Hormones and the Kidney

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SPEAKERS * AND CO-AUTHORS

R. P. AMES, *Department of Medicine, Columbia University College of Physicians and Surgeons, Presbyterian Hospital, New York* 32, *U.S.A.*

P. J. BENTLEY, *Department of Pharmacology, University of Bristol, England*

JENS BING,* *The University Institute for Experimental Medicine,* 71 *Norre Allé, Copenhagen, Denmark*

J. R. BLAIR-WEST, *Department of Physiology, University of Melbourne, Victoria, Australia*

K. D. BOCK,* *Medizinischen Klinik der Städtischen Krankenstalten, Essen, Germany*

A. J. BORKOWSKI, *Department of Medicine, Columbia University College of Physicians and Surgeons, Presbyterian Hospital, New York* 32, *U.S.A.*

J. J. BROWN,* *Medical Unit, St. Mary's Hospital, London, W.*2, *England*

P. J. CANNON, *Department of Medicine, Columbia University College of Physicians and Surgeons, Presbyterian Hospital, New York* 32, *U.S.A.*

J. P. COGHLAN, *Department of Physiology, University of Melbourne, Victoria, Australia*

W. F. COOK,* *Department of the Regius Professor of Medicine, Radcliffe Infirmary, Oxford, England*

J. H. CORT,* *Institute for Cardiovascular Research, Budejovicka* 800, *Prague* 4, *Czechoslovakia*

J. CORVILAIN,* *Laboratoire de Médecine Experimentale, Fondation Reine Elisabeth, Université Libre de Bruxelles, Belgium*

P. MARY COTES,* *National Institute for Medical Research, London, N.W.* 7, *England*

J. CRABBÉ,* *Laboratorium voor Experimentele Geneeskunde, Katholieke Universiteit te Leuven, Rega-Instituut, Leuven, Belgium*

J. O. DAVIS,* *Section on Experimental Cardiovascular Disease, National Heart Institute, Bethesda* 14, *Maryland, U.S.A.*

D. A. DENTON,* *Department of Physiology, University of Melbourne, Victoria, Australia*

P. FOURMAN,* *Medical Unit, Rockefeller Building, The Royal Infirmary, Cardiff, Wales*

J. R. GODING, *Department of Physiology, University of Melbourne, Victoria, Australia*

F. GROSS,* *Ciba Limited, Basle, Switzerland*

J. S. HANDLER, *Laboratory of Kidney and Electrolyte Metabolism, National Heart Institute, Bethesda, Maryland, U.S.A.*

H. HELLER,* *Department of Pharmacology, University of Bristol, England*

O. M. HELMER,* *Lilly Laboratory for Clinical Research, Marion County General Hospital, Indianapolis* 7, *U.S.A.*

M. J. IMRIE, *Department of Physiology, University of Manchester, England*

S. JARD, *Department of Biology, Centre d'Energie Nucléaire, Saclay, France*

J. KAZIMIERCZAK, *The University Institute for Experimental Medicine,* 71 *Norre Allé, Copenhagen, Denmark*

P. P. LAMBERT, *Laboratoire de Médecine Experimentale, Fondation Reine Elisabeth, Université Libre de Bruxelles, Belgium*

