Summaries – Résumés

Recherches sur l’épuration extra-rénale à l’aide du charbon actif
H. Yatzidis

En 1961 nous avons noté que le charbon actif est capable d’absorber in vitro des quantités appreciables de certaines substances du plasma urémique ou du liquide du tractus intestinal. Des dosages répétés sur des plasmas urémiques ont démontré qu’un gramme de charbon actif en poudre peut capter simultanément environ: 9 mg de créatinine endogène, 8 mg d’acide urique, 1,75 mg de phenols, 0,30 mg d’indi-can, 1 mg de guanidines, 35 mg d’urée, 0,35 mEq d’acides organiques et des quantités minimes de magnésium, de calcium et de phosphate, tandis que son action est nulle envers le sodium, le potassium, le chlore, le bicarbonate et le sulfate.

Entre 1961 et 1964, nous avons étudié systématiquement l’influence du charbon actif administré par voie buccale sur les manifestations biologiques et cliniques de l’insuffisance rénale avancée. Douze malades ont été soumis à une cure comportant la prise de 20 à 50 g par jour de charbon actif, avec ou sans sorbitol associé. Le contrôle biologique fait deux fois par semaine a révélé une nette et constante diminution des phenols et, à un moindre degré et plus rarement, de l’acide urique. Contrastant avec cet effet biologique, à vrai dire limité, l’amélioration de l’état clinique était quelquefois impressionnante, surtout en ce qui concerne les symptômes gastro-intestinaux (nausées, vomissements, métrorhisme). Aucun inconvenient n’a été observe, même après 4 à 20 mois de traitement continu par le charbon.

Depuis la fin de 1962, nous avons expérimenté chez le chien un appareil permettant de soumettre le sang circulant à une absorption par le charbon. Le dispositif est constitué d’un cylindre en verre de 20 × 6 cm, dont les extrémités sont munies de filtres métalliques, rempli de 200 g environ de charbon actif en granules (particules de 0,50 mm) dont l’efficacité est de 50% de celle du charbon en poudre (Fig.). Le sang artériel passe sur le charbon actif et retourne dans la circulation veineuse. Chez l’homme urémique, une séance de 30 à 60 minutes donne un résultat remarquable sur le syndrome clinique et sur certaines perturbations biologiques. La construction et le montage de l’appareil, la conduite d’une séance d’épuration et les résultats obtenus dans les 20 premières Haemo-Perfusions furent détaillés dans un rapport présenté à Amsterdam en 1964 (1). Depuis, de nouvelles constatations ont confirmé l’intérêt de l’Haemo-Carbo-Perfusion en tant que méthode à la fois pratique et efficace d’épuration, trouvant sa place dans le traitement de l’insuffisance rénale et de certaines intoxications, en particulier dans les formes sévères d’intoxication par les barbituriques (2).

Bibliographie
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Obturated Venous Catheter for Repeated Haemodialysis in Acute Renal Failure
J. Funder and J.O. Wieth Lancet /; 148-150 (1964)
An obturated venous catheter permitting repeated veno-venous haemodialyses is described. Experiences from 100 dialyses performed on 47 patients are reported. Employing tubes of internal diameters from 2.5 to 4.0 mm, a blood flow averaging 700-800 ml per minute was achieved in the first as well as in the following dialyses.
The number of surgical cut downs on the great saphenous vein was reduced to one third of previous common use. The rate of wound infection was lessened, and the potential risk of sepsis from cut down wounds was greatly reduced. The incidence of septicaemia was not affected. This is ascribed to the special composition of the material, ¼ of the patients having severe infectious complications to their
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basic disease. No embolic and no serious thrombotic phenomena were observed. Use of this form of cannulation was no obstacle to early mobilization of patients.
For haemodialysis of children a veno-venous shunt through two obturator tubes, one guided to the upper part, one to the lower part of the caval vein, is recommended.
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The Treatment of Severe Aspirin Poisoning
Forced diuresis is a logical method of treating salicylate poisoning, and it has been demonstrated by several workers that the excretion of free salicylate is increased if the urine is made alkaline. The removal of salicylate by haemodialysis and simultaneous forced diuresis has been measured in six patients with acute aspirin poisoning, and has been compared with the effects of forced alkaline diuresis alone in five patients with poisoning of the same severity.
In each patient clinical improvement was related to reduction in serum salicylate level.
If delays in obtaining use of the artificial kidney are taken into account, forced alkaline diuresis is shown to be comparable in efficiency to haemodialysis in producing clinical and biochemical improvement over the eight-hour period following diagnosis.
Our method of treatment is to stimulate the flow of about 500 ml per hour of alkaline urine, by the intravenous infusion of 2% sodium bicarbonate, 0.9% sodium chloride and 5% dextrose solutions, in rotation. A total volume of 6-8 litres is necessary to produce 3-4 litres of urine in the first 8 hours’ treatment. The rate of infusion is controlled according to the patient’s clinical state,
the hourly volume of urine, and the serum salicylate level, which should be measured each hour. Sodium bicarbonate is omitted from the infusion when the urine attains a pH of 8.0, as measured by indicator paper.

