BEVANS, M.: J. chron. Dis. **5,** 153 (1957).
102. SEEGAL, B. C. and LOEB, E. N.: J. exp. Med. **84,** 211 (1946).
103. SEELEMANN: Zur Bakteriologie der Herderkrankungen. In: Kritische Betrachtungen des Herdgeschehens. Hanser, München 1955, cited by KOELSCH, F. and K. A.: Z. inn. Med. **15,** 941 (1960).
104. SIEGAL, S., STEINHARDT, R. W. and GERBER, R.: J. Allergy **24,** 1 (1953).
105. SIEGEL, A. C., RAMMELKAMP, C. H. JR. and GRIFFEATH, H. I.: Pediatrics **15,** 33 (1955).
106. SPÜHLER, O., ZOLLINGER, H. U., ENDERLIN, M. and WIPF, H.: Experientia (Basel) **7,** 186 (1951).
107. SPÜHLER, O., ZOLLINGER, H. U. and ENDERLIN, M.: Schweiz. med. Wschr. **81,** 904 (1951).
108. STETSON, C. A., RAMMELKAMP, C. H. JR., KRAUSE, R. M., KOHEN, R. J. and PERRY, W. D.: Medicine (Baltimore) **34,** 431 (1955).
109. STREHLER, E.: Schweiz. med. Wschr. **81,** 104 (1951).
110. STUDER, A., ZBINDEN, G. and FUST, B.: Schweiz. med. Wschr. **88,** 469 (1958).
111. TALBOT, N. B., CRAWFORD, J. D. and COOK, C. D.: New Engl. J. Med. **256,** 1080 (1957).
112. THALHAMMER, O.: Öst. Z. Kinderheilk. **4,** 312 (1950).
113. THORN, G. W., MERRILL, J. P., SMITH, S., ROCHE, M. and FRAWLEY, T. F.: Arch. intern. Med. **86,** 319 (1950).
114. (TSCHERVJAKOVSKI, N. Y. and KOVALJOV, V. F.) Н. Я. Червяковский и В. Ф. Ковалев, Терапевтический архив. **1,** 40 (1951).
115. TUSCH, E.: Wien. klin. Wschr. **67,** 961 (1955).
116. VALLERY-RADOT, P., LAROCHE, C., MILLIEZ, P. and LARGUE, G.: Sem. Hôp. (Paris) **32,** 3017 (1956).
117. VECSEI (WEISZ), P. and KEMÉNY, A.: Acta physiol. Acad. Sci. hung. Suppl. **20,** 58 (1962).
118. VOGT, H., WÜTHRICH, F. and REUBI, F.: Helv. med. Acta, Ser. A, **19,** 357 (1952).
119. VOLHARD, F.: Die doppelseitigen hämatogenen Nierenerkrankungen. In BERGMANN, G. v. and STAEHELIN, R.: Handbuch der inneren Medizin. 2nd ed. Springer. Berlin 1931, Vol. 6.
120. WERTHEIM, A. R., LYTTLE, J. D., LOEB, E. N., EARLE, D. P. JR., SEEGAL, B. C. and SEEGAL, D.: J. clin. Invest. **32,** 359 (1953).
121. WILMERS, M. J., CUNLIFFE, A. C. and WILLIAMS, R. E. O.: Lancet **2,** 17 (1954).
122. ZOLLINGER, H. U.: Die interstitielle Nephritis. Karger, Basel—New York 1945.
123. ZOLLINGER, H. U., ENDERLIN, M. and SPÜHLER, O.: In Symposium on the Influence of the Hypophysis and the Adrenal Cortex of Biological Reactions. Schwabe, Basel 1952.

Prof. Dr. Artúr HÁMORI, Pécs, II. Belklinika, Hungary.

SODIUM RETENTION AND OEDEMA

By

M. FÖLDI

SECOND DEPARTMENT OF MEDICINE, UNIVERSITY MEDICAL SCHOOL, SZEGED

"Much confusion has been spread by the unitarian expounders of oedema formation. For oedema is the result of a multitude of causes, and any attempt to explain it on the ground of a single factor must soon come to a deadlock . . ." These words of RUSZNYÁK [1] written in 1938 were directed against workers who arbitrarily singled out one of the then known causative factors of the condition (increased capillary pressure, increased capillary permeability, hypoonkia, sodium chloride retention, etc.) and at the expense of all the others made it responsible for the development of oedema. RUSZNYÁK's words are perhaps more timely to-day than they have ever been.

An outstanding date in the "latest chapter of the modern history" of oedema research of the year 1950, when from the acidified urine of an oedematous patient DEMING and LUETSCHER [2] successfully extracted with chloroform a substance which on injection into animals induced sodium retention. Soon after, in 1955, organic chemistry scored a success, by NEHER and WETTSTEIN's synthetizing the pure substance — aldosterone [3]. It is easily understood why aldosterone dominates today most pertaining research, and why many authors are apt to regard the oedema problem as definitively settled by the discovery of aldosterone.

In this report one of the aims has been to review in the present state of knowledge the role of aldosterone in the various forms of oedema and conditions associated with sodium retention. This of necessity involves a discussion of its position in the physiology of volume regulation. The inference from my chain of reasoning will be, on the one hand, that apparently aldosterone is a highly significant intrinsic part of the intricate mechanism which controls the volume of body fluids, and if disturbed, conduces to oedema formation; on the other hand, that in the same manner as aldosterone is not the only factor in maintaining the normal state, so it is not, in itself, responsible for the development of any of the various forms of oedema.

Extracellular fluid volume, the proportion in it of circulating plasma, and the ratio between the extracellular and intracellular spaces are as precisely regulated constants of the normal organism as are its chemistry, its ionic composition, etc.

Extracellular fluid volume is preeminently regulated *via* the control of the organism's sodium balance. The latest measurements show the human body to contain 3000 to 3500 mEq of sodium, of which 1400 mEq are in the bones in the "dry state" and the rest dissolved in the extracellular space. In the latter, sodium remains strictly unchanged in both absolute amount and concentration. There is no need to discuss at length the point that, *via* VERNEY's [5] ADH mechanism, sodium ion and water retention and excretion go almost hand in hand. Pathologic cases of hyponatraemia and hypernatraemia are the only exceptions to the rule. It is generally accepted that pathologic water retention leading to oedema is invariably accompanied by sodium retention. With increased sodium intake there is increased sodium excretion by the kidney, the gut, and the sweat and salivary glands; in excessive salt depletion sodium may be reabsorbed in these glands to its almost total disappearance from the urine. The central nervous system regulates water intake through the sensation of thirst, to which the organism reacts sensitively by adapting extent and rate of osmosis and the volume conditions to the needs of the moment. It has been shown in animal experiments that there is an area in the hypothalamus medial and rostral from the centre of hunger which, when injected with hypertonic salt solution or stimulated with electric current, gives rise to polydipsia; in that state the experimental goat overcomes obstacles and even solves certain test problems to get at water. It would appear that the thirst centre reacts both to intracellular dehydration and, most remarkably, to contraction of the extracellular fluid space; it is probably connected directly with the osmoreceptors which regulate ADH secretion and are known to lie in the supraoptic and paraventricular nuclei of the hypothalamus [6, 7, 8, 9].

There is nothing strange in that the glands should retain sodium when a sodium-low diet is given or there is a considerable loss of salt from diarrhoea or profuse sweating. However, it is rather striking to find that sodium excretion is reduced, and often quite suddenly, when the attendant circumstances are entirely different; when the intake of sodium is adequate and no loss of it can be demonstrated.

Thus a sudden fall in sodium excretion is experienced on quiet standing, loss of blood, in a state of water depletion, on producing venous congestion in limbs, and shock.

Studied separately, these conditions can easily be reduced to a common denominator.

Salt deprivation leads to a serious disturbance of peripheral circulation, conspicuously resembling traumatic shock: decrease of circulating blood volume, cardiac output, and blood pressure, are seen [10].

Standing quiet brings the pumping action of the muscles in the lower extremities to a standstill whereas this is the main driving force behind reflux; a substantial amount of blood comes to be pooled in the legs diminishing the

circulation elsewhere; local venous pressure rises; the STARLING equilibrium is upset; and a proportion of the water in the plasma, large enough not to be neglected, is lost to the circulation in the subcutaneous tissue of the lower extremities. In final analysis, standing still amounts to a reduction in circulating blood almost as if blood had indeed been lost. In this, not the upright posture itself but the haemodynamic changes brought about by it, are of first importance; accumulated evidence shows that standing still in water fails to elicit a reduction in sodium excretion [11]. Severe water depletion likewise threatens to reduce the circulating blood volume. In experimentally produced congestion in the legs the haemodynamic sequelae are the same as those induced by standing still. Finally, shock means a loss of circulating blood.

Clearly, the conditions and states enumerated above would involve, but by all means threaten to involve, the organism in loss of circulating blood, decrease of the extracellular space and cardiac output, and lowering of pulse pressure, and thereby give rise to severe circulatory disturbances, and interfere with the blood supply and oxygenation of vital organs, including the central nervous system; — all this would be liable to occur were it not for the existence and timely operation of effective regulatory mechanisms.

These regulatory mechanisms induce sodium and water retention to make up for the shrinkage in the volume of circulating blood. Of the haemodynamic changes they produce, first importance attaches to the fact that renal blood flow is reduced and more blood is directed to areas of momentarily greater significance: the myocardium and the central nervous system.

In these processes the sympathatic system has a decisive role.

A reduction in renal blood flow is always associated with a fall in glomerular filtration rate. Therefore, if tubular sodium reabsorption remains unchanged, sodium retention will set in; a fall in glomerular filtration rate of 1 ml/min increases daily sodium retention by as much as 2 mEq. In such cases increased tonicity of the efferent arterioles is frequently recognized by a rise in the filtration fraction. VANDER [12] and BARGER [13] are right in stressing that this increases blood concentration during glomerular filtration so that blood of higher colloid osmotic pressure is supplied to the peritubular capillaries whereby tubular transport is accelerated, and thus sodium reabsorption is increased.

Recent investigations have indicated that the haemodynamic changes in the kidney start humoral processes in it, which too serve volume regulation.

An important intrinsic part of the regulatory mechanism here discussed is aldosterone. A fall in the volume of circulating blood has been shown to be followed in a matter of minutes by a strikingly rapid rise in the aldosterone concentration of the blood [14]; upon the effect of aldosterone the glands retain sodium. I have failed to find data on the question whether or not

increased secretion of the antinatriuretic aldosterone is concomitant to a decreased secretion of the natriuretic corticoid hormone, described recently [15].

Observations of GOWENLOCK et al. [11] convincingly illustrate the operation of this dual, humoral and haemodynamic, mechanism; in the standing position aldosterone secretion was found to increase, yet if in the recumbent position considerably more aldosterone was injected than had been produced during standing, the antinatriuresis that followed was much slighter, owing probably to the absence of the effect of the upright posture on renal haemodynamics and sodium excretion [16].

Controlling aldosterone secretion is still a moot problem. Most authors agree in that the prime mover is the volume of actually circulating blood, perhaps a decrease in extracellular fluid volume [17, 18, 19], respectively an imbalance between the capillary and the colloid osmotic pressures [20]. FARRELL et al. suggest on theoretical grounds [21, 22, 23, 24, 25] that in the angle formed by the common carotid and the thyroid artery as also in the right atrial wall there exist receptors which are sensitive to changes in tension. A fall in pulse pressure stimulates the receptors in the neck and thereby increases aldosterone secretion; a rise in pulse pressure intensifies the activity of the receptors in the atrial wall and this leads to a decrease in the secretion of the hormone.

GOORMAGHTIGH and ELANT [26] reported as early as 1929 that denervation of the carotid sinus resulted in hypertrophy of the zona glomerulosa. As is well known, this is the zone where aldosterone is formed, and its hypertrophy was demonstrated to follow experimentally induced mitral disease in the dog [27]. In the experiments of FARRELL et al. denervation of the "thyrocarotideal junction" failed to produce the increase in aldosterone production which characterizes hypovolaemia. According to these authors the peripheral receptors are governed by an integrating centre in the area of the pineal gland in the diencephalon. When they damaged this centre, aldosterone secretion decreased, but when they injected extracts prepared from this area, it increased. The substance responsible for this phenomenon has been named glomerulotrophin. Following denervation of the thyrocarotideal junction the level of aldosterone in adrenal venous blood started to rise within half an hour, and took from one to three weeks to return to normal. This finding favours the participation of some other mechanism in the control of aldosterone secretion [28]. So does the observation [29] that while in acute experiments there is decreased aldosterone secretion when the right atrial wall has been drawn tight by suture placed in it, in cardiac decompensation, where there is chronic tightening of the wall, the hormone is secreted at a higher than normal rate.

Though unable to confirm their experimental findings, DAVIS [30] agrees with FARRELL and BARTTER in that the stimulus to which the adrenal cortex

responds with aldosterone secretion is a decrease in the volume of circulating blood, and that the mechanism involved is humoral. He found that if the adrenal of a normal dog was perfused with blood from a donor dog suffering from chronic phlebohypertonic-oedematous-secondary hyperaldosteronism, the aldosterone concentration in adrenal venous blood rose substantially [31]. Other experiments of his showed that after blood loss or partial occlusion of the inferior vena cava, the characteristic increase in aldosterone secretion failed to present itself in the nephrectomized animal. Accordingly, he put forward the view that the hormone which stimulates aldosterone production (ASH), is formed in the kidney. DAVIS also demonstrated that intravenous infusion of an aqueous renal extract, renin or hypertensin, increased aldosterone secretion. In a variety of animal species, he showed that after the intake of some sodium-free food degranulation of the juxtaglomerular cells set in, and that on maintaining the salt-free diet for a time, cellular granulation gradually increased. His conclusion is that to salt deficiency, as a stimulus, the juxtaglomerular cells react in exactly the same manner as the secretory glands. The renin content of the kidney parallels these histological changes. DAVIS ascribes to renin a trophic effect on the zona glomerulosa.

ACTH appears to be a synergist in the mechanism which controls aldosterone secretion [32, 33, 34, 35].

It is a widely entertained assumption that in the central nervous system there is direct connection between the centres controlling aldosterone and antidiuretic hormone (ADH) secretion, further, that injuries suffered by either the hypothalamic centre to which the pineal body is subordinate, or the supraoptic and paraventricular nuclei, or finally the pathways connecting the two centres, may disturb the regulation of sodium and water excretion. Damage to the peripheral receptors of the reflex arcs naturally results in similar disturbances.

Further disturbances of sodium excretion have been described to occur in diseases of the central nervous system, as the centre, and in the mediastinum, as the supposed zone of the receptors [36, 37, 38, 39].

These findings throw light on correlations of quite peculiar interest. Let us start from an example. A substantial loss of blood is followed by a redistribution of the circulating blood — less of it flows through the skin and the kidney — and a fall in glomerular filtration rate accompanied by a decrease in sodium excretion which is produced "automatically" by intrarenal mechanisms. However, sodium excretion decreases after blood loss even if care has been taken in the experiment to ensure a constant perfusion pressure in the kidney and thereby a normal glomerular filtration rate [40]. A considerable fall in renal blood flow, renal ischaemia, starts renin formation which in turn results in the formation of hypertensin; at the same time, both renin and hypertensin stimulate the adrenal to secrete sodium-retaining aldosterone. It is in

this way that hypovolaemia, and perhaps also stimulation of the receptors in the thyrocarotideal junction, bring about aldosterone secretion; and that by the mechanism described by GAUER and HENRY [41], reduction of the tension of the left arterial wall, reflectorily intensifies antidiuretic hormone secretion; following a fall in capillary pressure the STARLING equilibrium shifts in favour of the forces that cause the fluid to be reabsorbed, whereupon fluid enters the vascular pathways from the interstitial space. By way of the thirst centre, the resulting cellular dehydration gives rise to the sensation of thirst. At the site of bleeding, serotonine is released, which enhances tubular sodium reabsorption [42].

BARGER [43] stresses that in the regulation processes at work in hypovolaemic conditions, decisive importance attaches to a fall in the activity of the carotid sinus, respectively to the pressoreceptor reflexes initiated by it. This is the way in which, for example, the frequency of the heart's action increases after blood loss. But it is equally certain that here, too, the chief organiser of regulation is the central nervous system; the centre of epinephrine secretion is supposed to be in the paraventricular nuclei, where the osmoreceptor centre is known to be.

The available blood volume replenished with sodium and water is switched to the vital organs at a rapid heart rate.

It needs to be mentioned that the organism is capable of effective volume regulation even without functioning adrenals. Obviously, no further evidence is required to prove that aldosterone cannot possibly be the only factor in volume control. ROSENBAUM et al. [44] found that in patients suffering from Addison's disease, with practically no adrenal function, maintained on cortisone or DCA, postural changes and also sodium chloride infusions induced, without any changes in the glomerular filtration rate, the same rises and falls in sodium excretion as in normal subjects. It would appear that the "permissive action" of cortisone is sufficient to provoke volume regulation, at least under acute experimental conditions.

In earlier experiments [45] we have shown that if in a pair of dogs crossed circulation is brought about by humorally isolating the acceptor's head from the trunk and perfusing it with the circulation of the donor, and if thereafter isolated cerebral hypoxia, whether arterial or stagnant, is produced in the acceptor, the renal blood flow in the latter decreases. In other experiments it has been found that under such conditions there occurs a fall in sodium excretion. This phenomenon is independent of both the carotid sinus and the adrenal; apparently, the impulses are carried by nerves from the central nervous system to the kidney.

In the hypovolaemic conditions here discussed a part is no doubt played by disturbances in the oxygenation of the central nervous system, and so the mechanism described by us is certain to participate in the volume regula-

tion phenomena, whether these are haemodynamic or antinatruretic in character.

I propose to deal briefly with another mechanism that controls sodium excretion; this reflex mechanism we have described in earlier work [48, 49, 50], but only in its aspect of raising sodium excretion.

Applying the crossed circulation method outlined above, we found that hyperosmotic sodium chloride solution injected into the cephalic circulation increased sodium excretion in the isolated trunk of the acceptor dog. Clearly, the impulses causing the increase travelled down nerve tracks into the trunk, directly to the adrenal; in adrenalectomized acceptor dogs the increase failed to occur. We do not yet know whether the increase was due to a decrease in aldosterone secretion or, possibly, to the secretion of some corticoid hormone of natruretic action.

Under the same experimental conditions it was possible to induce a similar rise in sodium excretion by the injection of an antidiuretic hormone preparation, instead of a hyperosmotic sodium chloride solution.

I trust, all these justify the conclusion that aldosterone is o n e of the factors which control sodium excretion and participate in volume regulation. Nevertheless, one more addition would improve the stock of evidence already discussed. According to current knowledge, sodium from the glomerular filtrate is reabsorbed in four different parts of the renal tubule:

1. From the filtered sodium 80 to 85 per cent is actively reabsorbed in the proximal tubules.

2. Reabsorption continues in the ascending leg of the loop of Henle, in the "countercurrent" system.

3. Thereafter, in the distal tubules during sodium-potassium exchange.

4. Lastly, in the collecting tubules in the course of ammonia-ion exchange.

As far as our present knowledge carries us, aldosterone can exert its effect only in the third of these four parts of the tubule.