L. G. LAJTHA,* *Paterson Research Laboratories, Christie Hospital and Holt Radium Institute, Manchester 20, England*
J. H. LARAGH,* *Department of Medicine, Columbia University College of Physicians and Surgeons, Presbyterian Hospital, New York 32, U.S.A.*
J. H. LAWRENCE, *Donner Laboratory of Medical Physics, Lawrence Radiation Laboratory, University of California, Berkeley 4, California, U.S.A.*
A. F. LEVER,* *Medical Unit, St. Mary's Hospital, London, W.2, England*
B. LICHARDUS, *Institute for Cardiovascular Research, Budejovicka 800, Prague 4, Czechoslovakia*
R. D. LOWE, *Medical Unit, St. George's Hospital, London, S.W.1, England*
P. LOWY, *Division of Biology, California Institute of Technology, Pasadena, California, U.S.A.*
MARY G. MCGEOWN,* *Department of Medicine, Institute of Clinical Science, Belfast, N. Ireland*
I. H. MILLS,* *Department of Medicine, St. Thomas's Hospital, London, S.E.1, England*
J. N. MILLS,* *Department of Physiology, University of Manchester, England*
F. MOREL,* *Department of Biology, Centre d'Energie Nucléaire, Saclay, France*
J. P. NAETS,* *Laboratoire de Médecine Experimentale, Fondation Reine Elisabeth, Université Libre de Bruxelles, Belgium*
J. ORLOFF,* *Section of Kidney and Electrolyte Metabolism, National Heart Institute, Bethesda 14, Maryland, U.S.A.*
A. C. PALADINI,* *Facultad de Farmacia y Bioquimica, Universidad de Buenos Aires, Argentine*
D. G. PENINGTON,* *The London Hospital, London, E.1, England*
M. POLLYCOVE, *Donner Laboratory of Medical Physics, Lawrence Radiation Laboratory, University of California, Berkeley 4, California, U.S.A.*
D. REGOLI, *Ciba Limited, Basle, Switzerland*
K. R. REISSMANN,* *University of Kansas Medical Center, Kansas City 3, Kansas, U.S.A.*
J. I. S. ROBERTSON*, *Medical Unit, St. Mary's Hospital, London, W.2, England*
J. S. ROBSON,* *Department of Therapeutics, Royal Infirmary, Edinburgh 3, Scotland*
W. H. SAWYER,* *Department of Pharmacology, Columbia University, College of Physicians and Surgeons, New York 32, U.S.A.*
G. SCHAECHTELIN, *Ciba Limited, Basle, Switzerland*
O. A. SCORNIK, *Facultad de Farmacia y Bioquimica, Universidad de Buenos Aires, Argentine*
R. SEPHTON SMITH,* *Department of Haematology, The Hospital for Sick Children, London, W.C.1, England*
A. M. SICINSKI, *Department of Medicine, Columbia University College of Physicians and Surgeons, Presbyterian Hospital, New York 32, U.S.A.*
S. W. STANBURY,* *Department of Medicine, The Royal Infirmary, Manchester 13, England*
S. THOMAS,* *Department of Physiology, University of Manchester, England*
M. TREE, *Medical Unit, St. Mary's Hospital, London, W.2, England*
D. VAN DYKE,* *Donner Laboratory of Medical Physics, Lawrence Radiation Laboratory, University of California, Berkeley 4, California, U.S.A.*
K. S. WILLIAMSON, *Department of Physiology, University of Manchester, England*
MARELYN WINTOUR, *Department of Physiology, University of Melbourne, Victoria, Australia*
H. WIRZ,* *J. R. Geigy, S.A., Basle 21, Switzerland*
R. D. WRIGHT, *Department of Physiology, University of Melbourne, Victoria, Australia*

PARTICIPANTS IN DISCUSSION

J. ANDERSON, *Department of Medicine, King's College Hospital, London, S.E.*5, *England*

H. G. BRAY, *National Institute for Medical Research, London, N.W.*7, *England*

T. M. CHALMERS, *Department of Medicine, Middlesex Hospital, London W.*1, *England*

I. CHESTER JONES, *Department of Zoology, The University, Sheffield* 10, *England*

J. DE GRAEFF, *Department Medicine II, University Hospital, Leiden, The Netherlands*

A. GORMAN HILLS, 3757 *Carmen Court, Miami* 33, *Florida, U.S.A.*

H. J. LANGFORD, *Department of Medicine, The University of Mississippi Medical Center, Jackson* 6, *Mississippi, U.S.A.*

MARY F. LOCKETT, *Department of Physiology, Medical School, Birmingham* 15, *England*

R. MCSWINEY, *Department of Chemical Pathology, St. Thomas' Hospital, London, S.E.*1, *England*

W. W. PAYNE, *Institute of Child Health, Hammersmith Hospital, London, W.* 12, *England*

E. J. ROSS, *University College Hospital Medical School, London, W.C.*1, *England*

J. D. H. SLATER, *Professorial Medical Unit, Middlesex Hospital, London, W.*1, *England*

PREFACE

At least one student graduated in physiology in the 'thirties knowing almost nothing about the kidney. As far as I remember my failure to study this part of the subject was a calculated risk based on an analysis of the questions set in previous years and an inability to learn all physiology in the last month or two before finals. Twenty years later I found myself involved in an investigation largely involving the kidney—which served me right I suppose.