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Treatment by forced diuresis should not be attempted in the presence of hypotension, which is an indication for urgent haemodialysis, or where renal function is suspect for any other reason. In severe aspirin poisoning, promptness of action is vital, and we regard this condition as a medical emergency which demands the closest supervision.

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Mannitol Diuresis: A Method of Renal Protection During Surgery

General anesthesia and surgery cause acute depression of renal function. Previous studies from this department have shown that the maintenance of sustained hydration and infusion of hypertonic mannitol solution will prevent acute functional renal failure during various surgical procedures. Six patients with chronic renal impairment were selected for study to determine if sustained hydration and mannitol infusion would prevent further acute depression of renal function during urologic procedures.

Prior to anesthesia, hydration and diuresis were initiated by the intravenous infusion of hypotonic saline (1 part normal saline to 2 parts 5% dextrose and water) in an amount equal to 10 ml/kg of body weight plus the overnight urine volume. Hydration was sustained by matching the rate of infusion with the urine volume every 30 minutes during the surgical procedure. Osmotic diuresis was produced and sustained by the intermittent infusion of 20 grams of mannitol as needed to maintain urine flow between 60 and 180 ml/h. The amount of mannitol required varied between 40 and 85 g.

Renal function as estimated by creatinine clearances and urine flow was maintained at the levels obtained during control studies prior to surgery in all patients. The postoperative courses were uncomplicated and renal function showed no further impairment as the result of surgery.

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The observations of this study and previous studies suggest that hydration supplemented by mannitol infusion has a renoprotective effect for the surgical patient and should supplant the traditional fluid restriction imposed on surgical patients.

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Measurement of Renal Function in Hemorrhagic Hypotension
Effect of Mannitol

Hypertonic (20%) mannitol has induced marked increases in urinary flow rate and chemical renal clearances following episodes of hypotension in man.

Experiments to examine specific renal hemodynamic effects (1, 2, 3) of mannitol were performed in the dog at pressure ranges from 50 mm Hg to normotensive states, during anuric,
oliguric, and normal urinary flow rates. Cardiac output (3) was measured by directly implanted electro-magnetic probes. Renal blood flow was measured by cannulation of the renal vein (DRBF), or by clearance-calculated flows:

RBF
Cpah
Epah X (1-Hct)

In oliguric and anuric hypotensive states (50-75 mm Hg) mannitol (5 ml/min i.v.) diuresis induces a washout of PAH which previously accumulated in the renal tubules. As a result, RBF and Cpah are transiently and factitiously elevated (average 30 minutes after infusion started). At this time DRBF indicates only a 13% average increase. In normotension DRBF increases an average of 30 % while Epah and filtration fraction fall, and RBF is again falsely elevated (average 55 minutes). RBF and DRBF later show close agreement in all these conditions when a steady state is achieved (47-94 minutes after infusion started). Hemodilution was also induced in all these states during mannitol as proven by a consistent fall in arterial hematocrit.

Concomitant measurement of cardiac output indicates (Fig. 1) that the rise in DRBF is related to plasma volume expansion and hemodilution induced by rapid mannitol infusion (3). The calculated renal fraction of the rising cardiac output in all states fails to increase during mannitol, further confirming that the source of the increased DRBF is not intra-renal. Since Epah is decreased during mannitol, in normotension and hypotension, even after a steady state is achieved, the associated small rise in DRBF is believed to be partly accomplished through an intra-renal redirection of blood flow through non-secretory tissue.

References
The Reversal of Rejection in Human Renal Homografts with Subsequent Development of Homograft Tolerance

The rejection process in humans receiving renal homografts can seldom be entirely prevented. At varying periods after operation, acute deterioration of renal function signals the onset of graft repudiation, accompanied by fever and other evidence of a systemic response. The physiological derangements attending such a rejection crisis can be regularly reversed by the addition of actinomycin C and massive doses of prednisone to pre-existing therapy with azathioprine. In 1 of the 10 patients, a similar reversal was possible by the addition of actinomycin C and prednisone in a patient previously treated with total body irradiation. The degree of functional recovery has been essentially complete in those patients who could be followed up and observed carefully for the longest periods.

A state of host-graft nonreactivity has seemed to follow the successful treatment of such a rejection crisis. Resumption of the same therapy which failed to prevent the initial attack on the graft has been sufficient to prevent a secondary rejection attempt in all but one case.