The exclusive role played by aldosterone is contradicted by the fact that in healthy individuals prolonged administration of the drug fails to give rise to chronic sodium retention; nor is there retention in patients with aldosterone-secerning adrenal tumour. But in patients oedematous from some other cause, it is possible to induce progressive sodium retention by treating them with aldosterone [45].

The experimental results obtained by BARGER et al. [56] in the dog are of great significance in this connexion. Following unilateral infusion of aldosterone into the renal artery they studied the urine of each kidney separately, and found that on the side of the infusion there was increased potassium but unchanged sodium excretion. At the same time, in animals with artificially induced heart defect, a decrease in sodium excretion was observed on the side of the injection.

I have dwelt upon questions of theory in some detail, but I think it is well to have the fundamental considerations precede the problems, in which clinicians concern themselves more directly. In the following I propose to discuss oedema in cardiac decompensation and in the nephrotic and nephritic syndromes. A characteristic common to all three conditions is sodium retention. To begin with, I should like to point out that the former view, according to which the kidney in the oedematous organism fails to secrete sodium chloride because this is caught in the interstitial oedema fluid and simply does not reach the kidney, has become obsolete. In oedema the amount of glomerular filtrate and that of serum sodium are frequently normal, which means that salt is present in the kidney, and yet is not secreted. Obviously, what has changed, is renal function. The experiment of BARGER [57] has proved this; in the normal dog sodium infused into one renal artery, increased sodium excretion on that side; in the dog with cardiac failure, no such rise presented itself.

Concerning the cause of cardiac oedema, until some years ago the most widely accepted view had been that propounded by MERRILL [58], that the reduced glomerular filtration was alone responsible for reduced sodium excretion. To-day decreased glomerular filtration is no longer thought to be the only factor in play; a place is assigned to increased tubular reabsorption in the mechanism of cardiac oedema. However, MERRILL's report contains a statement which is still unchallenged and has suggested further work for other investigators; it is an account of the haemodynamic changes of importance in the pathophysiology of cardiac oedema so very precise as to merit verbatim quotation, at least in part:

". . . These patients tended to have an inadequate cardiac output by the catheter method utilizing the direct Fick principle, and a low renal blood flow by the para-amino hippurate method . . . The renal blood flow was reduced to about one-fifth normal, when the cardiac output was approximately half normal, indicating a specific diversion of blood away from the kidney. It is suggested that a similar shunting of blood from the kidneys may be important in those patients who have a normal renal blood flow and normal cardiac output at rest, but who develop evidence of heart failure and edema on exertion. When the cardiac output becomes inadequate to meet the demands of exercise blood may be diverted from the kidneys to other parts of the body whose metabolic needs are greater."

This statement served as the starting point for the recent studies concerned with the part played by the sympathetic nervous system in the formation of cardiac oedema. BROD [59] showed that in heart failure infusion of the sympatho-adrenalytic agent, dibenzylamine, increased renal blood flow and sodium excretion. BARGER et al. [43] demonstrated that in dogs with valvular defect, dibenzylene injected into the renal artery on one side produced increases in sodium excretion and renal blood flow on the same side.

This conception of cardiac oedema formation is in essence identical with that commonly referred to as forward failure, in distinction from backward failure which regards generalized phlebohypertony as the decisive link in the chain of oedema causation, and incriminates the rise of capillary pressure consequent upon the increased venous pressure, the upsetting of the STARLING balance, and predomination of forces which press the fluid from the blood vessels towards the interstitial space. The backward failure conception, generally credited to STARLING, has been disputed by several authors on the alleged ground that it is one-sided. In fact it is beyond any doubt that the two basic mechanisms, backward failure and forward failure, act in combination, and I cannot help feeling that whoever impute lopsided hypothesizing to STARLING have never worked themselves through his fundamental work and contest the issue on the basis of passages cited, torn from their contexts. To illustrate my point I quote a few original lines of STARLING and add his own list of the factors concerned in the production of oedema:

"... probably under no circumstances can dropsy be ascribed to an abnormal change in one only of these processes ... In nearly all cases the dropsy is due to the simultaneous alteration of two or more of these factors ...."

Table of causative factors in oedema

I

Increased transudation

A) Increased capillary pressure.
B) Increased capillary permeability.
C) Hydraemia.
D) Increased molecular concentration in tissues.

II

Diminished absorption

A) By lymphatics.
  a) Paralysis of limbs.
  b) Obstruction of lymph trunks.
B) By veins.

This cannot of course be an up-to-date list of the main causal factors, but it is still substantially valid and by no means one-sided.

In what way is aldosterone concerned in the production of cardiac oedema? The views voiced in the literature on this point vary widely. According to BARGER [27], the exact role of this hormone in the fluid retention of congestive heart failure *remains to be determined.* Neither congestive heart failure in the human, nor in the experimental animal is always accompanied by high rates of aldosterone excretion.

That aldosterone is not the chief factor in producing sodium retention in cardiac oedema seems to be clear from the observation that aldosterone antagonists are inhibiting the effect of aldosterone in the renal tubules; their natruretic effect is insignificant [63, 64].

I have already dealt with BARTTER's theory of aldosterone secretion. HEGGLIN et al. [65] have shown that in heart failure acute haemodynamic alterations influence aldosterone excretion in a way congruent with that theory, but that under chronic conditions no permanent correlation is demonstrable between haemodynamic alterations and changes in aldosterone excretion.

The part played by aldosterone is difficult to estimate, for the hormone may be excreted at an increased rate without an increase in its adrenal secretion. The explanation is the congestive liver's reduced ability to decompose aldosterone [66, 67].

The findings of BUCHBORN et al. [68] are of extreme importance. In a large number of cardiac patients, with and without decompensation, these authors studied the glomerular filtration rate and the urinary aldosterone and sodium contents, to establish correlations between their respective values. They found a close and statistically very significant negative correlation between sodium and aldosterone secretion; upon the action of aldosterone the effect of increased tubular sodium reabsorption adds itself to the antinatruretic effect of reduced glomerular filtration. According to their calculations, reduced glomerular filtration accounts for about 15 per cent, and increased aldosterone activity for from 63 to 75 per cent, of sodium retention. In evaluating these results one must of course take into consideration the complicative factor of aldosterone inactivation. In cardiac decompensation also, water retention is followed by sodium retention. Increased antidiuretic hormone secretion might be a factor concerned in water retention [47].

In our opinion disturbed oxygenation is in a large measure responsible for the general and renal haemodynamic phenomena and for those observable in sodium and water secretion. As our investigations on this point have been reported currently, and as our theory based has been published in a monograph [47], it will suffice to formulate the major results as follows.

1. The function of the circulation is to maintain oxygen supply at the optimal level.

2. In heart failure the circulation is unable to perform this function; the increased arterio-venous oxygen difference shows that oxygen supply to the tissues is unsatisfactory.

3. Experimental arterial hypoxia causing discomfort in healthy individuals exerts an antidiuretic and antinatruretic effect [47, 69].

4. In cardiac decompensation oxygen inhalation frequently improves renal blood flow and the resulting diuresis leads to increased sodium excretion [70]. The results of our pertaining investigations which are not

without antecedents [71, 72, 73, 74], have been fully confirmed by KLÜTSCH et al. [75].

5. In heart failure oxygen inhalation raises cardiac output [76, 77] and reduces venous pressure and tonicity [75, 78, 79].

As regards the receptor area sensitive to hypoxia, I would summarize the situation as follows.

1. As already mentioned, in our crossed circulation experiments isolated hypoxia of the central nervous system was found to have altered renal haemodynamics and function so as to be identical with those seen in cardiac decompensation.

2. Under conditions as above, venous pressure and tonicity are increasing [80].

3. Histological changes characteristic of hypoxia have been found in the brain of patients who had died from heart failure [81].

4. Hypoxia together with antidiuresis induces electroencephalographic lesions [82].

On these ground it seems justified to postulate that the seat of the hypoxia-sensitive volume-regulating centre is in the central nervous system.

Observations of BARNES and SCHOTTSTAEDT [83] throw an interesting light on the role of the central nervous system in the volume regulation of patients suffering from heart failure; a sense of depression or of despair reduces sodium and water secretion, sudden agitation of mind raises sodium excretion, and wholesome stimulating recreation brings about an increased excretion of both sodium and water.

The part played by the lymphatic system in the mechanism of cardiac oedema I will discuss but briefly. STARLING [60] stated as far back as 1909: "In heart disease a fact is present which is not operative in simple venous obstruction, namely a hindrance to the outflow by the lymphatics in consequence of the rise of pressure and stagnation of the blood in the superior vena cava near the heart." In 1951, we provided experimental evidence for the truth of this statement [84].

KATZ [85] and KATZ and COCKETT [86] tackled the problem of the lymphatic system's participation in the genesis of cardiac oedema by a new line of approach. They departed from the well-established fact that an acute rise of pressure in the inferior vena cava substantially increases the lymph flow from the exposed and cannulated thoracic duct, and at the same time reduces diuresis and sodium excretion. They found that the increase in lymph flow failed to present itself in nephrectomized animals. From this they inferred that the increase in lymph flow was of renal origin. In their view, the large quantities of water and sodium flowing back into the circulation through the thoracic duct explain the sodium and water retention in congestive heart failure.

In our opinion this view is fundamentally erroneous. The increase in lymph flow due to a pressure rise in the inferior vena cava derives from the liver, as was postulated by STARLING [60]; we ourselves have established that, contradictory to the finding of KATZ and COCKETT, preceding nephrectomy does not suppress the increase in lymph flow following an increase of pressure in the inferior vena cava [87]. The fact just mentioned, namely that in congestive heart failure lymph is prevented from flowing into the venous system, is another reason why KATZ and COCKETT's conception must be rejected.

Although problems of therapy are beyond the scope of this paper, I should like to mention the theoretically interesting recent finding that digitalis antagonizes the effect of aldosterone in that it inhibits the renal action of the hormone [88, 89]. A similar effect is exerted by heparin [10, 91].

Finally, some words should be included concerning those forms of oedema developing in acute diffuse glomerular nephritis which are not due to associated cardiac decompensation.

It is generally known that in acute diffuse glomerulonephritis generalized oedema may appear within a matter of hours. This is incontestable evidence showing that in acute glomerulonephritis renal salt and water retention cannot possibly be the principal cause of oedema, but that it is of extra-renal origin. Current knowledge has substantiated the claim of those authors (VOLHARD, NONNENBRUCH, KROGH, KYLIN, EPPINGER) who have since long maintained that increased capillary permeability was the decisive factor in acute diffuse glomerulonephritic oedema. SARRE [95], using LANDIS' method, demonstrated the increase in capillary permeability.

With the capillary permeability increased, protein-rich fluid streams forth from the vascular bed into the interstitial space. A sudden decrease of circulating plasma volume, for which to some extent urinary loss of protein is also responsible, leads to sodium and water retention by way of the regulatory mechanisms described earlier.

In the nephrotic syndrome the pathological process begins with increased glomerular capillary permeability. The result is proteinuria, and this gives rise to hypoproteinaemia and dysproteinaemia, which then produce a reduction in the colloid-osmotic pressure of the plasma proteins. The STARLING balance is upset, and the water of the plasma is lost into the interstitial space, thus a decrease of circulating plasma volume results.

At the beginning of this report it has been pointed out that the decrease in circulating plasma volume leads to increased aldosterone secretion. The nephrotic syndrome is the form of hyperaldosteronism, in which aldosterone secretion is the highest. According to GAUER [92], hypovolaemia stimulates also ADH secretion and water retention. Accordingly, in the nephrotic syndrome renal salt and water retention are essentially produced secondarily, as the results of aldosterone and ADH secretion. In this disease the lymphatic system trans-

ports oedema fluid from the interstitial space at its full capacity [84], whereby a pathological state of equilibrium is produced, and if this is upset, for instance by a substantial draining of oedema fluid, the result may be circulatory insufficiency and impaired renal function.

I have come to the end of my report. I feel I cannot abuse your patience to the extent of summarizing the data I have mentioned. Instead, I would finish by saying that although a wealth of knowledge has been acquired in the last years, we have not yet arrived at the stage of an ultimate synthesis of the physiology and pathology of volume regulation.

REFERENCES

1. Rusznyák, I.: Plasmaeiweisse und Ödem. In: Bernhold H., Kylin, V., Rusznyák, F.: Die Eiweisskörper des Blutplasmas. Steinkopff, Dresden, 1938.
2. Deming, A. B., Luetscher, J. A.: Proc. Soc. exp. Biol. (N. Y.) **73,** 171 (1950).
3. Neher, R., Wettstein, A.: Acta endocr. **18,** 386 (1955).
4. Reidenberg, N. M.: Arch. intern. Med. **107,** 578 (1961).
5. Verney, E. B.: Proc. roy. Soc. B. **135,** 25 (1947).
6. Andersson, B.: Acta physiol. scand. **28,** 188 (1953).
7. Andersson, B., McCann, S. M.: Acta physiol. scand. **33,** 333 (1955).
8. Andersson, B., McCann, S. M.: Acta physiol. scand. **35,** 191 (1955).
9. Andersson, B., Larsson, S.: Pharmacol. Rev. **13,** 1 (1961).
10. Elkinton, J. R., Danowski, T. S., Winkler, A. W.: J. clin. Invest. **25,** 120 (1946).
11. Gowenlock, A. H., Mills, J. N., Thomas, S.: J. Physiol. (Lond.) **146,** 133 (1959).
12. Vander, A. J., Malvin, R. L., Wilde, W. S., Sullivan, L. P.: Amer. J. Med. **25,** 497 (1958).
13. Barger, A. C.: Circulation **21,** 124 (1960).
14. Bojesen, E., Degn, H.: Nature (Lond.) **190,** 352 (1961).
15. Neher, R., Meystre, Ch., Wettstein, A.: Helv. chim. Acta **42,** 132 (1959).
16. Smith, H. W.: The Kidney. Oxford Univ. Press, New York 1951. pp. 432—435.
17. Bartter, F. C.: Metabolism **5,** 369 (1956).
18. Bartter, F. C.: Scand. J. clin. Lab. Invest. **10,** Suppl. **31,** 50 (1958).
19. Bartter, F. C., Biglieri, E. G., Pronove, R., Delea, C. S.: International Symposion on Aldosterone. Churchill, London 1958.
20. Davis, J. O., Ball, W. C.: Amer. J. Physiol. **192,** 538 (1958).
21. Gann, D. S., Mills, J. N., Bartter, F. C.: Fed. Proc. **19,** 605 (1960).
22. Bartter, F. C., Mills, J. N., Gann, D. S.: J. clin. Invest. **39,** 1330 (1960).
23. Bartter, F. C.: Recent Progr. Hormone Res. **15,** 306 (1959).
24. Anderson, C. H., McCally, M., Farrell, G. L.: Endocrinology **64,** 202 (1959).
25. Mill, J. N., Casper, A. G. T., Bartter, F. C.: Science **128,** 1140 (1958).
26. Goormaghtigh, N., Elant, L.: C. R. Soc. Biol. (Paris) **101,** 501 (1929).
27. Barger, A. C.: Circulation **21,** 124 (1960).
28. Gann, D. S., Bartter, F. C.: Amer. J. Physiol. **199,** 193 (1960).
29. McCally, M., Farrell, G. L.: Endocrinology **64,** 202 (1959).
30. Davis, J. O.: Amer. J. Med. **29,** 486 (1960).
31. Yankopoulos, N. A., Davis, J. O., Kliman, B., Peterson, R. E.: J. clin. Invest. **38,** 1278 (1959).
32. Bartter, F. C., Mills, J. N., Biglieri, E. G., Delea, C. S.: Recent Progr. Hormone Res. **15,** 311 (1959).
33. Singer, B., Stock-Dunne, M. P.: J. Endocr. **12,** 130 (1955).
34. Farrell, G. L., Fleming, R. B., Rauschkolb, E. W., Yatsu, McCally, M., Anderson, C. H.: Endocrinology, **62,** 506 (1958).
35. Davis, J. O., Bahn, R. C., Yankopoulos, N. A., Kliman, B., Peterson, R. E.: Amer. J. Physiol. **197,** 380 (1959).
36. Cort, J. H.: Lancet 1, 752 (1954).