Reading the "literature" only added confusion to ignorance so I suggested to the Committee of the Society for Endocrinology that it would be an excellent thing if the Society held a colloquium on Hormones and the Kidney. The Committee were unenthusiastic but could raise no positive objection and provided I did all the work, were willing for the colloquium to be organized. It seemed sensible to bring together people studying the effects of hormones on the kidney and those studying the hormones of the kidney. Hence the meeting reported here.

Of course, I did not do much organizing and managed to persuade others to do most of the work. It is pleasant to be able to express my gratitude to all the following helpful people.

Organization of the programme

After discussions and correspondence with Professors Chester Jones, Heller, de Wardener and with Drs. I. H. and J. N. Mills, Mary Pickford and J. S. Robson a tentative programme was outlined and invitations issued. The parathyroid session depended on the advice of Drs. Paul Fourman and W. S. Stanbury, the erythropoietin session on the advice of Drs. D. Bangham and Mary Cotes and the renin-angiotensin sessions on that of Professor W. S. Peart.

Invitations were sent out in some cases no more than three months before the colloquium and naturally not all the invited people could attend at such short notice. We were, however, extremely fortunate in the unexpectedly high proportion that could attend.

Cambridge arrangements

Professor Sir Bryan Matthews very kindly allowed us to use the Physiological Lecture Theatre and the Chief Technician, Mr. D. Canwell, and the projectionists, Messrs. Hatton and Hood saw that things ran smoothly in the Physiology Department.

Most participants stayed in Corpus Christi College where the Steward, Mr. B. G. Lucas, and the Assistant Domestic Bursar, Miss O. B. Rogers,

made all arrangements and the Catering Manager, Mr. Curtis, saw that the colloquium was not only an intellectual feast.

Chairmen

We were honoured by several distinguished Chairmen: Professors R. A. McCance, A. S. Parkes and Sir George Pickering, and Dr. D. Bangham.

Personal

During the last weeks preceding the meeting, I and my colleagues had to move our laboratories earlier than anticipated which left me at the critical time without even a typist. In this crisis my colleague Dr. Timothy Hunt, became a veritable maelstrom of activity and took most of the burden from my shoulders. The people who came to the meeting were all very kind and seemed to welcome the lack of too formal arrangements. The speakers went through their paces with precision and I did not have to threaten murder to many of them to winkle out their typescripts in reasonable time. After this success it was all the more unfortunate that illness delayed the sending of the material to press for six months—for this I apologize to all authors and readers. This delay is the only thing that went seriously wrong with the arrangements.

Editorial responsibility

The editor accepts no responsibility for the accounts of the papers read at the conference. Manuscripts are published as received from the authors. On the other hand the editor accepts entire responsibility for the reports of discussions. These indeed may be very faulty depending as they did on shorthand notes of intermittently audible contributions, scribbled notes made by the editor, and his memory, which last was almost entirely lost during the six months' delay in preparation of the material for Press. In most cases only those comments which were submitted in writing have survived.

P. C. WILLIAMS

CONTENTS

* This word is in the Shorter Oxford Dictionary and is currently used, correctly, by French physiologists where British physiologists wrongly use " diurnal ". The American coinage " circadian " seems otiose.

KIDNEY, SALT, AND WATER

Nycthemeral rhythms in electrolyte excretion

Circadian Variations in Renal and Adrenal Function: Are they Connected?*

M. J. IMRIE, J. N. MILLS AND K. S. WILLIAMSON

Renal excretion of many constituents—sodium, potassium, acid, chloride, phosphate, perhaps creatinine—commonly fluctuates in a regular fashion over the 24 hr, as does adrenal activity. The urinary rhythms are not directly due to rhythm of habit or environment, since they can maintain a 24-hr cycle in subjects whose habits follow a cycle of different length, 12, 21, 22 or 27 hr, even in an Arctic summer when climatic periodicity is virtually absent (Lobban, 1960). Similarly, in subjects sleeping by day the rhythm persists in its usual phase for a time, but it "adapts" to the new regime more easily than to a cycle of different length (Sharp, 1960; Martel, Sharp, Slorach & Vipond, 1962).