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Immunosuppressive Drug Therapy in Canine Renal and Skin Homografts

Seven drugs or combinations of drugs have been used to suppress the immune response to renal homografts in 79 bilaterally nephrectomized dogs: Actinomycin C alone; Imuran in combination with 6-methylaminopurine; Imuran in combination with 4-hydroxy-pyrazolo-pyramidine; Imuran in combination with Actinomycin C; Imuran in combination with Methotrexate; Imuran in combination with Azaserine; and Imuran in combination with 6-diazo-5-oxo-L-norleucine.

The combination of Imuran and Azaserine has proven the most effective for both survival and function of the transplant. The specificity of drug tolerance in long term survivors has been tested by subsequent skin homografts from the kidney graft donors and from indifferent third party donors. All skin grafts were rejected. Cross reaction with the kidney transplant is evaluated and discussed. Incipient rejection of the renal homografts was treated with Actinomycin C and cortisone and was effective in 50% of the cases. Two renal homografts from unrelated donors were transplanted into the same recipient. Results indicated the origin of the kidney rather than the aggressiveness of the host’s immune response is responsible to some degree for these prolonged survivals. Specific pretreatment of the host with antigen and drug therapy was tested; no prolonged survivors were obtained by these methods.

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The Effect of Oxytocin ‘Inhibitors’ on the Natriuresis which Accompanies Carotid Occlusion
J.H. Cort, J. Rudinger, I. Hagemann and B. Lichardus
Previous work (Cort and Lichardus, 1963) has established that short periods of carotid occlusion in chloralosed cats are accompanied by a rise in tubular rejection of Na. During this natriuresis a 'natriuretic factor' appears in the jugular venous drainage of the brain which is capable of inducing saluresis in a second cat when blood removed from the jugular vein in injected into the renal artery circulation of the

**Fig.** The effect of O-methyl(tyr)2oxytocin infusion on the pressor and renal response to carotid occlusion. Abscissa: time in 10 min periods. CO = periods of carotid occlusion. Infusion given from 30th to 110th min. ‘TRFNa’ = apparent tubular rejection fraction of Na, VU = rate of urine flow. C\textsuperscript{\textscript{\textfrac{1}{2}}} = inulin clearance. UVNa = excretion rate of Na. Arrangement of experiment provided for internal control, i.e. CO periods before infusion could be compared with CO periods during infusion in the same animal. The post-infusion CO periods demonstrated that the inhibition effect was reversible.

Available data suggest that this factor is not a steroid, not a steroidtrophin, not a catecholamine, and of the peptides neither vasopressin nor angiotensin can be incriminated. Since oxytocin-like substances induce saluresis when infused into mammalian species, the effect of oxytocin inhibitors has been tested on this pressor reflex natriuretic effect. The second amino acid in the oxytocin chain is tyrosine, and an inhibitor molecule results when the para-OH group on the phenyl ring of tyrosine is replaced by -OCH\textsubscript{3}, -OCH\textsubscript{2}CH\textsubscript{3} or -CH\textsubscript{2}CH\textsubscript{3}. When we have in the same para position either -H or -CH\textsubscript{3} no inhibitor effects can be seen–in fact, the phenylalanine2 derivative of oxytocin is just as active as the naturally occurring substance. The inhibitor effects

were found to apply as well to the natriuresis of carotid occlusion, as illustrated in Fig., where it can be seen that infusion of O-methyl-(tyr)2oxytocin at a rate of 1 gamma/min reversibly inhibited the natri-uretic, but not the pressor, component of carotid occlusion. The suggestion from these results is that the 'natriuretic factor' which appears in the jugular venous blood during carotid occlusion is related to, but not necessarily identical with, oxytocin or its precursors. The inhibition mechanism would appear to be related to the steric size of the group in the para-phenyl position of the 2 amino acid.

Reference


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Mutual Suppression of the Uricosuric Effects of Sulfapyrazone and Salicylate
A Study in Interactions Between Drugs

Uricosuric drugs as a rule inhibit tubular reabsorption of uric acid, and drugs that cause retention of uric acid apparently inhibit tubular secretion of uric acid. When two uricosuric drugs are used simultaneously, drug antagonism may sometimes ensue. A striking example of antagonistic drug effects is afforded by the observation that, in man, salicylate, itself uricosuric in high doses, inhibits the pronounced uricosuria produced by probenecid, sulfinpyrazone and zoxazolamine. This suppressive action of salicylate has been assumed to be due to its successful competition with these drugs, and with uric acid, for renal tubular transport; one aspect of this competition is expressed as inhibition of tubular secretion of uric acid by small (and large) doses of salicylate, which partially counterbalances the inhibition of tubular reabsorption of uric acid produced by uricosuric agents.