37. SCHWARTZ, W. B., TASSEL, D., BARTTER, F. C.: New Engl. J. Med. **262,** 743 (1960).
38. SCHWARTZ, W. B., BENNETT, W., CURELOP, S., BARTTER, F. C.: Amer. J. Med. **23,** 529 (1957).
39. ROBERTS, H. J.: Ann. intern. Med. **51,** 1420 (1959).
40. GOODYER, A. V. N., MATTIE, L. R., CHETRICK, A.: Proc. Soc. exp. Biol. (N. Y.) **97,** 422 (1958).
41. GAUER, O. H., HENRY, J. P.: Klin. Wschr. **34,** 356 (1956).
42. LITTLE, J. M., ANGELL, E. A., HUFFMAN, W., BROOKS, E.: J. Pharmacol. exp. Ther. **131,** 1 (1961).
43. BARGER, A. C., MULDOWNEY, F. P., LIEBOWITZ, M. R.: Circulation **20,** 273 (1959).
44. ROSENBAUM, J. D., PAPPER, S., ASHLEY, M. M.: J. clin. Endocr. **15,** 1459 (1955).
45. GÖMÖRI, P., KOVÁCH, A., TAKÁCS, L., FÖLDI, M., SZABÓ, GY., NAGY, Z., WILTNER, W.: Magy. belorv. Arch. **7,** 129 (1954).
46. FÖLDI, M., KOVÁCH, A., TAKÁCS, L., KOLTAY, E.: Acta med. Acad. Sci. hung. **7,** 19 (1955).
47. FÖLDI, M., SZABÓ, GY.: Die Regulation der Natrium- und Wasserausscheidung. Akadémiai Kiadó, Budapest 1959.
48. FÖLDI, M., KOVÁCH, A., PAPP, M., KOLTAY, E.: Z. ges. exp. Med. **129,** 15 (1957).
49. KOVÁCH, A., FÖLDI, M., PAPP, M., ROHEIM, P., KOLTAY, E.: Lancet 1, 338 (1959).
50. FÖLDI, M., KOVÁCH, A., PAPP, M., KOLTAY, E., SOMLYAI, L.: Acta physiol. Acad. Sci. hung. **17,** 407 (1960).
51. WINDHAGER, E. E., WHITTEMBURY, G., OKEN, D. E., SCHATZMANN, H. J., SOLOMON, A. K.: Amer. J. Physiol. **197,** 313 (1959).
52. GOTTSCHALK, C. W., MYLLIE, M.: Amer. J. Physiol. **196,** 927 (1959).
53. BERLINER, R. W., KENNEDY, J. J., ORLOFF, J.: Amer. J. Med. **11,** 274 (1951).
54. ALBRICH, K. J.: Circulation **21,** 869 (1960).
55. NELSON, D. H., AUGUST, J. T.: Lancet 2, 883 (1959).
56. BARGER, A. C., BERLIN, R. D., TULENKO, J. F.: Endocrinology **62,** 804 (1958).
57. BARGER, A. C.: Metabolism **5,** 480 (1956).
58. MERRILL, A. I.: J. clin. Invest. **25,** 389 (1945).
59. BROD, J., FEJFAR, Z.: Schweiz. med. Wschr. **85,** 1 (1955).
60. STARLING, E. H.: The Fluids of the Body. Constable, London 1909.
61. MULLER, A. F., RIONDEL, A. M., MANNING, E., MACH, R. S.: Schweiz. med. Wschr. **86,** 1335 (1956).
62. DRISCOL, T. E., MAULTSBY, M. M., FARRELL, G. L., BERNE, R. M.: Amer. J. Physiol. **191,** 140 (1957)
63. EDMONDS C. I.: Lancet. 1, 509 (1960).
64. THOMAS, J. P., BARTTER, F. C.: cit. Lancet 1, 209 (1961).
65. SIEGENTHALER, W., TRUNIGER, B., RUTISHAUSER, W., W., LÜTHY, E., HEGGLIN, R.: Schweiz. med. Wschr. **91,** 259 (1961).
66. CHART, J. J., GORDON, E. S., HELMER, P., LE SHER, M.: J. clin. Invest. **35,** 254 (1956).
67. YATES, J. E., URGUHART, J., HERBST, A. L.: Amer. J. Physiol. **194,** 65 (1958).
68. BUCHBORN, E., KOCZOREK, KH. R., WOLF, H. P.: Klin. Wschr. **37,** 71 (1959).
69. ULLMANN, E.: J. Physiol. (Lond.) **155,** 417 (1961).
70. FÖLDI, M., SOLTI, E., KOLTAY, E., MEGYESI, K., RÉV, GY., SZÁSZ, J.: Klin. Wschr. **34,** 857 (1956).
71. KORÁNYI, S.: A vesebajok functionális pathologiája és therápiája klinikai előadásokban. M. Orvosi Könyvkiadó Társulat, Budapest 1930.
72. BEDDOES: 1800, cit. BARACH, A. L.: Bull. St. Francis Hosp. (Roslyn) **9,** 1 (1952).
73. BARACH, A. L.: cit. (72).
74. BASCHIREI, L., GRASSI, B., MAZZUCHI, G. F., GUIDI, P. L.: Folia cardiol. (Milano) **14,** 201 (1955).
75. KLÜTSCH, K., HEIDLAND, A., SCHNEIDER, K. W.: Klin. Wschr. **38,** 842 (1960).
76. FEJFAR, Z.: Acta cardiol. (Brux.) **12,** 13 (1957).
77. FEJFAR, Z.: Ciba Foundation Colloquia on Ageing. Vol. 4. Churchill, London 1958.
78. FÖLDI, M., SOLTI, F., RÉV, GY., RÉFI, Z.: Acta med. scand. **158,** 249 (1957).
79. LINHART, J., PREROVSKY, I.: Cardiologia (Basel) **38,** 21 (1961).
80. FÖLDI, M., SOLTI, F.: Acta med. Acad. Sci. hung. **10,** 49 (1956).
81. ERBSLÖH, F.: (1958) cit. Kongr.-Zbl. ges. inn. Med. **195,** 20 (1959).
82. SAWYER, C. H., FULLER, G. R.: Electroenceph. clin. Neurophysiol. **12,** 83 (1960).
83. BARNES, R., SCHOTTSTAEDT, W.: Amer. J. Med. **29,** 217 (1960).
84. FÖLDI, M., RUSZNYÁK, I., SZABÓ, GY.: Magy. belorv. Arch. **4,** 166 (1951).
85. KATZ, Y. J.: Circulat. Res. **6,** 452 (1958).
86. KATZ, Y. J., COCKETT, A. T. K.: Circulat. Res. **7,** 118 (1960).

87. Földi, M., Papp, M.: In press.
88. D'Amico, G., Gesana, A.: Experientia (Basel) **17,** 112 (1961).
89. Kupfer, S., Kosovsky, J. D.: Amer. Heart J. **61,** 284 (1961).
90. Schlatmann, R. J. A. F. M., Prenen, H., Jansen, A. P., Majoor, C. L. H.: Lancet **1,** 314 (1960).
91. Cejka, V., de Vries, L. A., Smorenberg-Schoorl, M. E., van Daatselaar, J. J., Borst, J. GG., Majoor, C. L. H.: Lancet **1,** 317 (1960).
92. Gauer, O. H.: cit. Sarre, H.: Med. Klin. **56,** 594 (1961).
93. Földi, M., Rusznyák, I., Szabó, Gy.: Magy. belorv. Arch. **4,** 161 (1951).
94. Smith, E. B.: Lancet **1,** 799 (1960).
95. Sarre, H.: Med. Klin. **56,** 594 (1961).

Prof. Dr. Mihály Földi, II. Department of Medicine, Szeged, Hungary.

PAEDIATRIC ASPECTS OF RENAL DISEASES

By

E. KERPEL-FRONIUS

DEPARTMENT OF PAEDIATRICS, UNIVERSITY MEDICAL SCHOOL, PÉCS

The principal peculiarities of renal pathology in childhood are seen in the following facts.

1. Renal performance is poorest in young infancy.

2. Malformations occupy an important position in the clinical material.

3. The clinical aspects of the classical renal diseases, diffuse glomerulonephritis and nephrosis, have many age-bound features.

4. The aetiological distribution of primary diseases leading to renal failure differs from that seen in adults. Chronic renal diseases slow down development and growth. Renal dwarfism and rickets are common occurences.

These age-bound peculiarities are dicussed in brief as follows.

1. Clinical sequelae to the limitations of renal function in infants

In Fig. 1. is shown the "schedule of maturation" of certain renal performances.

In the newborn the ability to excrete a water load is limited, he excretes merely 10 per cent of the same volume of water per kilogram body weight, as the adult. The GFR, too, is low and the concentrating capacity is half of that of the adult. These functions do not mature at the same rate: water excretion reaches the adult level at the age of one month, the concentrating capacity at 3 months and the GFR at 1 year of age.

Likewise, the young infant's capacity to excrete electrolytes and H^+ ions may be limited.

The infant is furthermore handicapped by the fact that in terms of kilogram of body weight oxygen consumption, insensible perspiration and the cardiac output per minute are about twice greater than in the adult, whereas water content and plasma volume per kilogram of body weight are about the same. Thus, in water deprivation the water stores are depleted twice as fast as in the adult and circulatory disturbances develop easily. This rapidly decreases the clearances, which are already small under physiologic conditions.

Owing to the fragility of homeostasis in young infants extrarenal renal

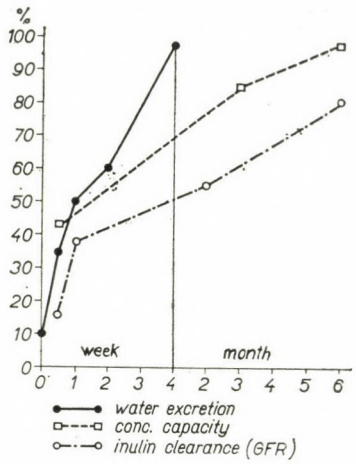


Fig. 1

insufficiency, azotaemia, hypo- and hypernatraemia, hyperpotassaemia, oedema, water intoxication, dehydration, acidosis may occur with great rapidity.

2. Malformations

The incidence of malformations is by necessity higher in children than in adults as some of these patients do not reach adulthood.

Malformations of the urinary tract play an important role. Urine flow may be obstructed at any place from the renal pelvis to the urethra and most of these may sooner or later cause uraemia, with or without infection.

There are *hypoplastic* and *polycystic* kidneys; in such cases a discrepancy arises between the functioning renal parenchyma, which is lagging behind in development, and the body mass which continues to grow, and this leads ultimately to renal failure, as growth continues.

Besides these gross malformations we are learning more and more about the *congenital, mostly hereditary functional defects of the kidneys.*

These give rise to different syndromes, depending on which function of the tubule is affected by the inborn defect. The reabsorption of water, phosphate or some amino acids may be defective, or the acidifying processes may be affected. These defects may occur alone or in combinations, which greatly increases the number of "syndromes" we may encounter.

Such diseases are rather uncommon, but have a great scientific interest because in connexion with them many genetical, pathophysiological and diagnostic problems come to light. Some are dangerous to life, others interfere with development, growth, cause D-refractory rickets, dwarfism, and some also mental retardation.

3. Classical renal diseases

The *nephrotic syndrome* is one of the less common renal diseases; about seven times as many cases of nephritis as of nephrosis are admitted to our department. Here we are going to discuss exclusively the prognostic problem. The typical cause of death today is renal failure, because since the advent of antibiotics the course of the disease has become so protracted that there is mostly time for glomerular insufficiency to develop. For this reason prognosis is based on the results of serial clearance studies, continued eventually for years.

On the basis of nearly 800 cases RILEY has found that at least 48 months after the onset of nephrosis, without steroid treatment, mortality rate was 38.7 per cent, whilst in the steroid-treated group it was 23.1 per cent. In our own, 10-year material at least 24 months after the onset of the disease, the mortality rate was 15.2 per cent. This number will, of course, increase. Death due to renal insufficiency ensued in one of our observations 9 years after the onset of the disease. Although definitive evaluation will have to wait for several years, yet we think that protracted hormone treatment not only makes life bearable for the patient by ensuring long periods of freedom from oedema, but also prolongs life, lowers mortality-rate and increases the incidence of complete recovery from the disease.

I should like to mention yet another curious fact. According to the data compiled by CSORDÁS, of the 46 patients with nephrosis treated in our department 13 were gypsies. This, as related to the percentage of the gypsy population, means that the incidence of nephrosis is about 10 times higher among gypsies. Similar observations may serve as the starting point in the elucidation of aetiological problems.

Of the clinical aspects of *diffuse glomerulonephritis* only two problems, aetiology and prognosis, will be dealt with here. The high incidence of impetigo nephritis is age-bound, it practically occurs only in young children. The disappearance of scarlet fever nephritis is a remarkable fact: While prior to the extensive use of penicillin 24 per cent of our cases of nephritis had been due to scarlet fever, not a single case of nephritis occurred among our 2300 cases treated with penicillin. Counting with a minimal incidence rate of 1.5 to 2 per cent in our 12-year material, we ought to have encountered at least 35 to 45 cases of nephritis. These observations make it likely that the development of nephritis can be prevented in the overwhelming majority of the cases, if the initial streptococcal infection is treated early with penicillin.

In the child nephritis is a benign disease. Although in textbooks the incidence of fatal outcome, obviously on the basis of earlier data, is estimated at 2 to 5 per cent, we have lost of our own 444 cases during the acute phase only 2, one having died of heart failure, the other of renal failure associated with Schönlein—Henoch's purpura.

In childhood, acute nephritis seldom turns chronic; the incidence of such cases is estimated at 1 to 2 per cent in the text books.

4. Symptomps and signs of renal failure in childhood

In post-mortem material GAUTIER has found the aetiological distribution of cases of acute renal failure based on "organic" lesions as follows.

Table 1

Causes of acute renal failure in 71 cases

Acute cortical necrosis	41 cases
Acute tubular necrosis	14 cases
Acute glomerulonephritis	4 cases
Thrombosis of renal blood vessels	8 cases
Other causes	4 cases

It is remarkable how infrequently acute glomerulonephritis, and how frequently renal necrosis led to fatal renal failure. A different picture would

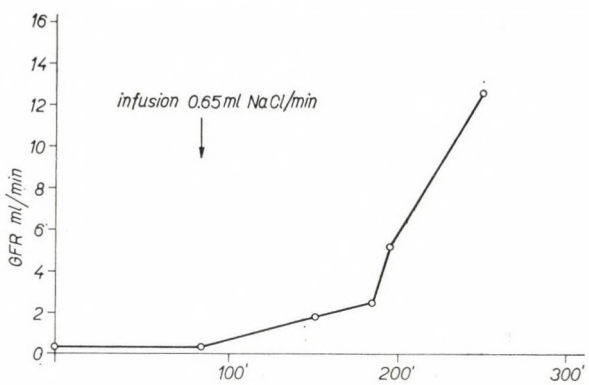


Fig. 2

result if the frequency distribution of recovered patients would be studied. Glomerulonephritis would be in the leading position, because in about 5 per cent of the cases we find NPN values over 100 mg per 100 ml, with severe oliguria. However, renal insufficiency responds to conservative treatment and fatal outcome is rare, and even those are due to heart failure or eclampsia mostly. For this reason it is rarely justified to indicate artificial kidney treatment for the relief of anuria due to acute nephritis of the child. The situation is different in the case of cortical and tubular necrosis. According to the data published by GAUTIER, during the first year of life only 4 of 48 cases survived, and over one year of age the mortality-rate still was as high as 50 per cent.

Some patients die of true uraemia, in other cases the direct cause of death is an often iatrogenic disturbance of electrolyte metabolism.

Functional renal failure due to dehydration is treated successfully by rehydration. In most cases, following routine treatment of dehydration with glucose-saline solution, diuresis and clearance values increase rapidly. This is illustrated by Fig. 2 originally published by CALCAGNO.

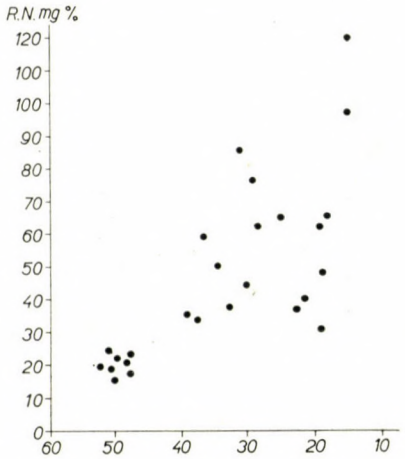


Fig. 3

If in spite of rehydration NPN continues to increase and bicarbonate to decrease, it can be surmised that renal insufficiency is maintained by rapidly developing structural alterations. In exceptional cases oliguria or anuria ensues and the retention of the hypotonic solution (half saline half glucose) administered leads to water intoxication and hyponatraemia.

Owing to the frequency of diarrhoea, and on the other hand, to age-bound limitations of renal function, the incidence of functional renal failure is highest during infancy.

An important question is that of the role acute functional renal failure in the fatal outcome of severe dehydration. The answer is difficult, because the picture is complex, several serious physiological alterations being present simultaneously. According to our observations the severity of stagnant cerebral hypoxia, due to rapidly developing shock, is most often the decisive prognostic factor. NPN values, although mostly higher, certainly reflect the severity of shock and anoxia, they, however, reach "uraemic" levels only in the exceptional cases in which severe renal structural damage develop.

Although we think that true uraemia is only exceptionally among the immediate causes of death in infantile dehydration, according to Fig. 4,

showing the correlation between some humoral changes and prognosis in our material, decreased renal performance still plays a certain role in mortality rate.

Large deviations in any of the factors studied: acidosis, natraemia potassaemia, or anoxia aggravate prognosis.

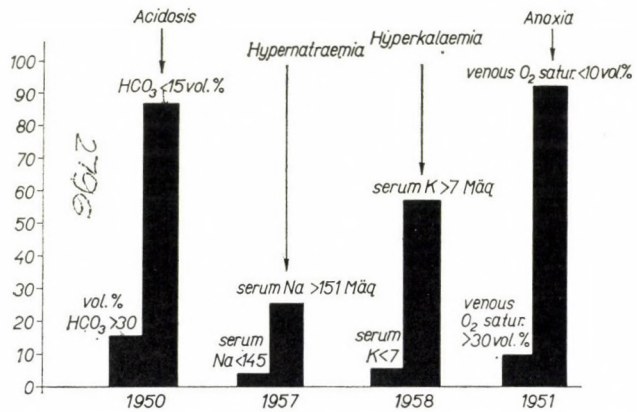


Fig. 4

In the genesis of the first three alterations renal insufficiency, too, has a part to play. Even if uraemic death is exceptional, the severity and duration of renal insufficiency, besides anoxia, is undoubtedly one of the determinants of prognosis.

The commonest causes of *chronic renal failure* in childhood are malformations, nephrosis, pyelonephritis, nephrocalcinosis. Acute nephritis, however, is rarely followed by chronic nephritis and diabetic nephrosclerosis mostly manifests itself only after childhood.

The child suffering from chronic renal insufficiency is remarkably free from complaints even in the azotaemic phase and the result of routine urine analysis may be negative. Therefore the correct diagnosis, missed by the practitioner, is often established late in the uraemic phase when the child is admitted to the hospital because of "retarded growth", "anaemia" or rickets. Detailed studies of renal function, performed late, mostly reveal only the hopelessness of the situation.

Prof. Edmund KERPEL-FRONIUS, Department of Pediatrics University of Pécs, Hungary.

NEUROLOGICAL ASPECTS OF RENAL DISEASES

By

B. HORÁNYI

NEUROLOGICAL CLINIC, MEDICAL UNIVERSITY, BUDAPEST

The nervous symptoms occurring in connexion with severe functional changes in renal activity may be summed up in three syndromes.

1. *The nervous system syndrome*, which develops in conjunction with *true uraemia* due to renal failure, is characterized by headache, deterioration of intellectual functions, disturbances of consciousness, eventually associated with a peculiar kind of psychomotor agitation, myoclonus of usually medium amplitude occurring in a haphazard way, spastically exaggerated autoreflexes, pyramidal symptoms, positional and postural reflexes, etc. The clinical picture of true uraemia is composed, of course, not only of the nervous syndrome outlined.

2. *Eclamptic pseudouraemia*, or *acute pseudouraemia* (VOLHARD). The pathological basis of this syndrome is formed by the interaction of at least two pathological events, viz. a rapid increase of intracranial pressure, on the one hand, and acute disturbances in cerebral circulation (thrombus formation, haemorrhages, severe haemodynamical changes), on the other. Correspondingly, the clinical picture, too, will be composed of symptoms due to increased intracranial pressure (headache, vomiting, bradycardia, generalized epileptic convulsions), on the one hand, and, on the other, of the focal symptoms that can be traced back to circumscribed nervous lesions resulting from the impairment of circulation, e.g. palsies, hemianopsia, disturbances of speech, etc. Neither the increase of intracranial pressure, nor the impairment of circulation is in direct pathogenetical correlation with renal failure, and for this reason the term pseudouraemia is misleading. The term eclampsia is seldom used in neurology (instead, generalized convulsions are spoken of), and it does not apply to the condition, because severe, or even fatal acute pseudouraemia may exist without epileptic convulsive manifestations. Therefore both names ought to the eliminated from the medical language, their use being not recommendable from the didactic point of view, either. Instead, we might use the term *acute nephrogenic cerebral syndrome*, because this implies nothing from the pathogenetical point of view and includes every possible variation of the clinical picture.