Presumably, when the customary circadian periodicity in habit and environment is suspended, there is some continuing rhythmic stimulus to the kidney; its rhythm can be completely disrupted by giving alkaline potassium salts at night (Mills, Thomas & Yates, 1954), and when their administration ceases the kidney immediately resumes its normal rhythm in the expected phase. The stimulus is not nervous, since normal rhythms are seen in a transplanted kidney (Gunn, Unger, Hume & Schilling, 1960). This paper considers the evidence that the adrenal cortex provides the rhythmic stimulus.

Three possible lines of investigation suggest themselves: the coincidence or otherwise of "adaptation" in the adrenals and the kidneys when, for example, a subject changes to night work and day sleep; the existence or non-existence of rhythms in patients with abnormalities of adrenal function; and experimental disturbance of adrenal function.

The most thorough study of the association between renal and adrenal rhythms under abnormal conditions is that of Martel *et al.* (1962), who, in an Arctic summer, observed subjects over 8 days after a change from day to night activity, and over another 8 days after the return to normal routine. In the conditions of their experiments, the sodium excretory rhythm "reversed" within 4 days whilst the excretory rhythms of potassium and of ketogenic steroids only reversed after 6–8 days. The adrenals thus appeared to be associated with the potassium rather than with the sodium rhythm. Similar evidence, with roughly synchronous adaptation of excretory rhythms

*The experiments with metopirone were incorporated in a thesis submitted by M.J.I. for the degree of M.Sc. at Manchester University.

for sodium, potassium, and 17-hydroxycorticosteroids in a subject flying from Minneapolis to Korea, is given by Flink & Doe (1959).

Observations on human patients are as yet few, contradictory, and often inadequately reported, and will be discussed below.

The experiments here reported concern pharmacological interference with the adrenals with three blocking drugs: prednisolone which, like cortisol and other "glucocorticoids", prevents corticotrophin secretion; metopirone (SU-4885, Ciba), which prevents the synthesis of cortisol by specifically blocking 11-β-hydroxylase; and spironolactone (Aldactone, Searle), which blocks the action of steroids upon the kidney.

EXPERIMENTS

Prednisolone experiments

Prednisolone was given to two normal subjects, to L for 4 days, and to T for 2 days, in five oral doses of 5 mg spaced uniformly over the 24 hr, with the intention of continuously suppressing ACTH production. L remained fasting and recumbent until 16.00 hr; T ate breakfast but no lunch and carried on ordinary laboratory activities. Urine was collected as a single night sample, and a series of roughly hourly samples thereafter until 15.00 hr (T) or 16.00 hr (L), after which further samples were discarded until bedtime, and the subject was free to consume caffeine and food until about 3 hr before going to bed. Renal behaviour was thus studied over about 18 hr in each 24.

Figures 1 and 2 show the disorganization of urinary rhythms produced by prednisolone. Potassium excretion remained at the low night level throughout the morning and early afternoon, whilst sodium excretion behaved in an

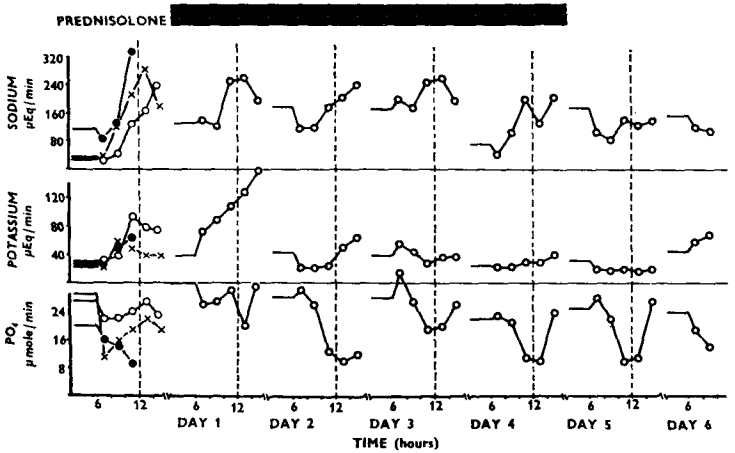

FIG. 1. Subject L. Excretion of sodium, potassium and phosphate during 4 days of prednisolone administration and 2 following days, with the day immediately before the experiment and 2 other control days. Points represent the mid-point of the period of collection, in this and all other figures. Discontinuous lines indicate midday.