The mechanism involved in the mutual suppression of uricosuric effect between sulfinpyrazone and salicylate involves more than competition at the renal tubular level. Two sites of interaction between sulfinpyrazone and salicylate were demonstrated, namely, competition for binding sites on plasma proteins and that for renal tubular transport. Sulfinpyrazone is displaced from binding sites on plasma proteins by salicylate at total plasma salicylate concentration between 15 and 25 mg%. Sulfinpyrazone appears to compete successfully with salicylate for tubular secretion, and salicylate apparently blocks the inhibitory effect of sulfinpyrazone on tubular reabsorption of uric acid.

In the dog, this antagonism between drugs on uricosuria is not demonstrable, nor could a paradoxical response to salicylate be elicited.

References
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Studies on the Treatment of Cystinuria with D (-) Penicillamine
R.W.E. Watts and J.C. Crawhall
Abstract from the British Renal Assoc. Meeting on January 30th, 1964

The excretion of cystine by cystinuric patients is diminished by the administration of D (–) peniciUamine, the urinary cystine being replaced by the much more soluble cysteine-penicillamine mixed di-sulphide. The excretion of lysine, ornithine and arginine is unaltered by D (–) peniciUamine administration.

The effect of continuous D (–) penicillamine administration (between 1.05 g and 2.4 g of the drug per 24 hours in divided doses) on the cystine excretion of four patients who were given the drug for between five months and one year was demonstrated. Four other patients have been treated for shorter periods of time. It is possible to keep the urinary cystine excretion below 250
mg per 24 hours with this regime, although the precise dose which is needed must be determined for each patient by determining the urinary cystine excretion during treatment. The only untoward side-effects which we have encountered have been erythematous eruptions and mild fever, which appeared on the ninth day of treatment in 4 of our 8 cases; one patient also developed a generalised lymphadenopathy. Corticosteroid treatment resulted in the prompt subsidence of these manifestations, and the administration of D (–) penicillamine could be resumed after steroid therapy had been stopped.

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The Effect of Vasopressin on the Water Diuresis and Excretion of Na, Cl, K and Urea in Infants
J. Martínek, M. Janovský, V. Stanincová and R. Slechtová

Water diuresis was followed in 4 groups of infants: (1) 2 weeks old, (2) 1½-2½ months, (3) 2½-4½ months, (4) 5-7 months old, after giving 5% glucose in place of the morning feed in amounts of 4-4.5% of body weight (in newborn infants 3% of body weight). Several days later under the same conditions of water loading 1 miliumit/kg body weight of vasopressin Parke Davis was injected i.v. at the height of water diuresis (usually 1 h after water load). The amount and Na, Cl, K and urea concentrations of urine collected by indwelling catheter at 15 min intervals for 2 h were determined. As a control the entire procedure with injection of normal saline instead of vasopressin was repeated.

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Table: M/MOTES AFTER WATER LOAD

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>30</th>
<th>45</th>
<th>75</th>
<th>105</th>
<th>120</th>
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Urine flow decreased in groups 1 and 2 insignificantly; in the 3rd and 4th groups the falls of diuresis were statistically significant (Fig.). A definite antidiuretic effect was seen from 2½ months of age, that is at the age when plasma antidiuretic activity appears after osmotic stimulus (1). In the first two groups vasopressin was not followed by the excretion of hypertonic urine; in the 3rd group the urine was slightly hypertonic (390 mOsm/l) and in the 4th urinary osmolarity reached 435 mOsm/l. Free water clearance was negative in 3rd and 4th groups. A significant increase in sodium excretion following vasopressin administration (83%) was seen only in the 3rd group, with simultaneous increase in Cl excretion.

The results are discussed from the point of view of sensitivity of the infant nephron to ADH and compared with findings of other authors.


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Serum Antiheparin Activity in Chronic Renal Insufficiency
M. Vavrík
13th Physiological Meeting of the Czechoslovak Physiol. Soc. January 1964, Plzeň (CSR)

Among the abnormalities of coagulation in chronic renal disease is a functional inadequacy of thrombocytes. According to O’Brien (1955) there is a close relation between these blood
elements and the so-called antiheparin activity of serum, and for this reason was it decided to
determine whether this activity is different in the presence of chronic renal disease as compared
to healthy controls.
Serum antiheparin activity was estimated by means of our own method, the principle of which
has been published (Vavrík, 1963). In 18 subjects with chronic renal failure, the duration of
whose disease was at least one year and whose glomerular filtration was below 26 ml/min,
measurements were made and compared with those from 20 healthy controls.
It was shown that with chronic renal failure antiheparin activity is markedly less than in healthy
controls (P < 0.001).
It is concluded that our finding of a low serum antiheparin activity in chronic renal insufficiency
is evidence for a disturbance of haemostatic homeostasis in renal disease, determined by a new
method.
References
M. Vavrík