3. *Chronic pseudouraemia*, i.e. the cerebral changes induced by hypertension due to nephrosclerosis. This entity is identical with the hypertensive encephalopathy occurring in hypertensive vascular disease, it may differ from the latter only in that the vascular changes are more severe. According to those said before we might call this syndrome *nephrogenic hypertensive encephalopathy*. The widely used term *angiospastic encephalopathy* is incorrect, because, as it will be seen later, the cerebral blood vessels are unable to become spastic

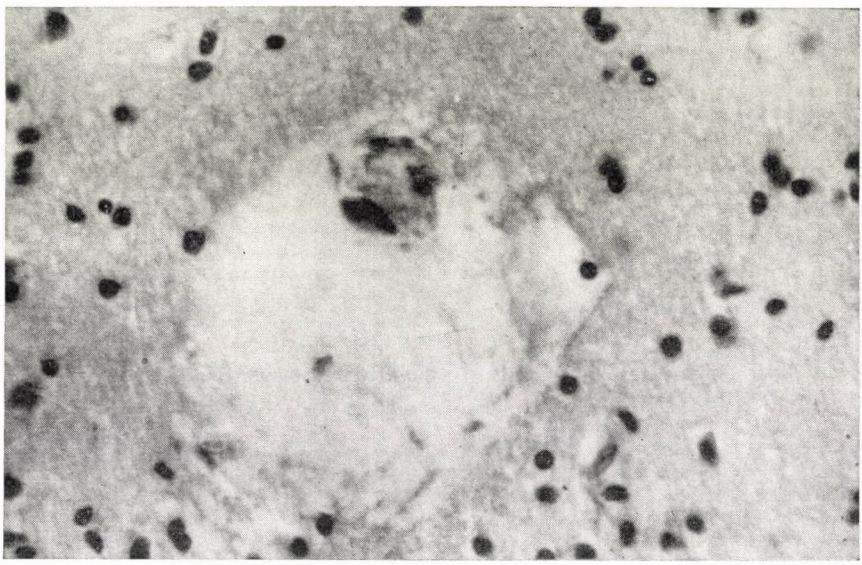


Fig. 1. Extensive oedema around a capillary. Nissl's stain

because of the vascular changes forming the basis of the syndrome. The histological changes on which the syndrome is based are not angiospasms, but thrombotic and haemorrhagic vascular lesions.

The clinical symptoms produced by the nephrogenic nervous complications mentioned are well-known; much less is known, however, about their pathogenesis. For this reason we are going to deal in the first place with the histological substrates of these nephrogenic nervous entities, striving in this way to facilitate a better understanding of the development of these symptoms. The answers to the questions that emerge in this connexion have been sought by analyzing the histological changes found in 30 cases showing nephrogenic nervous complications, as well as the pertaining data in the literature.

I. The commonest changes found in the nervous system were in the capillaries and precapillaries. The endothelial cells were swollen, or, on the contrary, shrunk, staining intensely; staining by fat dyes often revealed in them the presence of lipid substances. In some areas the endothelial cells were

increased in number. The basal capillary membrane was often broken away from the endothelial layer. In many areas around the capillaries homogeneous masses staining with eosin with variable intensity, showing often metachromasia with NISSL's stain, containing often erythrocytes and occasionally one or two leucocytes, were visible. The described outflow of plasma in the direc-

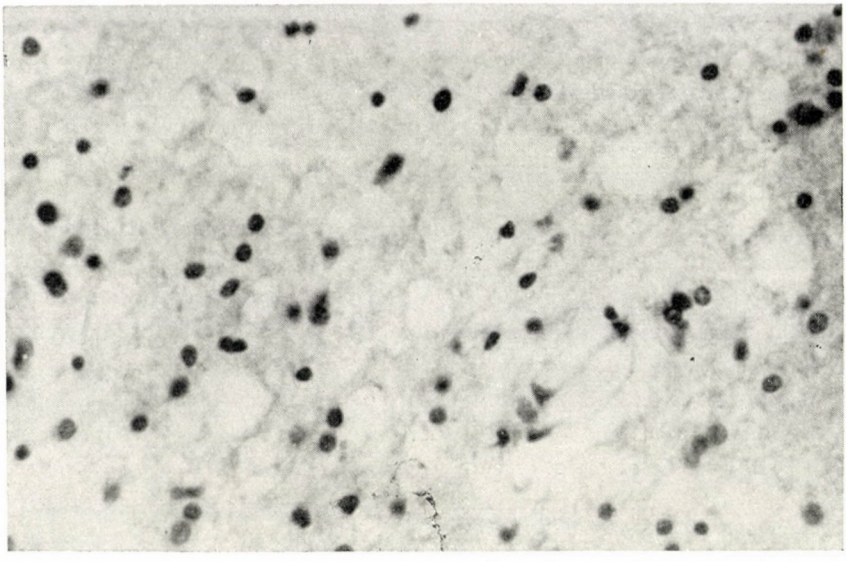


Fig. 2. Porous structure of tissue, resulting from fluid outflow. Nissl stain

tion of the adjacent nervous tissue was in some cases or in some areas of such a measure that we could almost apply to it the term serous microapoplexy, suggested by WILKE. In some areas the extravasation of erythrocytes was more ample, whereby microhaemorrhages had arisen, first of all in the brain stem. In more severe cases the wall of the capillaries or precapillaries showed necrosis, the precapillary wall became homogeneous in toto.

The histological patterns outlined above indicate that in uraemia and in acute nephrogenic cerebral syndrome the most important pathogenetical feature is the alteration in the permeability, barrier-function of the capillaries, the increase in permeability. The histological pattern resembles in many respects that of serous inflammations.

In general, the change of the capillary wall or the perivascular oedema formation is more marked in the white than in the gray matter. It is most severe in the white matter of the cerebral hemispheres, first of all in the occipital lobe. This seems to account for the high incidence of anopsia in uraemia and especially in the acute cerebral nephrogenic syndrome. In many cases capillary wall changes and perivascular oedema formation of considerable

severity were observable in the brain stem, especially in the tegmentum of the pons and mesencephalon, in the white matter of the cerebellum, as well as in the oblong medulla.

The outflowing fluid rich in proteins is histotoxic, especially for the myelin sheaths. At first, the myelin sheaths around the capillaries and precapillaries show paler staining, then they become fragmented. In our cases there had been no time for the fatty degradation of the myelin sheaths showing the so-called oedema-necrosis, because death intervened. From this also follows that in our cases most of the histological changes developed not long before death. As a result of the extravasation of fluid the white matter, and in a smaller measure the gray matter, showed a sieve-like loosening, and cavities could be seen in them.

The extravasation of fluid resulting from the increased permeability of the vascular wall damages by various mechanisms the nervous tissue, first of all the myelin sheaths. The direct histotoxic action has already been mentioned. The perivascular accumulation of fluid diminishes the oxygen supply of the nervous tissue. In consequence of the outflow of fluid namely the diameter of the tissue cylinder supplied by the capillary increases, which in the marginal areas, in the so-called lethal angles, interferes with the oxygen supply to the myelin sheaths or cells, owing to the lenghthening of the oxygen-diffusion radius. Finally, as we shall see, the extravasation of fluid gives rise also to serious degenerative changes in the perivascular glial structures; and these have an important role to play in the metabolism of nervous tissue.

The pathogenesis of the vascular change is unclear. It is likely that an interaction by several factors is responsible. First of all, changes in the chemical composition of blood and the disturbances in cerebral circulation play a role. Once permeability has increased, the chemical changes in the brain tissue may damage secondarily the capillaries. Notably, according to submicroscopic studies (NIESSING) the basal membrane of the cerebral capillaries is built of protein molecules in fibrillar arrangement. Changes in the chemical structure of the brain tissue, first of all the changes in pH, produce changes in the submicroscopic structure of the membrane, gaps appear between the protein fibrils, as a result of which capillary permeability increases.

It cannot be ruled out, either, that the cerebral capillaropathy arises, at least in part, in response to the same aetiological factor which is responsible for the changes in the capillaries of the renal glomerules. This may be suggested by the observation that in our material no parallelism existed between the measure of renal insufficiency (as estimated from the NPN level) and the severity of the cerebral capillaropathy. It is difficult, of course, to tell why are just the cerebral and renal capillaries damaged by the same factor? Probably the two capillary systems possess certain common biological properties.

II. Besides the above outlined capillaropathy an almost universally occurring phenomenon is the change detectable in the oligo- and macroglia, and in a lesser measure in the microglial apparatus, both in uraemia and in the acute nephrogenic cerebral syndrome. Especially in the white matter, the oligodendroglial cells become swollen, their processes break off, the nucleus is stunted and pressed to the side, then disappears, whereby cavities of variable size,

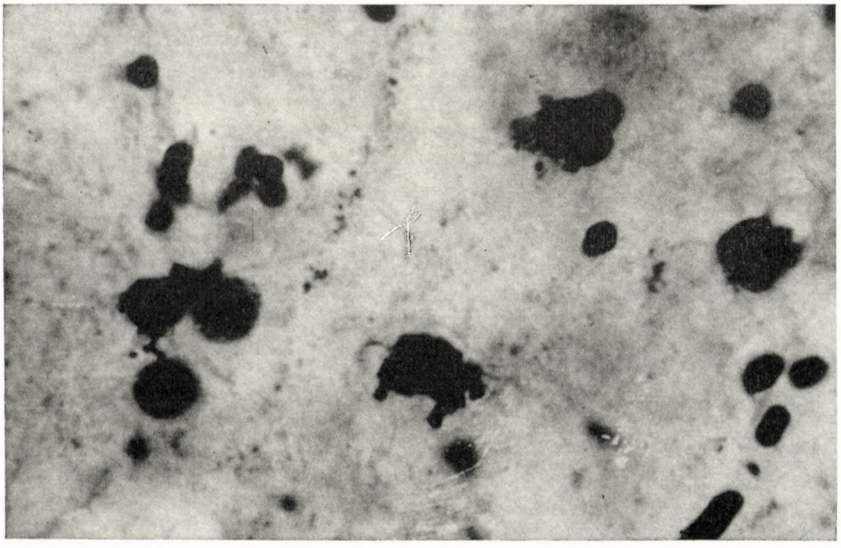


Fig. 3. Hypertrophic oligodendroglial cells, with fragmented processes. Silver impregnation according to Penfield

depending on the measure of swelling of the cell, appear. The above-mentioned sieve-like nervous tissue pattern is apparently based on that change, besides the similar process in the microglial cells.

The changes of macroglial cells are even more characteristic. The perivascular endings of the macroglial cells, which together form the membrana perivascularis gliae performing barrier function, become swollen, then show granular disintegration, and finally disappear. Apparently through taking up fluid from the capillaries, the processes and the body of the cells become hypertrophic, then disintegrate into granules. We call this process clasmatodendrosis. In our experience this is one of the most important signs indicative of fluid flowing into nervous tissue. It is likely that this change may develop also postmortem, but only long after death, because according to the investigations of BROMAN the blood-brain barrier is still functioning as late as at 18 hours following death with intact nervous system.

According to the above, the fluid coming from the capillaries of the nervous system enters, at least early in the process, not the tissue interspaces,

but the oligo- and macroglial cells. Recent evidence tends to indicate namely that in the nervous system there exists no so-called ground substance that would fill the interspace between nervous elements. Apart from the capillaries, the nervous tissue is composed merely of the innumerable processes of nerve and glial cells, with 100 to 150 Å wide intercellular spaces between them. The

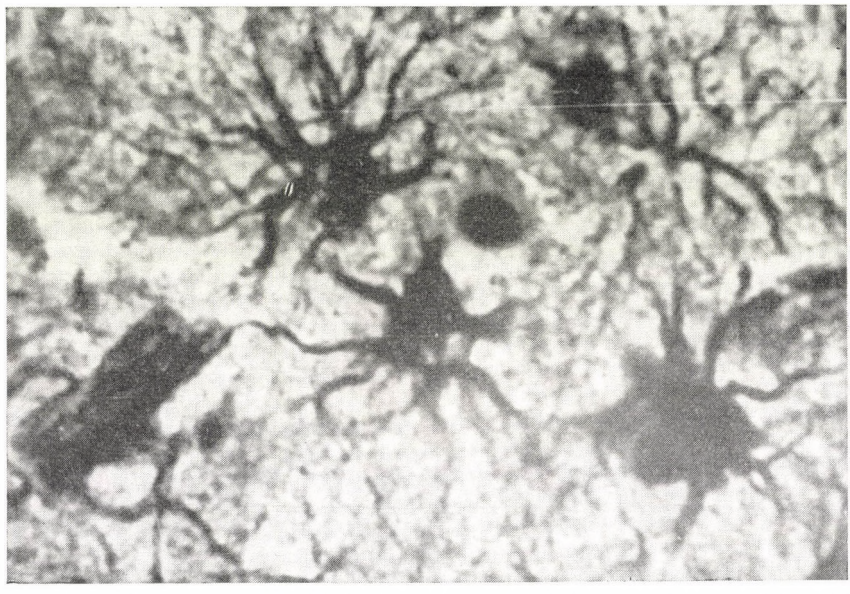


Fig. 4. Hypertrophic macroglial cells in the upper part of the frontal cortex. Gold sublimate impregnation according to Cajal

"ground" substance is composed exclusively of these spaces. In them finely granular material is found and is flowing constantly. This flow ensures the nerve cell metabolism taking place over very large surfaces. The materials required for the metabolism of the nerve cells enter the intercellular spaces directly from the capillaries or reach them by way of the macro- and oligoglial processes. Thus, the macro- and oligodendroglial cells have an important role to play in the nutrition of the neurones. This function is seriously interfered with by the glial changes produced by the outflow of fluid.

But changes in the glial cells may diminish the metabolism of active nervous elements also in another way. Notably, according to the present view, the so-called pump function of the oligo- and macroglial cells plays the most important part in the maintenance of fluid flow in the intercellular spaces, so important in the nutrition of nervous elements. These glial cells swell and shrink at regular intervals, performing what might be called cellular systole and diastole. This change in size of the glial cells represents the driving force

for the fluid in the intercellular spaces. The diminution of this activity due to the above outlined glial cell changes lessens the metabolic rate, and together with it the functional capacity, of the active nerve elements.

The most important role in the above described changes of glial cells seems to be played by the loss of fluid due to increased capillary permeability. But a direct action of the urea accumulated in blood may also play a part

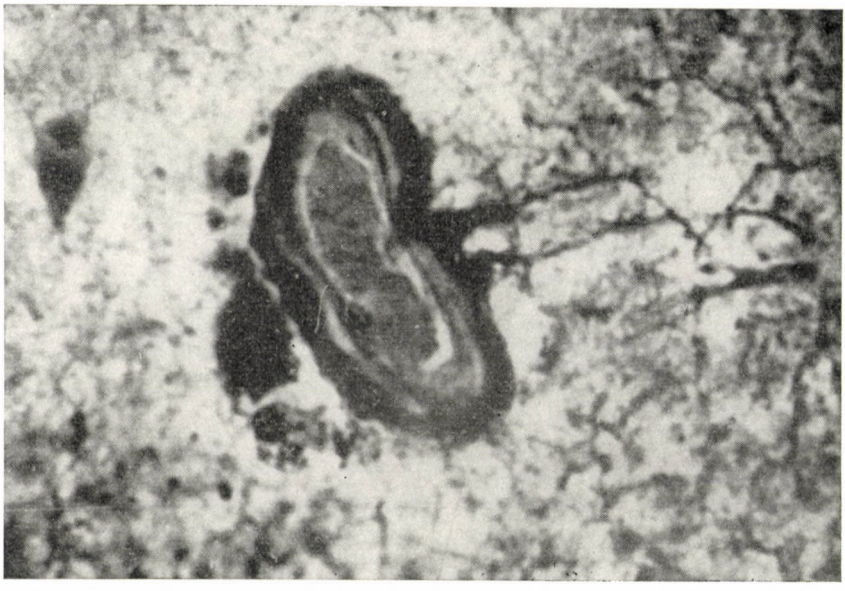


Fig. 5. Swollen perivascular microglial endings. Perivascularly, granular material, impregnating with gold. Cajal's gold sublimate impregnation

in it. ALPERS has namely succeeded in producing closely similar macroglial cellular changes in rabbits by the intravenous injection of urea.

In the initial stages of the process the oligoglial, but probably even more markedly the macroglial, cells increase in number diffusely or locally in the form of glial nodules in various areas of the nervous system, first of all in the brain stem, in the white matter of the cerebral hemispheres and in the white matter of the cerebellum. Since such increases in the number of glial cells can be observed also in such areas in which there is no demonstrable damage to the nervous elements, it is likely that the glial proliferation is a result of the slight, but long-lasting hypoxia produced by the capillaropathy. It is known namely that in general the glial cells respond by proliferation to this stimulus, just like the connective tissue cells do in other parts of the body.

The changes described above are usually more severe in the acute nephrogenic cerebral syndrome, than in uraemia. In the former condition the perme-

ability of the blood vessels is so greatly increased, that haemorrhages, first of all in the brain stem, are a common occurrence.

The nervous complications of uraemia and the acute nephrogenic cerebral syndrome are mostly permeability problems. This might be made use of in therapy, too. It would be justified to administer as a preventive measure

Fig. 6. Granular disintegration of the membrana perivascularis gliae. Cajal's gold sublimate impregnation

drugs decreasing permeability (calcium, allegedly extract of horse chestnut, etc.).

III. In uraemia, and in a greater measure in the acute nephrogenic cerebral syndrome, we can observe in addition histological changes indicative of various changes in cerebral circulation, that vary in severity from individual to individual. The signs of a slowing down of blood flow, such as prestasis, stasis, leucostasis, and rather often the formation of thrombi in the minute blood vessels, can be observed extensively in the various stages of organisation. As a result of the circulatory disturbances the nerve cells showed at many sites ischaemic changes indicative of an impairment of oxygen supply. It was in the first place in the posterior cerebral cortical areas that pseudolaminar nerve cell necroses (so-called elective paranchymal necroses) suggested a disturbance of circulation. Here and there minute circumscribed necroses, too, were observable.

This indicates that in uraemia, and especially in the acute nephrogenic cerebral syndrome, we always have to take into consideration disturbances

and eventually a failure of cerebral circulation. This is indicated also by HEYMAN's observation that cerebral blood flow may be diminished in uraemia. For this reason in every case of uraemia and imminent acute cerebral nephrogenic syndrome efforts should be made to improve cerebral circulation, with the control of the condition of the heart. Strophanthin should be administered

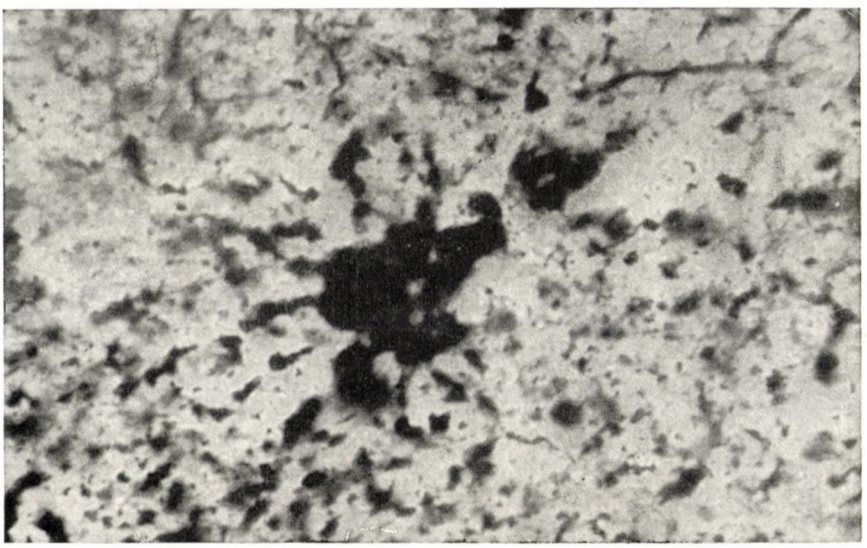


Fig. 7. Granularly disintegrated, previously hypertrophic macroglial cell in the white matter of the occipital cortex. Cajal's gold sublimate impregnation

because according to the investigations of SOLTI and PÉTER it increases cerebral blood flow, not only through an action on the heart, but directly as well. It may be desirable to prescribe papaverine, too, because it increases the cross section of the cerebral vascular bed.