irregular fashion, being often quite high at night, and showing at most a small morning rise. These changes were immediate in subject T, who took his first dose at 19.00 hr; but L, who took his first dose at 23.15 hr, showed a

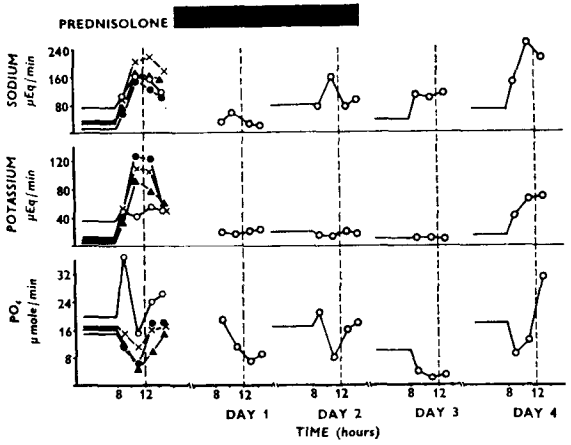

FIG. 2. Subject T. Two days' prednisolone administration, otherwise as in Fig. 1, but with 4 control days.

TABLE 1

Ratio of electrolyte excretion rate between 08.00 *and* 12.00 *hr to that at night before, during, and after administration of prednisolone*

Period	*Day*	*Subject* L *Na ratio*	*K ratio*	*Subject* T *Na ratio*	*K ratio*
Normal before prednisolone	1	2·7	2·2	1·7	1·15
	2	4·0	2·0	8·4	7·8
	3	2·0	3·0	5·4	10·2
	4	—	—	4·1	9·0
During prednisolone	1	1·3	3·0	—	—
	2	0·7	0·5	0·8	0·7
	3	1·3	1·0	—	—
	4	1·5	1·0	—	—
After prednisolone	1	0·7	0·7	2·2	1·0
	2	0·7	1·3	2·7	4·0

normal rise in potassium, sodium and chloride excretion on the first morning. The disturbance of urinary pattern outlasted the period of prednisolone administration. In T, who took the drug for only 2 days, a normal rhythm returned on the 2nd day after he stopped taking it, but L had not resumed a

normal pattern when the observations ceased, 2 days after he stopped taking the drug. This corresponds well enough with the known persistent depression of adrenal function after a course of prednisolone.

The disturbance of sodium and potassium excretory rhythms may be summarized in a table showing the ratio of the morning to night excretion. Under normal conditions this is well above unity for both sodium and potassium, but when the usual rhythms are absent, in subjects under the influence of prednisolone, it falls to near or below unity.

Phosphate excretion, by contrast, behaved as regularly as in control experiments, falling sharply in the morning on every day in each subject.

Neither creatinine determinations, nor plasma analysis, were performed during these experiments.

Since ACTH controls the production of cortisol and has relatively little effect upon aldosterone production, these experiments suggest that the phosphate rhythm is independent of cortisol, the potassium rhythm closely dependent, and the sodium rhythm perhaps, but less clearly, dependent.

Metopirone experiments

Metopirone can only be used to inhibit adrenal activity for short periods since, when it prevents cortisol production, the anterior pituitary is released from the customary inhibition and produces large amounts of ACTH, which in turn stimulates the adrenals; although these cannot attach a β-hydroxyl group to the steroid nucleus, they turn out large amounts of steroids which are by no means devoid of physiological activity. For this reason, we confined our observations to a 5-hr period after taking the drug. Subsequent assay of urinary 17-hydroxysteroids showed, however, that we could safely have continued our observations over a longer period, since excretion was still indetectably low 9 hr after administration.