According to those outlined above in the uraemic cerebral complications partly the capillaropathy with increased permeability, and partly the different kinds of impairment of circulation with hypoxic tissue complications play the decisive role. However, direct toxicosis of the nervous tissue cannot be ruled out, either. ÖSTERREICHER has shown that in certain parts of the nervous system, for example in the oliva, excessive amounts of urea may be accumulated in the nerve cells.

The histological changes described explain clearly the symptoms of uraemia and the acute nephrogenic cerebral syndrome. The peculiar changes in consciousness (intellectual, mental activity) may be explained by the lesions found in every case in the reticular formation, and myoclonus may be explained by the presence of changes in the reticular formation, oliva, and eventually in

the cerebellum. The focal phenomena (e.g. a positive Babinski's sign) may be due to circumscribed haemorrhages, necroses, and the exaggerated reflexes to the diffuse changes in the reticular formation.

IV. In neurological and medical diseases associated with deficient nutrition or fluid intake or in psychotic entities, acute delirium may develop with severe azotaemia, but eventually with hardly affected renal function. Essentially, the syndrome is based on extrarenal uraemia; the conditions has been termed *encéphalite azotémique* and is distinguished from the other forms of uraemia by French authors. As it is known, KERPEL-FRONIUS, GÖMÖRI et al. have clarified the mechanism of azotaemia developing in connexion with dehydration. In the Hungarian literature FEJÉR has discussed the neuropsychiatric aspects of the disease. According to our histological studies, in such cases we find the same changes as in uraemia, but in much more severe form. The damage to the capillaries and precapillaries in the nervous system is most conspicuous; in many areas extensive necroses of the vascular wall can be seen, with extravasation of fluid rich in protein and exudative in nature, as well as with haemorrhages. In such cases not only a fluid of transudative character containing micromolecular proteins, but also exudative plasma containing macromolecular proteins and cytotoxic enzymes will enter the nervous tissues. This is why the histological changes in the nervous system and the symptoms are more severe. It is remarkable and difficult to explain why we find hardly any damage to the renal glomerules. Thus, in this case the capillary system of the brain responds differently to the same injury as does that of the kidney.

The condition should be thought of with any acute delirium, especially, if it is preceded by insufficient fluid intake. In every one of such cases the blood NPN should be determined and renal function tests should be performed.

V. *Nephrogenic hypertensive encephalopathy*. According to our studies, in every one of such cases the following changes can be found in the cerebral arterioles, and, less markedly, in the larger blood vessels. Between the endothelial layer and the elastic membrane, well developed in the cerebral vessels, a homogeneous mass staining yellowish-brown with Nissl's stain, is imbibed. This mass usually stains also with Scarlet R, with variable intensity. Usually, the homogeneous mass occurs in a smaller or larger part of the blood vessel. In cross sections it occupies at first just one part, but soon it imbibes the subendothelium circularly. In subsequent phases the elastic membrane disintegrates without hypertrophy and doubling; the homogeneous mass imbibes also the media. As a result of this, the blood vessel loses its contractility, and the tone of the vascular wall decreases. At first the subendothelial mass narrows the lumen of the blood vessel, or even occludes it. Later, as a result of the loss of tone and necrosis of the elastica and media, the lumen dilates, microarterioectases develop, from the ruptures of which

haemorrhages may arise. In the early phase this arteriohyalinosis occurs only here and there in the cerebral blood vessels, but later it is found to be more and more extensive.

Those outlined above are of great clinical importance. In the nephrogenic hypertension such changes develop in the wall of the cerebral arterioles as impair the contractility of the blood vessel, or prevent it from adjusting itself to changes in blood pressure. With such a structure of the vascular wall no angiospasm can be spoken of. Therefore in our opinion it is hardly justified to speak about a cerebral vascular crisis or episodes of angiospasm in nephrogenic hypertension. The changes cannot be termed angiospastic encephalopathy. The development of the temporary cerebral focal phenomena (e.g. numbness, mono- or hemiparesis, hemianopsia, etc.) observable in chronic nephrosclerosis may be explained probably in the following way. The vascular lumen is narrowed or totally obstructed. As a result, blood flow slows down or ceases in the area supplied by that vessel. In consequence of the reduced blood flow the oxygen tension of the blood increases (owing to the greater rate of utilisation) and CO_2 tension increases in that area. This, through local action on the vascular wall, may cause capillary dilatation, which in turn reduces even more the rate of blood flow. Especially in the cortex, the cerebral blood vessels have ample anastomoses at the capillary level, but also at the arteriolar level. If the lumen of the blood vessels in adjacent areas is not narrowed and blood pressure is sufficient, the area supplied by the affected blood vessel will be supplied by the collateral circulation from the adjacent vascular area, thus, the oxygen tension will not fall below the critical level and no function will be lost.

The transient focal symptoms, usually thought to be of angiospastic origin, may develop in the following way. Some arteriole may become occluded. The corresponding focal symptom develops. And when after some hours or days the collateral circulation begins to take over with the proper level of blood pressure, the symptom disappears. The high blood pressure accompanying the transient focal symptoms is apparently of such a compensatory significance. But it is also possible that some blood vessel had become occluded or its lumen had narrowed long ago, and yet no symptoms developed, because compensation was possible. When, however, in such a case blood pressure drops suddenly for one reason or another, collateralisation may become insufficient and the corresponding symptoms will appear.

From the clinical point of view, at least three conclusions can be drawn from the circulatory changes outlined above. *a)* In nephrogenic hypertension we should not think of vascular crisis, when focal symptoms develop for a while; it would be best to eliminate this term altogether from use in relation to the brain. *b)* Apart from the extremely severe cases, we should not strive to lower blood pressure at any cost in the case of nephrogenic hypertension accompanied

by cerebral complications, i.e. in nephrogenic hypertensive encephalopathy, because by so doing we may inadvertently interfere with the compensatory mechanism trying to overcome the functional difficulties represented by the narrowing or occlusion of a blood vessel. *c)* With every cerebral symptom of ephemeric nature vasodilators (e.g. papaverine, aminophyllin) should be given, but possibly without lowering the blood pressure. The rate of cerebral blood flow should be increased.

We must be extremely cautious with the use of anticoagulants, because, as I have already mentioned, the vascular changes cause a loss of tone, dilatation, and eventually rupture of the affected blood vessel, that may lead to severe haemorrhages. With minor haemorrhages it cannot be told whether the focal symptom is due to thrombosis or to a microhaemorrhage. More of the patients with nephrogenic hypertension die of apoplexy than of the patients with hypertensive vascular disease; among the latter, however, death due to thrombosis is more common.

We have discussed the nervous changes developing in consequence of renal disease. There is, however, also another relationship between renal disease and the nervous system. Notably, it has been revealed recently that certain structures of the nervous system, besides certain hypothalamic areas first of all the subcommissural organ and probably also the pineal body, play an important role in the regulation of the circulating blood volume, electrolyte and water metabolism. Until quite recently it has been thought that the subcommissural organ, to be found on the top of the oralmost part of the Sylvian aqueduct, under the posterior commissure, is not present in man. A short while ago it has been shown to be present in man in a rudimentary form. It has been suggested that the subcommissural organ and probably also the pineal body would contain so-called volume receptors, of which changes in circulating blood volume would be the adequate stimuli. Experimental investigations have revealed that the subcommissural organ has a central role to play in the control of aldosterone secretion, and the latter is known to regulate the retention or output of sodium. Pathological changes, or experimental destruction, of the subcommissural organ may give rise to severe changes in circulating blood volume, and electrolyte and water metabolism. Lesions to that organ may lead to so-called cerebral salt retention, or, on the contrary, to cerebral salt loss. The investigations into these fascinating problems represent one of the most actual aims in theoretical neurology.

Prof. Dr. Béla HORÁNYI, Neurological Clinic of University, Budapest VIII., Balassa utca 6., Hungary.

OPHTHALMOLOGIC ASPECTS OF RENAL DISEASES

By

P. WEINSTEIN

MEDICAL POSTGRADUATE SCHOOL, BUDAPEST

Ophthalmology borders on the other branches of medicine especially through the vascular system, and first of all in the field of renal diseases. In their advanced stages the various renal conditions show such characteristic changes in the ocular fundi that the experienced ophthalmologist can diagnose them at a glance.

In this paper the changes in the ocular fundus occurring in nephritis, nephrosis and nephrosclerosis, the retinal symptoms of the pregnancy kidney, and of Kimmelstiel—Wilson's syndrome will be dealt with.

By way of introduction it is to be pointed out that every change of the ocular fundus associated with renal diseases is correlated with hypertension, and especially with its malignant form.

In view of this fact let me outline at first the ocular changes characteristic of hypertension. On the basis of these changes the hypertensive disease can be divided into four phases. In phase 1 the blood vessels are branching off at an obtuse instead of the usual acute angle, the venules around the yellow spot are tortuous, and there are copper wire arteries. Phase 2 is characterized by arteriovenous crossings, and sometimes adjacent to them fine haemorrhages or oedema, the so-called prethrombotic sign. These two phases represent the benign stage of hypertension, when the kidney is certainly intact. In phase 3 malignant hypertension begins to produce its changes. The arterio-venous crossings are marked, lakes of haemorrhage, degenerative grayish-white retinopathic foci appear and in such cases it is most likely that the kidneys are already affected, especially when at the periphery there are rough granules of pigment, indicating choroid involvement; albuminuric choroiditis is an almost certain sign of renal involvement. In phase 4 papilloedema joins the mentioned changes, and at the same time there appears on the macula lutea the star-shaped focus, called albuminuric retinitis earlier, and angiospastic retinitis since VOLHARD. This change is absolutely indicative of renal involvement and the process is particularly malignant when, as it has been emphasized by RADNÓT, too, oedema of the papilla extends over to the retina. In some cases the haemorrhages are absorbed and papilloedema disappears in response to treatment, but the blood vessels remain narrowed, with the so-called silver

wire arteries appearing at sites. All these mean that in spite of the improvement of the ocular changes, a chronic process has developed in the kidney.

Is it possible to differentiate on the basis of the changes in the ocular fundus between primary and secondary renal diseases? The ocular changes are characterized in the malignant phase of hypertension, when also nephrosclerosis is present, by a constriction of the arteries and a dilatation of the capillaries and venules, i.e. Ricker's terminal stasis, a spastic-atonic condition. A sign of this is the hyperaemia of the papillae. In chronic nephritis the arteries, capillaries and venules are all constricted, the papilla is pale and the peripapillary oedema dominates the picture.

In nephrosis the ocular fundus is intact, because there is no hypertension in that condition. In his book on the renal diseases VOLHARD mentions a case of nephrosis reported by KORÁNYI in which retinal oedema was associated to the extensive oedema of the other parts of the body. This is a rarity, because while the pressure in the tissues is not more than a few mm Hg, intraocular pressure is about 20 mm Hg and thereby, unless local causes give rise to it, retinal oedema is prevented from developing.

The changes in the ocular fundus occurring in pregnancy toxaemia are similar to those outlined above. It has been known for long that in this condition temporary impairment of vision owing to retinal arterial spasm is a characteristic symptom. Later, the diastolic pressure in the ocular fundus significantly increases, as it has been reported by ERŐSS and TARJÁN, among others. Another characteristic change is the oedema of the ocular fundus, manifesting itself with an increase of the so-called retinal reflexes. These reflexes are not uncommon even physiologically in hypermetropic individuals and young persons, but can be visualized mainly temporally from the papillae, whereas in pregnancy toxaemia they are detectable on the nasal side as well, as reported by FINNERTY. It is characteristic of these pathological reflexes that in response to acetazolamide they disappear, while the physiological ones do not. Finally, toxaemic retinopathy develops, displaying essentially the same changes as those caused by malignant hypertension in the fundus.

What is the mechanism of the retinal changes in renal disease and in malignant hypertension? The systematic research of the recent decades has contributed most valuable information in this field. BJÖRK has found in extensive studies that in hypertensive, renal disease the characteristic retinopathic foci develop exclusively when diastolic pressure is permanently over 120 mm Hg. In assoaciation with systolic hypertension or when the diastolic pressure is lower than 120 mm Hg there are never changes in the ocular fundus. Another precondition is the decrease of the minute volume; thus, even when diastolic pressure is higher than 120 mm Hg retinopathy will develop only if the minute volume is decreased. Finally, the third precondition is that the diastolic pressure in the eye ground should increase discordantly. All these mean that systemic

hypoxia has developed and the tissues sensitive to oxygen deficiency, first of all the retina, respond by the development of the corresponding retinopathic foci, because hypoxia increases the permeability of the vascular wall and thus haemorrhage and transudation easily develop in the fundus. From this point of view the investigations of BELMONTE GONZALES disclosed the interesting evidence that in the first stage of hypertension the blood count is normal, in the second stage polyglobulia appears, in the third stage the erythrocyte count is normal again and finally, in the fourth stage, marked anaemia is found. This was pointed out already in 1933 by LITZNER, who stated, and we could confirm it in our own ivestigations, too, that in nephrosclerosis, in which there are severe changes in the fundus, the blood count is mostly closely similar to that found in pernicious anaemia, with marked basophilic punctations, low erythrocyte count and finally with every sign of hypoxia. GÖMÖRI, too, has mentioned the occurrence of anaemia in chronic glomerulonephritis. With respect to the above it is most interesting that in coarctation of the aorta there are no changes in the fundus, in spite of the high diastolic pressure; in this condition, however, the retinal blood vessels are not constricted, diastolic pressure therefore is not increased and thus no retinal hypoxia develops. In contrast to this, in Takayusu's syndrome, the so-called pulseless disease, in which brachiocephalic circulation is impaired and thus retinal anoxia, too, develops, marked retinopathic changes are found, which are identical with those in anaemia or hypertension.

It is remarkable that the acute retinal anoxia, for example in embolism of the central retinal artery, or quinine intoxication, when the retinal blood vessels are so constricted that they are almost invisible, peristasic retinopathy never occurs, but as a result of the sudden local anoxia the retinal ganglionic cells and consequentially the optic nerve undergo atrophy. During such a sudden anoxia, the blood supply of the choroid is unaffected and thence the retina can get its blood supply. In hypertensive retinopathy the chronic glomerulonephritis develops gradually, slowly, and in such cases the blood vessels of the choroid are seriously affected and thus the retinopathy, too, will be marked.

Those elaborated above are completed by the recent investigations of PICKERING et al., who have studied the retina following blood loss. They started out from the old observation that the ocular fundus in pernicious anaemia resembles closely the pattern seen in hypertensive retinopathy. Similar patterns have been known to occur after profuse gastric or uterine haemorrhage, and traumatic blood loss. In these conditions it is again the anoxia that is responsible for the development of retinal changes. PICKERING has made serial studies of the retina in 8 cases of grave gastric haemorrhage and observed in every one of them severe changes in the fundus reminiscent of those found in hypertension and pernicious anaemia, although the sight of these patients

was not impaired. Without exception, these changes became most marked when blood pressure dropped suddenly.

Thus, in the sense of this conception the extremes meet; in malignant hypertension and cases of profuse gastric haemorrhage associated with a sudden fall of blood pressure we find the same changes in the ocular fundus, angiospastic retinopathy in one case and hypoxaemic retinopathy in the other.

In conclusion, let me say a few words about the appearance of the fundus in Kimmelstiel—Wilson's syndrome. The characteristic feature of this is that the diabetic patient develops the triad of hypertension, retinopathy and intercapillary glomerulosclerosis. In some cases marked oedema is also observable. It is not easy to diagnose the condition, since a similar clinical picture may develop in non-specific nephrosclerosis. In our own material about 30 per cent of the diabetics show retinopathy, whereas Kimmelstiel—Wilson's syndrome occurs much less often. Diabetic retinopathy is characterized, almost specifically, by the presence of punctate haemorrhages and degenerative foci. In diabetes punctate haemorrhages are, though infrequently, visible in the conjunctiva, too. According to recent data in the literature, confirmed also by FORGÁCS, most of these changes are not haemorrhages, but venular microaneurysms. In diabetes the most serious change is the so-called proliferating retinitis, which means that besides those in the fundus haemorrhages occur in the vitreous body, too, and the organisation of these causes the proliferation. We have made serial tests for creatinine clearance in patients with diabetic retinopathy and found pathologically low values (around 24 mg) exclusively in the cases displaying proliferating retinitis. From this we have concluded that only the proliferative form of diabetic retinopathy is characteristic of Kimmelstiel—Wilson's syndrome. RADNÓT, too, has expressed a similar opinion when stating that the diabetic renal changes are characterized by rubeosis, the appearance of new blood vessels, in the fundus.

Although nothing definite is known about it, there are a few interesting data concerning the underlying pathomechanism, notably that as a result of the alteration in the protein compositon of the basement membrane of the vascular wall permeability greatly increases. This phenomenon may in some way be brought into correlation with the pituitary-adrenal ACTH-cortisone system, because for example in animals with alloxan diabetes diabetic retinopathy and Kimmelstiel—Wilson's syndrome may be induced by the administration of ACTH. Recently, more and more reports are appearing on cases of Kimmelstiel—Wilson's syndrome in which sugar tolerance improved significantly, sugar disappeared from the urine, the blood sugar was reduced and the severe changes in the fundus disappeared almost completely. In two of our such cases post-mortem study by RUTTKAI has revealed the presence of fibrosis and glandular apoplexy, respectively, in the hypophysis.

Finally, let me quote Balassa's saying, often cited by my late master, Emil Grósz, one of the best friends of Sándor Korányi: „Medicine Without surgery would be similar to a bird whose wings have been cut off, and without ophthalmology it would be like a bird deprived of its eyes.' This saying is not actual any longer, because both surgery and ophthalmology cooperate closely with internal medicine, to the benefit of the patient and of science.

Dr. Pál Weinstein, Medical Postgraduate School, Budapest XIII. Szabolcs 4. 35., Hungary.

RADIOLOGICAL ASPECTS OF RENAL DISEASES

By

Z. Zsebők

FIRST DEPARTMENT OF SURGERY, MEDICAL UNIVERSITY, BUDAPEST

The most important radiological method of renal diagnosis is excretion urography, and therefore this will be dealt with here, in the first place.

Only such details will be touchedupon, the knowledge of which is indispensable for the rational use of this procedure.

The theoretical essence of excretion urography is that if we inject into a vein some nephrotopic organic iodine compound, usually a salt of di-iodopyridone-acetic acid-diethanolamine, it will be rapidly excreted by the kidneys, and subsequently we may obtain information from the changes in the concentration of the radiopaque medium as to the

1. excretory activity of the kidney;
2. the shape, and eventual gross morphological changes in the calices and renal pelvis; and
3. the passage of urine.

A precondition of successful urography is normal renal function, though minor deviations from the normal do not preclude the possibility of carrying out the examination. However, just as for example in acute glomerulonephritis the inulin clearance is changed, in conditions associated with disturbances in renal function there will be shifts in the excretion of the contrast medium, too. Those outlined above should be understood to mean that the examinations should never begun with excretion urography, but with other laboratory tests, and when for example the serum non-protein nitrogen level is over 50 mg per 100 ml, it is not advisable to apply excretion urography, in order to avoid further strain on the kidney.

Blood pressure significantly influences the success of the examination, filtration pressure being the function of the hydrostatic pressure of blood and of the blood pressure in the glomerular capillaries. In normotensive subjects the glomerular capillary pressure is about 70 mm Hg, the pressure in Bowman's capsule 10 mm Hg, and the colloidosmotic pressure of plasma 25 mm Hg. Thus, if we subtract the two latter values, we get a glomerular filtration pressure value of round 40 mm Hg. When, however, blood pressure is for any reason lower than that mentioned, ultrafiltration, and together with it the excretion of the medium, will decrease or cease, and urography will not be feasible.

A similar situation arises when the equilibrium is upset on the other side of the kidney, as an ultrafiltrating apparatus, because the passage is blocked by some reason, as a result of which urinary pressure in the calices and pelvis increases; the volume of the ultrafiltrate, and together with it the amount of the excreted medium, decrease and the examination will be a failure.

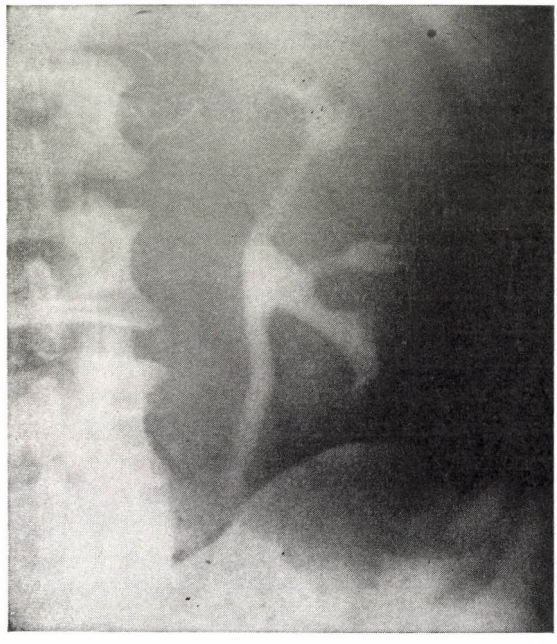


Fig. 1. Pyelogram made 5 minutes after the intravenous injection of 30 ml of Triopac 300

These few examples have been selected to illustrate which are the most important circumstances that influence the success of excretion urography.

It is another problem at which time following the injection should we carry out the X-ray examination to achieve success. Considering that in the case of an even and satisfactory excretion of the about 130 ml/min of ultrafiltrate, as a result of tubular reabsorption, an average of only about 0.7 to 1.3 ml/min of urine is excreted into the renal pelvis, taking into account the capacity of the pelvis and calices, a minimum of 5 minutes will have to pass until the calices and pelvis will contain urine with sufficient contrast medium in it to give a shadow.

In this connection it may be asked, in what measure urography is suitable for use in the assessment of renal function, and what are the ways and means by which we can achieve a good filling of the renal pelvis and calices with urine containing the contrast medium.

The answer to the first question is brief. Urography does not offer the possibility of assessing renal function with any measure of precision, whether diiodized or triiodized compounds are used, because the intensity of the shadow-cast by the urine containing contrast medium is influenced not only by the absolute amount of the iodine excreted, but also by the layer thickness. Thus, in a wide pelvis the concentration is less, but the layer thicker, thus the radio-

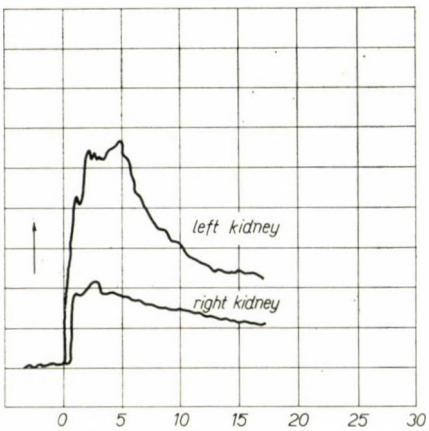


Fig. 2. Graphical representation of a renal function test with I^{131}

graphic shadow may be more distinct than that cast by the thin layer of urine containing a high concentration of medium in a narrow renal pelvis. In pathological cases renal function cannot be assessed by excretion urography, as for instance with a stone wedged in in one ureter it may happen that whereas on that side reflex anuria may be present preventing completely the excretion of the medium, on the contralateral side excretion may be absolutely normal.

Radiology has acquired a valuable new method for the appraisal of renal function in isotope nephrography, to be dealt with later. As the radiological renal diagnosis is based on the analysis of changes in the shape of the calices and pelvis, it is a fundamental condition that the renal cavity system should be filled readily and this can be realized only by the use of adequate methods, which, in turn, require exact knowledge of the fundamentals of renal physiology and of the contrast media used.

One of the main aims is to obtain an intensive X-ray shadow from the radiopaque medium. In this we get help from the circumstance that in general the glomerular clearance of the compounds used increases with their plasma concentration. The clearance rate of the different contrast media used is, however, different. Two types of contrast medium are used for urography,

notably diiodized and triiodized compounds. In general, the diiodized compounds are di-iodo-Pyridone derivatives, and the triiodized preparations contain the three iodine atoms in acetyl-amino- and diacetyl-diamino linkages, as Na and methylglucamine salts. The better known diiodized compounds are diiodone (Joduron, Diodrast) and its sodium salt (Uroselectan) and the triiodized ones sodium acetrizoate (Triopac), sodium diacetamidotriiodobenzoate

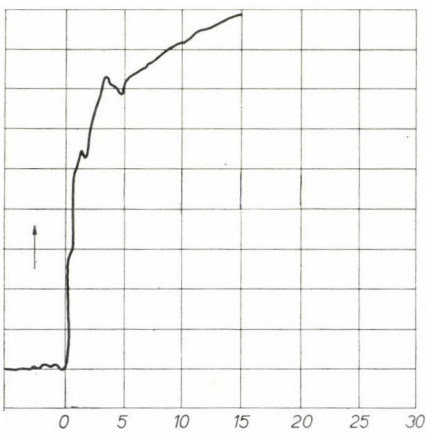


Fig. 3. Curves showing the function of diseased kidneys

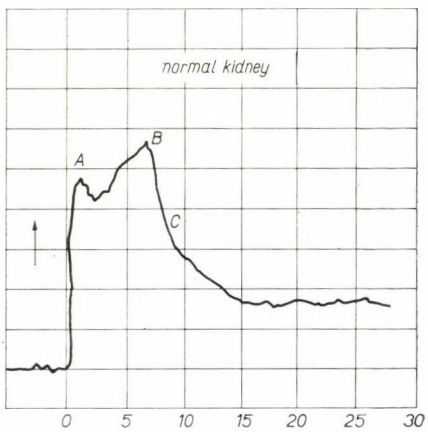


Fig. 4. Curves showing the function of diseased kidneys

(Hypaque), methylglucamin acetrizoate (Opacoron), diatrizoic acid (Urografin) and methylglucamin salt of N,N'-diacethyl-3,5-diamino-2,4,6 trijodobenzoic acid (Uromiro).

The pertaining experiments, usually relying upon comparison with the creatinine clearance and upon the isotope technique, have indicated that the diiodized compounds are excreted by glomerular filtration and tubular secretion, and have a clearance rate of about 760 ml/min.

The measure of tubular secretion being determined by the tubular maximum, in the presence of high plasma concentration of the medium, only the filtration rate will increase. The triiodized compounds differ in behaviour. They are characterized by the fact that the concentration of the medium exceeds 50 mg in 100 ml of plasma, the phenomenon of self-depression develops, tubular secretion will gradually decrease with the increase in glomerular filtration rate. These compounds have also a lower clearance rate, comparable to that of inulin, about 130 ml/min. Moreover, according to ultrafiltration studies, about 5 to 10 per cent of the triiodized compounds become linked to protein.

From those outlined above we may draw the conclusion that since the intensity of the shadow cast by the radiopaque medium depends in the first

place on the amount of medium administered and its clearance rate, and in a lesser measure on the capacity of, and excretion from the renal cavity system we shall obtain an intensive shadow from diiodized compounds applied in adequate quantities. Experience has shown that for a satisfactory urogram 6 to 8 mg/kg body weight of contrast medium should be injected.

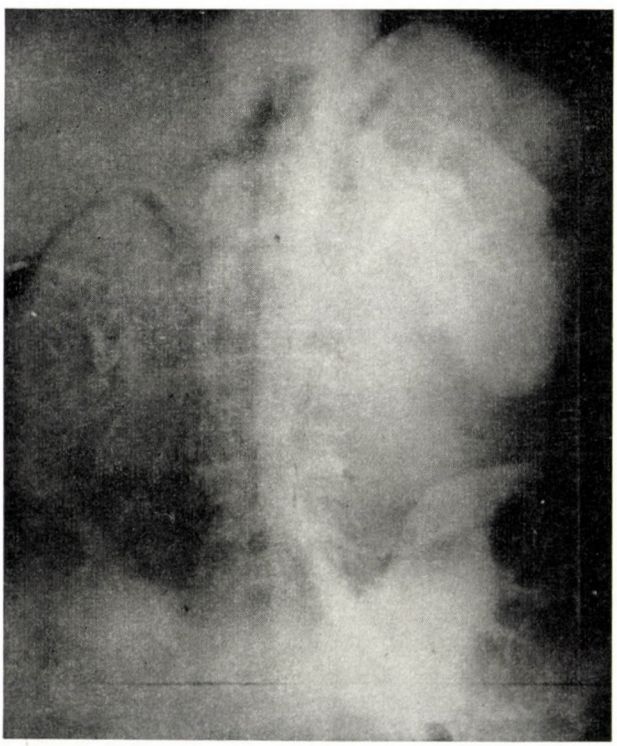


Fig. 5. Filling the renal artery and the kidney, respectively, by percutaneous puncture of the aorta

To this should be added that although the toxic dose of diiodized compounds is lower than that of the triiodized ones, in view of the absolute quantities applied, which are by far below the toxic limit, there is no reason to give preference to the triiodized compounds in urography, the less so, since according to the cumulative statistics of PENDERGRASS et al. the primary mortality rate of urography is extremely low considering that there is one death liable to occur among about 50,000 examinations.

It has been mentioned that by the use of isotopes renal function may be assessed rather reliably. The method is based on the building of an I^{131} atom into the diiodized contrast medium molecule, which is then used just as with conventional urography.

The required activity is about 2 mC/5 kg, i.e. the amount of isotope to be used is very small.

I do not wish to go into technical details, and all I want to point out is that by the method the various phases of renal excretory activity can be represented graphically.

The first one-third of the isotope activity curve represents the so-called vascular capacity, the segment, when the radioactive compound is in the renal

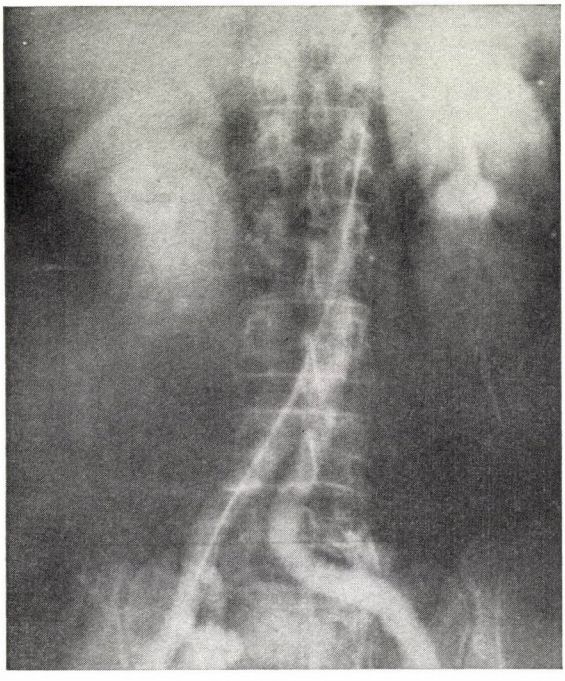


Fig. 6. Appearance of contrast medium in the kidney, after injecting it through a catheter passed up from the femoral artery to the level of the renal artery

arterial network. Two to three minutes after injection another rise of activity is visible, lasting for about 4 to 5 minutes, corresponding to the secretory phase. This segment of the curve is of the greatest diagnostic significance, because it is in that phase that the pathological changes in the excretory activity of the kidney are observable. The third and final segment of the renogram develops under normal conditions about 5 minutes later, and corresponds to the phase in which the radioactive medium leaves the calices and pelvis, so that this part of the curves shows a downward slope.

It is only natural that for example with obstruction due to any cause or with other functional disturbances significant deviations from the normal shape of the curve will be visible.

The two methods cutlined above make it possible to judge the renal cavity system and function. Recently many authors have suggested that for the examination of the morphological changes of the kidneys arteriography should be employed, either by indirect aortography, or by direct renal arteriography by means of a catheter passed from the aorte into the renal artery.

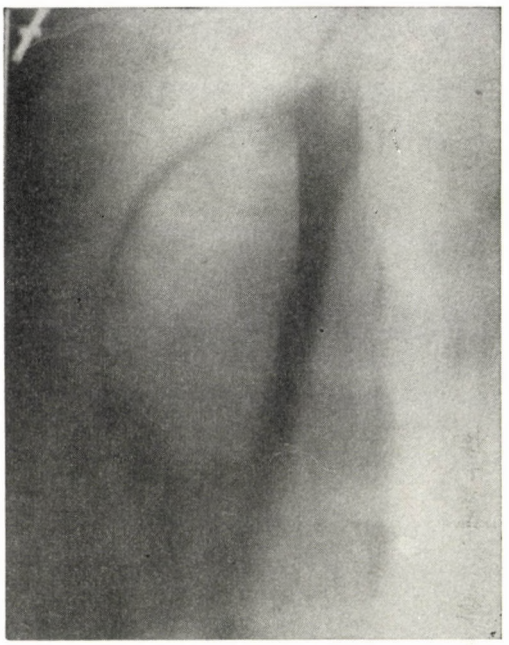


Fig. 7. Tomograms of kidney and adrenal gland after retroperitoneal air insufflation

The procedure is complicated, its result is not proportionate to the hazards involved, and therefore its significance is less than that of the negative, gas contrast medium radiological examinations. With the latter a negative contrast can be created perirenally by the retroperitoneal insufflation of oxygen or carbon dioxide, from the periorenal but preferable from the presacral approach, and information may be obtained as to the morphological changes of the kidney and adrenals, first of all by tomography.

Finally, allow me to mention X-ray cinematography, an excellent new method of functional diagnosis.

As those stated above indicate, modern radiological methods offer valuable help in clinical medicine and by their use we can advance further toward the successful diagnosis of certain renal diseases.

Dr. Zoltán Zsebők, Budapest VIII. Üllői út 78., Hungary.

GYNAECOLOGICO-OBSTETRICAL ASPECTS OF RENAL DISEASES

By

A. Kovács

DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY, MEDICAL UNIVERSITY, BUDAPEST

In obstetric and gynaecologic practice problems connected with surgical or medical diseases of the kidneys often arise. In some cases certain obstetric or genital conditions must be differentiated from renal disease, whereas in others pregnancy, extragenital disease and renal dysfunction occur side by side and we have to decide what should be done first. In some instances it must be determined whether the presence of some renal disease contraindicates a certain gynaecological or obstetrical intervention.

In this short paper it is impossible to present a complete list of the problems arising in connection with renal diseases in obstetric practice.

Owing to their importance and significance we mention the inflammatory and tuberculous affections of the kidneys, nephrolithiasis and the disturbances in renal function due to developmental malformations. The significance of these conditions varies, depending on the fact that the gynaecologist encounters them in connection with genital disease, during pregnancy or at delivery. A detailed discussion of the diagnosis and differential diagnosis of these conditions, their effects on the changes of genital organs or on pathological pregnancy may merit attention. It ought to be analyzed how, in the knowledge of the achievements of modern renal research, the obstetrician may judge the renal condition on hand, and how he can decide whether it has any influence upon the treatment or operation planned.

We ascribe great significance to the problem of renal lesions often occurring in conjunction with genital malignancies, irrespective of the fact that the patient has been operated on or has been subjected to irradiations only. This problem has been extensively discussed in the gynaecological, and, especially the urological literature. Most of such patients undergo namely gynaecological or urological treatment after operation or after irradiation, so that the surgeon who has operated on them or the radiologist who has treated them does not even know of the subsequent complications. Having realized the importance of this problem, we have begun cooperation with the urologists and our mutual work promizes interesting results.

In view of its significance and controversial nature, the problem of preeclamptic toxaemia will be dealt with in more detail. Even this cannot mean

more than to try and find the problems of common interest for the expert on renal pathology and the obstetrician in a maze of innumerable data from the literature. Just to approach this problem is a difficult task. There is namely no agreement as regards the appraisal of preeclamptic toxaemia. There is disagreement also as to the incidence of the condition, depending on when the symptoms observed in the second half of pregnancy are qualified as those of late toxaemia.

At our Department we consider a condition to be preeclamptic toxaemia when it presents at least one symptom of the triad hypertension, oedema and proteinuria. In the past 10 years, in a material of 18,000 deliveries we have observed preeclamptic toxaemia in about 5 per cent of those cases, in which neither the history, nor the tests performed had revealed any disease until around the time of labour, and the pregnancy had run a physiological course. As opposed to this, in 3500 cases, in which any kind of disease could be demonstrated independently of pregnancy or during pregnancy, the incidence of late toxaemia was over 10 per cent.

Experience has shown that following protracted or grave toxaemia, such changes may develop in the function of certain organs, with the kidneys among them, as will make a complete restitution of their function impossible.

ZANGENMEISTER, GIBBSON, YOUNG and many others have detected chronic nephritis after toxaemia. At our Department CSILLAG et al. found that in patients who had mentioned in the history renal or vascular disturbances (glomerulonephritis, pyelonephritis, scarlet fever, hypertension, rheumatoid affections, endocrine disorders, or preceding toxaemic pregnancy), toxaemia occurred more often and had a more severe course than in others. HAUSER et al. also observed the grave course of preeclamptic toxaemia in subjects with previous renal injury.

The gravest form of late toxaemia, eclampsia, which according to clinical experience may most often result in renal disease immediately after delivery or later, is encountered less and less frequently. Now we observe one or two cases of eclampsia in every two or three years. The development of eclampsia depends on several factors. These and their frequency will not be discussed here, the less so, because ample evidence pertaining to them can be found in the monograph on the problem published in 1959 by FEKETE.

In this country about 95 per cent of the pregnant women are regularly cared for. The mass screenings have already reduced the incidence of the more severe or protracted forms of toxaemia and play a decisive role in the diminution of the incidence of eclampsia. This phenomenon, together with the organized care of pregnants, is closely correlated with the changes in social relations and the improving living standards.