The three subjects remained fasting and recumbent, rising only to void urine; we collected first the urine produced during the night, and then, in two of the three subjects, a sample from 07.00 hr to 08.00 hr; the third subject did not wake until 08.00 hr. At 08.00 hr the subjects took metopirone (2 g) and produced hourly urine samples until 13.00 hr. Three metopirone and five to eight control experiments were performed upon each subject. On a few occasions blood was collected at 08.00, 10.00, and 12.00 hr, and plasma concentrations of phosphate, creatinine and potassium were measured.

The results were virtually identical in all three subjects. In control experiments sodium excretion (Fig. 3) rose from night values of around 50-100 μeq/min to reach a peak value of 200–400 between 10.00 and 12.00 hr, and potassium rose from 20-40 μeq/min at night to peak values around or over 100. When metopirone was taken, potassium excretion started to rise, fell again to approach the night value between 09.00 and 11.00 hr, and then rose again, approaching the control value during the last hour. With sodium, the initial rise in excretion was less evident, and excretion fell to and remained around the night level until observations ceased at 13.00 hr. Chloride

excretion followed a very similar course to that of sodium, alike in controls and after metopirone. No regular changes were seen in plasma potassium concentration, with or without metopirone.

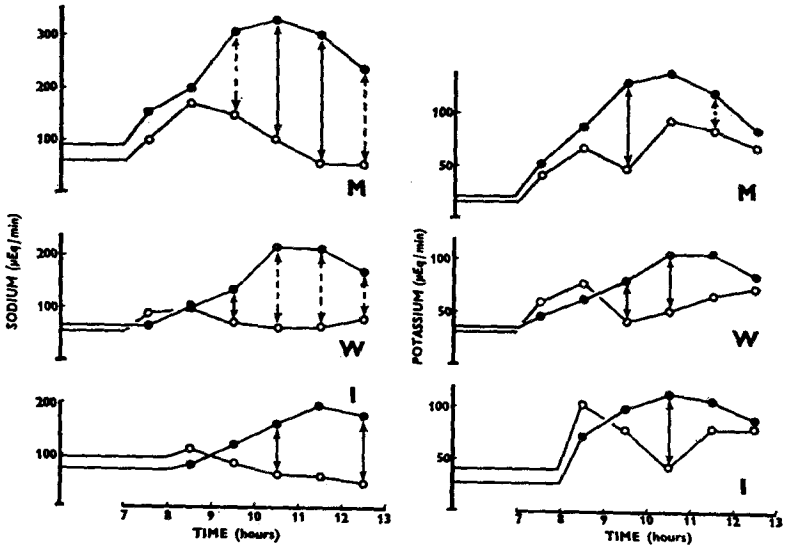

FIG. 3. Sodium and potassium excretion, subjects M, W and I. ●——●, mean of three control experiments in which subject remained recumbent until 13.00 hr; o——o, mean of three similar experiments in which subject took 2 g SU-4885 per os at 08.00. Initial horizontal portion represents excretion rate during the preceding night's sleep. ↕, ↕, indicate that differences of means were significant at the 0·05 and 0·01 level respectively.

Creatinine excretion (Fig. 4) showed no very regular changes in control experiments, though in W there was a moderate rise about an hour before the morning rise in sodium excretion. Excretion, however, was reduced in all subjects by metopirone, returning again to control values in the last hour or two. When plasma creatinine was measured, it showed no consistent change so that clearance of creatinine as well as minute excretion was depressed by metopirone.

Phosphate excretion (Fig. 4) in control experiments did not fall notably as it does in some subjects. It was, however, depressed by metopirone. When blood was collected, plasma phosphate was no lower in metopirone experiments than in controls, so the reduced excretion produced by metopirone has a different origin from that which often occurs spontaneously, in association with a fall in plasma concentration (Mills & Stanbury, 1955).

The interpretation of these observations is not simple, and is closely dependent upon the precise action of metopirone. That it inhibits cortisol synthesis, and leads to a secondary overproduction of 11-deoxysteroids, has been clearly demonstrated (see, for example, Liddle, Island, Lance &