There is agreement of opinion in that the significance of preeclamptic toxaemia can be measured in those effects it produces in the mother and foetus

in the final phase of pregnancy and at parturition, and later, when the patient with previous preeclamptic toxaemia is under treatment for renal lesion or some form of renal disease, for which the toxaemia is held to be responsible. In such cases it is still a controversial issue whether, independently of the toxaemia, the kidneys or vascular system had not been affected earlier by some disease. It is also questionable whether the diseases mentioned in the history had not acted as predisposing factors in the genesis of the severe toxaemia just as well as in the development of the renal disease believed to be secondary. On the basis of our clinical experience we do not think that such a contention would be far-fetched.

The question emerges, whether the symptoms observed in the second half of pregnancy in a woman with already existent renal disease invariably mean preeclamptic toxaemia, or else a manifestation of the renal disease under the effect of pregnancy. In connection with the appraisal of preeclamptic toxaemia some authors have analyzed the problem as to whether in toxaemia, or at follow-up we may or may not place the primary role of the renal lesion in the centre of the condition.

The problems outlined above are most interesting for the gynaecologist. In the available literature we have found 59 papers on preeclamptic toxaemia, all published last year. Almost half of them considers the disturbance of renal function to be in the centre of the pathological events. In more than 200 reports, also published last year, dealing with the problem of late toxaemia in connection with other obstetric questions, the authors have also attributed a decisive significance to the renal changes.

When analyzing the data in the literature, we find a remarkable tendency to classify into the usual classical entities the renal injury observed in preeclamptic toxaemia. Ultimately, this never succeeds, but this may explain why we find so many views as to the diagnostic criteria, treatment, and even the terminology of preeclamptic toxaemia, to mention only such terms as physiological proteinuria of pregnancy, pregnancy kidney, the various kinds of nephropathy, etc. When trying to find the origin of the various views underlying these terms, we must go back to the past century, to the era when the nephrogenic theory had dominated in the views concerning the pathogenesis of late toxaemia. It cannot be doubted that since late toxaemia has been known and analyzed, changes in the composition of the urine, just as any other findings indicative of changes in renal function, may be accepted as characteristic. However, from this does not necessarily follow that a renal disease observed after pregnancy complicated by toxaemia and producing similar symptoms is a result of the toxaemia.

According to modern research concerning toxaemia, lesion of the small-blood vessels should be looked upon as being the primary change. The changes in the organs and systems of organs are secondary, and develop in part as a

result of the changes in the small vessels. Thus, it may be stated that in the grave forms of preeclamptic toxaemia the renal parenchyma, too, is damaged and, among others, the changes in the composition of the urine are not due to renal changes, but to changes affecting the vascular system.

In the era of the nephrogenic conception, in 1891, SOLOVIOV already called attention to the fact that at the time changes in the urine are observed during pregnancy also changes in other organs, or in the body as a whole, may be present, attributing significance to the condition of the nervous system, among others. In the light of SOLOVIOV's statements it is justified to mention the entity referred to as an anaemic condition simulating eclampsia, described by NOVÁK and others. It is noteworthy that besides nervous, endocrine, reticulo-endothelial and renal changes anaemia is associated with every case of preeclamptic toxaemia. On the other hand, we have never observed late toxaemia in women regularly controlled from the beginning of pregnancy and given anti-anaemic treatment. Similar observations have been reported by DUBUIS, LAVANCHY, ASSUS, BAZHDEKOV, KOZLOVSKY, and others.

On the basis of all these it may be assumed that it is correct to consider the disturbance of renal function to be a significant, but not primary and essential feature in the development, treatment and prevention of preeclamptic toxaemia.

The tasks facing the obstetrician in the prevention of late toxaemia are generally known and accepted. When the pregnant woman is kept under systematic control from the onset of pregnancy, the slightest toxaemic symptom can be detected early. A proper mode of life should be prescribed and ensured for every pregnant woman. Systematic treatment should be begun immediately on observing the first symptoms of late toxaemia. It should be determined in what cases and when delivery should be started in preeclamptic toxaemia. Beyond these tasks, with which the health administration of this country is scoping more or less effectively, it would be desirable to cooperate more closely with the renal pathologists in the fight against toxaemia. This applies to the cases when the obstetrician needs help in deciding whether preeclamptic toxaemia in a given case is the cause of the renal symptoms, or else, the symptoms have developed on the basis of an already existent renal disease. Modern research has attempted to elucidate this problem by renal biopsy, and this procedure has lead to certain experimental results. It remains to be seen when such efforts will be applicable in practice.

In future the symptomatology and diagnosis of the early phase of preeclamptic toxaemia ought to be studied in more detail. When we say this, we think of the circumstance that we can do little at a time the so-called classic triad of late toxaemia is already observable, and we ought to make efforts to recognize its early factors.

We should like to call the attention of those concerned with the diseases of the kidneys to the fact that it would be desirable to analyze the development and course, as well as every injury in the background of the diesease, in such renal conditions, as are treated by them subsequent to preeclamptic toxaemia, besides determining in what measure the latter can be held responsible for the renal disease. It is thought that by so doing we might detect at least pre-existent renal lesions, or factors predisposing to renal disease.

Finally, in the cases in which preeclamptic toxaemia alone is to be made responsible for the subsequent renal lesion it would be advisable to call the attention of those active in the care of pregnants to the views of the renal pathologists as to what ought to be done.

This paper had the aim of finding the proper place of renal lesions in the framework of late toxaemia, in order to assist toxaemia research. If those elaborated above concerning the obstetrical aspects of renal diseases in general, and toxaemia in particular, have initiated ideas, the paper has served its purpose.

Dr. András Kovács, Budapest, Üllői út 78 Hungary.

REPORTS

FUNCTIONAL, MORPHOLOGICAL AND CORROSION STUDIES IN MASUGI NEPHRITIS

By

P. Gömöri, S. H. Tu, E. Szalay and B. Zolnay

Experimental studies have revealed that in the acute Masugi nephritis of the rabbit an oliguric pattern similar to that seen in human cases develops during the first few days. In that phase corrosion studies do not show serious changes. In corroded preparations the number of glomerules decreases first, then slowly increases (reparation), then decreases again slowly. In chronic Masugi nephritis the corrosion studies, in agreement with the functional and morphological examinations, show similarly grave changes of similar nature as those demonstrable in man. In chronic experimental nephritis the most characteristic change is the formation of a great number of recta vera arteries, as a result of shunts in the juxtamedullary glomerules. These ensure in experimental or human chronic nephritis the maintenance of tubular function.

NEW EXPERIMENTAL DATA CONCERNING THE DEVELOPMENT OF NEPHROPYELITIS

By

F. Rényi-Vámos and L. Horváth

After experimental infection of the urinary bladder, testicle and seminal vesicle inflammatory phenomena, irreversible changes may develop in the kidney. In the haematogenic development of the process significance is ascribed to inflammation of the renal regional lymph nodes due to cystitis, orchitis and seminal vesiculitis, that may interfere with the flow of fluids in renal tissue.

SIGNS OF RENAL FAILURE IN PATIENTS OPERATED FOR DISEASES OF THE LIVER, BILE DUCTS OR PANCREAS

By

E. Egedy, K. Stekker, E. Füredi and L. Fonyódi

Renal function has been studied before and after surgery in 34 jaundiced patients suffering from diseases of the liver, bile duct or pancreas. Symptoms indicative of renal failure occurred in 8 patients, 4 of whom died. It is suggested that the complications are caused by a summation of the effects exerted upon she kidney by the jaundice and the surgical stress. The shock-like effect was teen to develop during a considerable fall of blood pressure.

SWEAT EXCRETION IN ACUTE RENAL DISEASE

By

J. Rév and F. Solti

Sweat excretion and the amounts of K and Na in seat have been examined in 23 patients suffering from bilateral acute glomerulonephritis or pyelonephritis. Sweat was collected by means of the rubber glove method from both palms. Seven patients with acute nephritis recovered while at the Department and in these cases the tests were repeated after recovery. 13. subjects with normal circulation and with circulatory failure were used as the controls.

In the patients with bilateral acute renal disease the volume of sweat and the K in sweat were only slightly increased, and the values were comparable with those obtained in the individuals with normal circulation. However, the amount of Na in sweat was significantly increased, as compared with the normal. According to previous investigations in cardiac failure the volume of sweat, the amount of Na, and in a lesser measure that of K, are decreased significantly. After recovery from nephritis the volume of sweat was slightly decreased, there was practically no change in K output, whereas the Na content, that had been much higher than the normal at the peak of the illness, significantly diminished. Opposite changes were found in the urine.

The significance of the changes in sweat excretion in bilateral renal disease has been analyzed.

RENAL INJURY DUE TO p-N-OXYPHENYLGLYCINE

By

B. N. Li, T. Kemény and J. Sós

The compound p-N-oxyphenylglycine (POG) inhibits the utilization of tyrosine in the organism. By its administration we could influence thyroid function, and especially the synthesis of thyroglobulin.

Considering that besides the thyroid the kidneys contain tyrosine in the largest quantities, our investigations have been extended to renal function. Intraperitoneal administration of from 30 to 50 mg/100 g POG daily has been found to diminish the concentrating power without affecting the diluting activity. Urinary protein output increased to about six times the normal. The blood NPN level remained normal. After 2 or 3 days blood pressure suddenly rose, reached the peak of 150 mm Hg on the 10th day, to remain at that level throughout. Histological examination revealed characteristic crescent-shaped structures as the extracapillary exudate had displaced the glomerular loops laterally. Of the tubules it was first of all the primary and secondary ones of the cortex that exhibited degenerative changes.

The results obtained suggest that tyrosine is essential for normal renal function, and the inhibition of its utilization leads to functional and morphological changes in the kidney.

NERVOUS FACTORS IN EXPERIMENTAL URAEMIA

By

I. Dési, M. Antal and I. Fehér, and G. Simon

Electrodes were built into different areas of the cerebral cortex and subcortex in cats. The changes in cerebral activity after bilateral nephrectomy have been studied by electroencephalography until death.

When the general condition deteriorated and body temperature decreased, EEG changes of increasing severity appeared. The first in the subcortex, then in the cortex. In spontaneous activity high, slow toxic waves appeared to dominate the pattern after a time. At first in response to stimulation of the reticular formation, then also spontaneously, seizures were developed. With the increase of toxaemia the waves became slower and slower, the response to stimulation diminished then ceased, and some minutes before death complete electrical silence resulted.

Investigations into the pathomechanism revealed a significant increase of capillary permeability and cerebral oedema.

In the second part of the experiments similar EEG changes, increase of capillary permeability and cerebral oedema were induced by the injection of uraemia toxin prepared from the blood of uraemic human patients and of nephrectomized dogs.

It is suggested that for some of the nervous complications of uraemia partly the cerebral oedema and partly the uraemia toxin always demonstrable in the uraemic blood and cerebrospinal fluid are responsible. The toxin is supposed to have a subcortical site of action.

ENZYME ACTIVITY CHANGES IN THE RAT FOLLOWING UNILATERAL NEPHRECTOMY AND PARTIAL HEPATECTOMY

By

M. Tényi

It has been found in rats subjected to partial hepatectomy and unilatera nephrectomy that

1. after either intervention the glutamic acid-oxalacetic acid-transaminase (GOT) and aldolase (hepatectomy), and the GOT and sorbit-dehydrogenase (SDH) activities (nephrectomy) of the serum increased in connection with regeneration and hypertrophy, respectively,

2. the increase in GOT activity is slighter after nephrectomy than in the course of liver regeneration,

3. in the hepatectomized animals the most significant increase of serum GOT and aldolase activity occurred in the 2-globulin fraction, whereas following unilateral nephrectomy the increase of the GOT and SDH activities was found in the α-globulin fraction. In the untreated animals the highest activity was found in the β-globulin fraction.

RENAL CHANGES CAUSED BY SEROTONIN IN THE RABBIT AND RAT

By

E. Beregi, I. Földes, D. Jankovics and L. Csötörtök

In response to chronic serotonin treatment (3 to 5 mg/kg, daily) patchy ischaemia of the renal cortex, indicative of a constriction of the afferent vessels, develops in rats and rabbits. Besides the tubular changes glomerular ones, too, develop; protein appears in Bowmans capsule, the basement membrane of the glomerular loops increases in thickness. If chronic serotonin treatment follows sensitisation with horse serum and is associated with bathing the

animals in cold water, the changes described increase in severity slightly in the rabbit and markedly in the rat. Thus, like in the case of other serotonin effects, species differences should be taken into consideration.

SIGNIFICANCE IN PREGNANCY OF PREVIOUS NEPHRITIS

By

J. Erneszt

The normal organism tolerates the stress of pregnancy without pathological changes. In preeclamptic toxaemia we often find evidence of nephritis in the patient's history. It is commonly known that in the deterioration of renal function haemodynamic changes play the most important role. In late toxaemia of pregnancy the contraction of renal blood vessels is regulated by the hypertension and chronic cerebral hypoxia. According to our observations, late toxaemia of pregnancy is liable to develop in patients with previous renal disease, though during pregnancy the renal function tests yield normal results. Exact differential diagnosis has a vital importance in the cases of renal disease developing during pregnancy. In adults nephrosis often overmasks the oedematous-albuminuric phase of glomerulonephritis. The symptoms of acute nephritis may often be mistaken for those of the congested kidney occurring in heart failure. For this reason attention should be focussed on differential diagnosis and the occurrence of nephritis in the history.

JUVENILE NEPHRONOPHTHISIS

By

F. Láncos

A type of lethal nephrosclerosis showing the symptoms of primary tubular insufficiency, occurring exclusively in childhood and showing sometimes familial massing was described by Fanconi. In the 9 cases thus far reported the diagnosis was established almost exclusively at autopsy.

The present case had been diagnosed during life and diagnosis was confirmed by renal biopsy. The patient has been under our observation since 2 years. The parents are relatives, the paternal grandfather and the maternal grand-grandmother having been brother and sister. There were several cases of adrenogenital syndrome and epilepsy in the family. The patient at the age of two years was admitted to a hospital because of polyuria and polydipsia. Diabetes insipidus was diagnosed and posterior pituitary extract was administered without benefit. The child was admitted to our Department at the

age of 5 years; she was then severely anaemic, underweight and lagging in growth. The only pathological urinary change found were traces of albumin. The BPN level was significantly increased, endogeneous creatinine clearance was a fraction of the normal, concentrating power was poor. The low serum calcium, and high serum phosphorus values, acidosis, as well as the increasing osteoporosis, were indicative of renal failure. Blood pressure remained normal throughout the two years of observation, which is characteristic of the syndrome. To rule out other types of nephrosclerosis, amino acid excretion tests have been made, but the results obtained were normal. Likewise, urological examinations yielded normal results.

The diagnosis of nephronophthisis was confirmed by the renal biopsy revealing tubular and glomerular destruction and a secondary increase of connective tissue. Electronmicroscopy showed thickening of the basement membrane, poor differentiation and low mitochondrium content of the tubular cells.

By chronic norteslosterone treatment osteoporosis, weakness and fatigability were favourably influenced and the progression of the disease was slowed down.

PROGNOSIS OF WILMS' TUMOUR

By

Z. Erdős, E. Cserháti and I. Hittner

24 cases of Wilms' tumour treated during the past 10 years are analyzed. As compared with the 1/2 per cent incidence for adults, in childhood 20 per cent of the tumours are renal in origin. Treatment should consist of surgery without delay, followed by postoperative X-ray irradiation. In cases where the size of the tumour formed an obstacle to removal *in toto* preoperative irradiation was applied. In 70 per cent of the cases radical surgery was performed, in 15 per cent only part of the tumour could be resected, and in 15 per cent explorative laparatomy could be performed only. The two year survival rate was 50 per cent. No decisive improvement of the prognosis could be ascertained in the material studied.

In the case of Wilms' tumour the classic rules of prognosis are still valid: early diagnosis, gentle methods of examination, radical operation, ligation of blood vessels in intact tissue and postoperative irradiation.

FOLLOW-UP STUDIES IN PATIENTS RECOVERED FROM ACUTE URAEMIA

By

G. GÁL, A. NÉMETH and S. FAZEKAS

The following conclusions have been reached.

Following tubular renal lesion the restoration of renal function may be expected within one year.

After the actual renal disease is over, the patient should be spared lead a convalescent's life for 3 to 6 months; the time of resuming work should be determined on the basis of renal function tests, neurological and ophthalmological examinations. One year later neither pregnancy nor surgery seem involve more risks than in other subjects.

The sequelae to the nervous and cerebral changes associated with uraemic toxaemia persist for several years in most patients.

Streptomycin treatment ought to be avoided in the oliguric-anuric phase.

APPRAISAL OF RENAL REGULATION ON THE BASIS OF ELECTROLYTE EXCRETION IN BANAL INFECTIOUS DISEASES DURING UNRESTRICTED FLUID INTAKE AND DURING THE CONCENTRATION EXPERIMENT

By

M. GALAMBOS

In 12 girl patients between 6 and 12 years of age, free from renal disease, serum and urinary electrolytes have been studied in the acute stage of scarlet fever. As a control, the same examinations were carried out in 10 normal healthy children of the same age, before and during the concentration experiment.

In the patients the serum sodium, chloride and potassium levels significantly increased, and the bicarbonate level decreased during the experiment, while urinary excretion of sodium, chloride and TA greatly diminished. During the concentration experiment the mean urinary delta value exceeded only slightly the initial one, in half of the cases the delta was unchanged, or even decreased, whereas urine output increased, a sign indicative of forced osmotic diuresis. None of these changes could be noted in any of the controls.

THE SIGNIFICANCE OF INTIMAL MUCOPOLYSACCHARIDES IN LIPID DEPOSITION

By

S. Gerő, J. Gergely, T. Dévényi, L. Jakab, L. Kocsár, J. Székely and S. Virág

The significance of intimal mucopolysaccharides (MPS) in the process of atheromatous plaque formation has been studied by the isotope technique. In the aorta of rabbits with cholesterol atherosclerosis the S^{35} uptake by the MPS isolated from the vascular wall was much higher than in the controls. This indicates that the sulphated MPS of the aorta is increased.

Studies of the MPS isolated from the intima of atherosclerotic human aorta have shown that one group of these formed a specific complex with the beta lipoprotein and fibrinogen fractions of the plasma.

In further investigations it was examined how the human intimal MPS influence the aortic lipolytic activity in different species. It has been shown that in proportion to the increase in their concentration the intimal MPS inhibit the lipolytic activity of the aorta in the rabbit, rat and dog alike. The inhibitory activities of chondroitin sulphate and hyaluronic acid were weaker than that of the mixture of intimal MPS.

The ability of intimal MPS to link up with beta lipoprotein and fibrinogen, as well as their inhibitory action on lipolysis, may be correlated with their macroanionic property.

It is surmised that the deposition of lipids may be initiated by such chemical and/or physicochemical changes in the composition of intimal MPS, as, on the one hand, make it possible that MPS-beta lipoprotein complexes be formed, and, on the other, inhibit the lipolytic activity of the vascular wall proper. Both processes may be links in the formation of atheromatous plaques.

MULTIPLE SCLEROSIS AND DISSEMINATED ENCEPHALOMYELITIS

By

A. Juba

The morphological changes indicative of an involvement of neuroallergic mechanisms, first of all that of "serous tissue imbibition" have been studied in a few cases of cerebral demyelinisation (acute flare-up of multiple sclerosis, subacute Schilder's disease). Although marked serous tissue imbibition was visible around many of the fresh foci in the case of acute exacerbation

of multiple sclerosis, in the smallest initial demyelinisations only micro-macroglial reaction was demonstrable. Similar changes were found in the earliest foci of Schilder's disease; thus, the present cases did not confirm that neuro-allergic mechanisms would play a role of general significance.

INTERMEDIN EFFECT OF IMPLANTED FISH PITUITARY IN CASES OF PIGMENT DEGENERATION

By

E. Kubányi

A new material and a new technique of heterotransplantation are described. The material is the hypophysis of osseous fishes removed under aseptic conditions and stored by deep-freezing. The technique is that of gonadotropic stimulation, i.e. a hormonal effect attainable through "hypophilisation". The idea was suggested by the results of comparative studies of the histology of bony fish. In that species, as in the lowest vertebrates, the intermediate part of the pituitary represents the highest percentage among all animals. The group of melanophore cells regulates the activity by which the fish can change colour, under the control of the so-called pigmentary effector. It was on grounds of this fact that the author has tried to utilize the effect of the hormone intermedin. A brief account is given of the results achieved up to now. It is already possible to produce commercially lyophilyized fish hypophysis preparations of full activity. Experience has shown that the pituitary effect was most marked when the fish were spawning. Gonadotropic stimulation was effected by treating the fish with pituitary emulsion prepared from other fish. By fish hypophysis titration in adrenalinized frogs it has been shown that by hypophilisation the intermedin activity of the fish hypophysis could be increased by 40 per cent. An account is given of the experience obtained in the patient material of four ophthalmological departments and four general hospitals.

TRANSITORY RETINAL RESPONSE TO PITUITARY IMPLANTATION IN CASES OF RETINITIS PIGMENTOSA

By

A. Kahán

Considering that the melanocyte stimulating hormone (MSH) producing intermediary lobe is extensive in fish, and neogenesis of visual pigments is enhanced by MSH, the effect of fish pituitary implanted according to Kubányi, by administering intragluteally 0.25 g material stored by deep freezing has

been studied. Of 22 implantations 15 caused an amelioration of retinal functions, beginning on the fifth and vanishing on the twentieth day. The effec- consisted in

a) amelioretion of rod thresholds, amounting to 2.0 log $\mu\mu$ Lamb, in 4 cases;

b) in 3 cases, the extinguished ERG gave place to a negative wave of 250 μV

c) repeated implantation after the effect had ceased, released the same response.

Implantation of calf pituitary was found to be less effective. It has been concluded that the response was due to MSH and not to ACTH, suggesting the possibility that by injecting pure MSH the activity of photoreceptors may be raised.

DIAGNOSTIC LAPAROSCOPY IN GONADAL DISTURBANCES OF THE FEMALE

By

M. Csillag and K. Morócz

The hazards of laparoscopy are so much less than those of explorative laparotomy that the indication for the former intervention can be accepted much more often than for the latter. Laparoscopy is indicated by every endocrinological case in gynaecology when the method of feasibility of treatment depends on the intraabdominal finding.

Thus, among the gynaecological endocrine disorders laparoscopy is indicated by the following conditions. 1. Hypertrichosis, especially when the ovary is palpably enlarged, to differentiate the condition from Stein—Leventhal's syndrome. 2. Primary or lasting amenorrhea, to determine whether there is ovary or uterus in the organism and how well developed it is. 3. Recurrent dysmenorrhoea over longer periods of time, to determine whether there is persisting follicle, hyperplasia or tumour in the ovary.

Among 76 patients witch complaints like those mentioned above 37 displayed changes first of all in the ovaries that explained the disturbances. Laparoscopy will yield valuable information as to the true nature of the pathological condition especially when preceded by careful endocrinological examinations.

RESTORATION OF FLUID AND ELECTROLYTE BALANCE IN INTESTINAL OBSTRUCTION

By

I. Köves and E. Kelemen

After discussing the pathological changes following obstruction of the small intestine, the lethal factors are summarized as follows: 1. distension; 2. disturbances of the fluid and electrolyte balance and of the blood depots; 3. peritonitis; and 4. absorption of toxic substances.

Obstruction at the beginning of the small intestine is to be sharply differentiated from that at the terminal part. In high obstruction dehydration and disturbances of electrolyte metabolism develop rapidly and the accompanying metabolic alkalosis plays an important role. In low obstruction the significance of metabolic acidosis predominates.

The proper schedule of treatment may be outlined as follows. Gastric suction should be started without delay and also a drip infusion of an 1 in 1 mixture of physiological saline and sucrose containing 50 to 80 mEq of K, then of 500 ml whole blood and 250 to 500 ml of plasma. The infused fluid should be supplemented with the electrolytes necessary for restoring acid-base balance. The maximum amount administered should be 3000 ml. Further treatment should depend on the results of repeated ionograms circulating blood and plasma volume, haematocrit, urinanalysis, NPN, and the condition of the circulation. It is emphasized that besides careful observation the selection of the proper time for surgery is of paramount importance.

DUODENAL OSMOREGULATION IN THE RAT

By

F. Gelencsér, T. Gáti, J. Hideg and L. Selmeci

Intraduodenal injection of distilled water has been found significantly to increase the severity of the mucosal changes induced by the Shay operation. Hypertonic solutions (2.7 per cent or 5.4 per cent NaCl, or 1.24 per cent LiCl) completely prevented the development of ulcer. In the animals treated with NaCl solution the values for secretion, pH and total acidity were not different from the control ones, while in the case of LiCl the pH shifted towards the neutral and total acidity decreased significantly. On the basis of the results it is surmised that a duodenal osmoregulation protecting the mucosa is active in the rat.

MYCOBACTERIOSIS. CLINICAL AND EXPERIMENTAL DATA CONCERNING THE SIGNIFICANCE OF THE MYCOBACTERIUM VARIANTS ARISING IN THE ORGANISM

By

M. Lányi

Mycobacteriosis is a clinical conception. It means that in the organism we can find mycobacteria which differ in fundamental biological properties equally from the classic forms of Mycobacterium tuberculosis and the saprophytes. Three forms of the condition can be distinguished, 1. excretion of attenuated bacteria with weak virulence, but normal growth following prolonged INH treatment. 2. *Primarily resistant* bacteria are excreted. This is observable in individuals suffering from tuberculosis for a very long time, never subjected to antibacterial treatment and in whom exogenous resistant infection can be ruled out. On the basis of clinical observations it is assumed that in such cases variants produced in the course of prolonged parasitic symbiosis increase in number. 3. In the third form *atypical* bacteria not pathogenic for animals and showing peculiar properties on cultivation are excreted. Such variants could not be produced experimentally and were isolated exclusively from pathological material. The internal milieu of the organism is responsible for their arisal.

The mycobacteriosis observed in pneumological practice is thought to be a consequence of tuberculosis and a phenomenon associated with the decline of tuberculosis incidence.

ESTIMATION OF THE pH OF BLOOD IN THE DIAGNOSIS OF THE DISTURBANCES OF ACID-BASE BALANCE

By

D. Boda and L. Murányi

In modern clinical practice, for the correct diagnosis of acid-base disturbances it is essential to determine the pH of blood, alongside the tests for other factors, first of all the metabolic components.

The pH of a suitably pre-treated blood sample will supply information as to the other factors ensuring the acid-base balance, for example after one bubbling through with oxygen of 40 mm Hg/m pCO_3 the standard bicarbonate value, and after bubbling through with two gaseous mixtures of known com-

position, the other factors, bicarbonate and CO_2 tension may be determined. Evaluation is made considerably easier by the nomogram recommended by the authors.

CLINICAL AND LABORATORY METHODS OF EXAMINATION AS GERIATRICAL TESTS

By

Z. Dénes

One of founders and masters of geriatry as a branch of sciences was Sándor Korányi, who saw the essence of ageing in a narrowing down of the organism's adaptative capacity.

Clinical and laboratory tests are described suitable for the control of the preventive and therapeutic methods aimed at slowing down the rate of ageing and for the characterisation of old age.

1. Measurement of vital capacity.
2. Discussion of certain features of the differential blood count, with special reference to the aniso leucocytes and shrunken erythrocytes.
3. Studies of the enzyme peroxidase.

A HUMORAL SIGN INDICATIVE OF HYPERSPLENISM

By

E. Kelemen, F. Doctor, D. Lehoczky, I. Cserháti and K. Rák

Unlike the serum of normal subjects and patients suffering from disturbances of cytopoiesis, a single intravenous injection of 0.2 ml of the serum from hypersplenic subjects often increases in mice the number of the circulating neutrophilic granulocytes and thrombocytes in 2 to 5 days. Insofar as this test can be used as an indicator, it may be assumed that hypersplenic granulo- and thrombocytopenia arises not as a result of a lack of a stimulus taking part in regulation.

THE EFFECTS OF THYMECTOMY AND THYMIC SUBSTITUTION UPON EXPERIMENTAL ARTHRITIS

By

G. Csaba, M. Bodoky and I. Bernád

In earlier experiments it has been shown that thymectomy aggravates the course of experimental arthritis in the rat. When thymectomized animals are treated with cortisone, instead of relieving arthritis this treatment makes

it graver and gangrene develops in the paw. Thus, in such cases the antiphlogistic action of cortisone seems to be exerted through the thymus, inasmuch as the hormone would mobilize in the thymus mucopolysaccharides of the heparin type, that antagonize aldosterone and histamine, and it is in this way that inflammation would be relieved. In the absence of the thymus the paradoxical effect of cortisone becomes manifest.

Starting out from these observations, embryonic trachea has been implanted into the spleen of adult rats. The graft in the spleen gave rise to cysts similar to thymic cysts and producing large quantities of PAS-positive substance. This PAS-positive substance appears in the thymic cysts, too, and constitutes the precursor of acid mucopolysaccharides. Thus, by means of tracheal transplantation a morphological model of thymic cysts can be created.

The present experiments have shown that the morphological model could reproduce thymic function, insofar as the transplantation into thymectomized animals of such an "artificial thymus" resulted in the healing of arthritis and the paradoxical response to cortisone did not appear. By serum heparin determinations it has been proved that it is in fact through the heparin mechanism that the thymus interferes with the process of inflammation, because cortisone treatment is accompanied by an elevation of the serum heparin level. It is pointed out that the adrenal-thymus antagonism exists first of all between the mineralocorticoids and the thymus, whereas cortisone has a regulative activity, in the first place.

BILIARY ACID CONCENTRATION IN BLOOD SERUM IN DIABETES

By

Z. Aszódi and J. Zombory

The experiments carried out in recent years have contributed many data as to the synthesis of and the interrelations between the compounds of sterane structure. These results have induced us to collect clinical material for studying the correlations between cholesterol and biliary acids and to study sterane metabolism in such patients.

To facilitate comparison, the normal biliary acid level in blood had to be determined, because the pertaining data in the literature vary over an extremely wide range. The data for cholesterol are unequivocal.

After having developed reliable methods for the isolation, purification and fluorometric determination of biliary acids, the normal biliary acid level in serum was determined in such cases, in which no elevated levels were likely to occur. The mean normal level was found to be 0.37 mg per 100 ml in 63 tests in 25 patients.

Under normal conditions, sterane structure synthesis, metabolism and excretion are regulated by factors in the liver and serum, some of which are already known. Under pathological conditions, however, this balance becomes upset. In diseases associated with biliary obstruction the levels of bilirubin and biliary acids increase in serum, and also the cholesterol level is often elevated.

In 69 cases of jaundice due to various conditions (epidemic hepatitis, liver cirrhosis, cholelithiasis, cancer of the head of pancreas, cancer of gall bladder and liver) the 226 tests made showed elevated levels invariably, with the mean increase amounting to fivefold the normal value. In the same cases the bilirubin level was increased eightfold.

There are, however, diseases, first of all metabolic disorders, in which the biliary acid and cholesterol levels were increased without biliary obstruction. In the serum of diabetics namely the level of biliary acids was significantly elevated. To obtain detailed data, 213 tests for biliary acid, cholesterol and sugar in blood were made in 79 cases of diabetes.

In diabetes the biliary acid concentration in blood serum was found to amount to 3 to 4 times the normal level. The increase was the greater the more severe was the diabetes. The biliary acid level in the serum in diabetics treated with diet and oral antidiabetics was 10.2 per cent, that of the insulin-treated ones 45.2 per cent higher than that of diabetics treated with diet alone. It seems that oral antidiabetic (sulphanyl carbamide) preparations and insulin influence differently the complicated steroid metabolism of the diabetic individual.

It is common knowledge that in diabetes the serum cholesterol level is elevated corresponding to the severity of the disease. In every one of the three groups the cholesterol values were elevated. However, the difference in cholesterol level between the patients treated with diet alone and those treated with oral antidiabetic drugs was merely 1.9 per cent, and that between the former and the insulin-treated patients was 12.9 per cent.

Thus, in the serum of diabetics the increase of biliary acid concentration is much greater than that of the cholesterol level. It may be assumed that insulin alters cholesterol-biliary acid metabolism in a fashion different from the action of the oral antidiabetic drugs.

Experiments are being carried out in rabbits with alloxan diabetes to elucidate and explain the correlations found in humans.

PROTEIN ABSORPTION FROM SUBCUTANEOUS TISSUE IN VENOUS CONGESTION AND IN HYPOPROTEINAEMIA

By

G. Szabó and Ö. Zoltán

In the dog with experimental pericarditis, subjected to plasmapheresis, the local absorption and transport through the opened thoracic duct of subcutaneously injected I^{131} were studied. It has been found that in pericarditis the labelled protein was transported at a significantly faster than normal rate; while in normal animals 5.72 per cent (S. D. = 4.21) of the amount injected is eliminated through the opened thoracic duct in 140 minutes, the corresponding value in dogs with pericarditis was 22.59 per cent (S. D. = 12.65). In animals with intact lymphatics no significant increase in the rate of local protein absorption could be observed in phlebohypertension.

In acute plasmapheresis the amount of protein transported away through the lymphatics showed a slight, not significant increase (7.49 per cent; S. D. = 3.47); at the same time, absorption of the injected material was significantly increased. From the results it has been concluded that in generalized phlebohypertension the rate of protein transport from the connective tissue is not significantly increased, because, owing to the elevation of pressure in the great veins, lymph flow and the emptying of the lymphatics are interfered with. In hypoproteinaemia protein absorption is accelerated, but this is partly due to the fact that in that condition considerable quantities of protein are absorbed directly by way of the blood capillaries.

THE EFFECT OF A DIMINUTION OF THE EFFECTIVE CIRCULATING BLOOD VOLUME ON CEREBRAL BLOOD FLOW AND CEREBRAL VASCULAR RESISTANCE IN MAN

By

F. Solti, G. Szabó, M. Iskum, Á. Péter, J. Rév and K. Földesy

According to the results obtained, in response to stasis in the lower extremities cerebral blood flow decreases, cerebral vascular resistance increases, cerebral arteriovenous oxygen difference increases and cerebral venous pressure decreases. Thus, it may be assumed that in the development of the renal and circulatory changes accompanying the acute diminution of circulating blood volume the changes in cerebral circulation have a role to play.

EFFECT OF HYPOXIA ON CEREBRAL VENOUS CIRCULATION

By

M. Iskum, F. Solti, I. Komáromi, G. Simonyi and Z. Réfi

Acute hypoxia has been found to be soon followed by an increase of venous tone, and later by an elevation of cerebral venous pressure and systemic venous pressure. The changes regressed after hypoxia had ceased. Previous administration of dibenzylamine prevented the development of the hypoxic increase of venous tone and venous pressure.

ARTIFICIAL HIBERNATION IN THE PREVENTION OF POSTOPERATIVE THYROLAXIC CRISIS

By

C. Sztankai and V. Csernohorszky

During the past 10 years our Department has focussed considerable attention on the surgical treatment of hyperthyroidism and the underlying pathologic processes. As a result, treatment has become considerably more effective. Among the many factors which have contributed to this, artificial hibernation was one of the most important methods. It plays a significant role in preoperative management, in the potentiation of anaesthesia and in the prevention of postoperative reactions. It is considered the method of choice in the case of a thyrolaxic crisis, when deconnexion, and in severe cases hypothermia is recommended. Of the drugs high doses should be applied, in order to maintain effective levels.

In the cases requiring combined treatment the proper vitamins, steroids, anabolics etc. should be used as adjuvants.

It is an important practical rule that the hibernated patient suffering from Grave's disease should be kept under constant supervision in the emergency department.

Printed in Hungary

A kiadásért felel az Akadémiai Kiadó igazgatója — Műszaki szerkesztő: Farkas Sándor

A kézirat nyomdába érkezett: 1963. IV. 12. — Terjedelem: 10 (A/5) ív, 34 ábra

63.56965 Akadémiai Nyomda, Budapest — Felelős vezető: Bernát György

The *Acta Medica* publish papers on medical science in English, German, French and Russian.

The *Acta Medica* appear in parts of varying size, making up volumes.

Manuscripts should be addressed to:

Acta Medica
Budapest VIII., Korányi S. u. 2/a, I. Belklinika

Correspondence with the editors and publishers should be sent to the same address.

The rate of subscription to the *Acta Medica* is 110 forints a volume. Orders may be placed with "*Kultúra*" Foreign Trade Company for Books and Newspapers (Budapest I., Fő utca 32. Account No. 43-790-057-181) or with representatives abroad.

Les *Acta Medica* paraissent en français, allemand, anglais et russe et publient des mémoires du domaine des sciences médicales.

Les *Acta Medica* sont publiés sous forme de fascicules qui seront réunis en volumes.

On est prié d'envoyer les manuscrits destinés à la rédaction à l'adresse suivante:

Acta Medica
Budapest VIII., Korányi S. u. 2/a, I. Belklinika

Toute correspondance doit être envoyée à cette même adresse.

Le prix de l'abonnement est de 110 forint par volume. On peut s'abonner à l'Entreprise du Commerce Extérieur de Livres et Journaux «Kultúra» (Budapest I., Fő utca 32. — Compte-courant No. 43-790-057-181) ou à l'étranger chez tous les représentants ou dépositaires.

«*Acta Medica*» публикуют трактаты из области медицинских наук на русском, немецком, английском и французском языках.

«*Acta Medica*» выходят отдельными выпусками разного объема. Несколько выпусков составляют один том.

Предназначенные для публикации рукописи следует направлять по адресу:

Acta Medica
Budapest VIII., Korányi S. u. 2/a, I. Belklinika

По этому же адресу следует направлять всякую корреспонденцию для редакции и администрации.

Подписная цена «*Acta Medica*» — 110 форинтов за том. Заказы принимает предприятие по внешней торговле книг и газет «*Kultúra*» (Budapest I., Fő utca 32. Текущий счет № 43-790-057-181) или его заграничные представительства и уполномоченные.

32,— Ft

Index: 26.015