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Progrès des recherches pharmaceutiques

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2

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VORWORT

Mit dem vor einem Jahr erschienenen ersten Band der neuen Reihe „Fortschritte der Arzneimittelforschung" ist, wie schon dort im Vorwort ausgeführt wurde, ein Publikationsorgan gegründet worden, das periodisch über wichtige und aktuelle Forschungsgebiete berichtet. Diese Reihe nimmt somit eine Zwischenstellung ein zwischen den bekannten Periodica einerseits und den Monographien und Handbüchern andererseits. Die Aufnahme, die der erste Band gefunden hat, ermunterte den Herausgeber dazu, nunmehr den zweiten folgen zu lassen. In diesem Band wird in neun Kapiteln über verschiedene Forschungsrichtungen referiert. Die einzelnen Beiträge sind wiederum so gewählt worden, daß sie einen guten Überblick über einige aktuelle Arbeitsgebiete vermitteln, wobei wiederum chemische, pharmakologische und klinische Aspekte berücksichtigt wurden. Die einzelnen Artikel dürften dem aktiven Forscher manche Anregungen vermitteln, und so hofft der Herausgeber, daß auch der zweite Band dem in der Arzneimittelforschung tätigen Chemiker, Pharmakologen und Arzt ein nützliches und willkommenes Hilfsmittel sein werde.

Den Autoren sei für ihre Arbeit, die der ganzen Reihe ihren Wert verleiht, bestens gedankt. Dem Birkhäuser Verlag, insbesondere Herrn Dr. h. c. A. Birkhäuser und Herrn C. Einsele, sei wiederum der Dank für die ansprechende und gediegene Aufmachung des Werkes ausgesprochen.

PREFACE

The publication last year of the first volume of „Progress in Drug Research", as already mentioned in the preface of that volume, marked the start of a series which reports periodically on the latest advances and developments in important and topical research work. It bridges the gap which exists between periodicals on the one hand and monographs and text books on the other hand. The reception given to the first volume encouraged the editor to publish already within a year the second, in which nine topics are treated. Once again, the contributions have been selected so as to give a well-rounded picture of the different subjects, due weight being given to the chemical, pharmacological and clinical aspects. The individual articles should give the active research worker new impulses and ideas and the editor hopes, therefore, that this volume will be a useful and welcome aid for those chemists, pharmacologists and physicians who are active in pharmaceutical research.

Sincere thanks are due to the authors whose valuable collaboration has given the series the hall mark of quality. Messrs. BIRKHÄUSER, the publishers, especially Dr. h. c. A. BIRKHÄUSER and Mr. C. EINSELE, are again thanked for the presentation of the tome which is pleasing and of lasting quality.

PREFACE

„Progrès des recherches pharmaceutiques", dont le volume premier a paru voici un an, constitue un organe créé pour la publication de rapports périodiques sur l'état de la recherche en des domaines d'importance et d'actualité. Cette série nouvelle prend place ainsi entre les périodiques connus et les monographies et manuels. L'accueil rencontré par le premier volume a encouragé l'éditeur à faire paraître maintenant un second, dans lequel sont traités neuf thèmes différents de la recherche. Les articles ont été élaborés de manière à donner un bon apperçu de chacun des secteurs traités; ils embrassent à la fois les points de vue chimiques, pharmacologiques et cliniques. Chaque exposé est propre à apporter mainte suggestion au chimiste, au pharmacologue et au médecin engagés dans la recherche pharmaceutique; aussi l'éditeur espère que ce second volume sera pour eux un auxiliaire utile et bienvenu.

Que les auteurs trouvent ici les vifs remerciements que mérite leur travail: c'est lui qui confère sa valeur à la série toute entière. Des remerciements vont aussi aux Editions Birkhäuser, en particulier à Monsieur A. BIRKHÄUSER, Dr. h. c. et à Monsieur C. EINSELE, pour la présentation attrayante et distinguée de l'ouvrage.

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INHALT / CONTENTS / SOMMAIRE

Newer Diuretics

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1. Introduction

In the following sections several classes of diuretic agents have been discussed, first from the viewpoint of their contribution to a greater understanding of the renal physiology of salt and water excretion and, secondly, as these classes of agents may be useful in clinical therapy. To that end, we have restricted ourselves to those classes of agents that are at once sufficiently well understood and sufficiently potent to be useful in man. Some consideration is given to the relation of structure and activity where this seems appropriate, but reference should be made elsewhere for more detailed analysis of these considerations[1-3]). Nor is an exhaustive review of the literature on the biological and clinical attributes of the recent diuretics included; such publications even on chlorothiazide, an agent first presented in 1957, already run into the hundreds, and the literature on mercurial diuretics is equally voluminous.

There are many diuretic agents that have not been mentioned in the following pages. Thus, extracts of licorice, orthosiphon (kumis kooching, 'cats whiskers') or the more recently described sodium nimbidinate (from seeds of the Neem or margosa tree)[4]) are not included, nor has further reference been made to synthetic substances such as the phenothiazines[5-7]), the pyrrolidylamines[8]) or other chemical classes which have been chiefly described in the chemical literature. Potential inhibitors of renal glutaminase[9]) have not been included.

The chain of experiment and logic, which progressed from the discovery of carbonic anhydrase by MELDRUM and ROUGHTON[10]) in 1932, through the alkalinization of urine by sulfanilamide and the association of this action with renal carbonic anhydrase, to a proposed mechanism for the acidification of urine; the correlation of chemical structure and *in vitro* activity which led to acetazolamide, an agent not only of practical use but perhaps more important an agent which in turn served as a tool to greater understanding of renal physiology, and, more recently, to chlorothiazide and related saluretic agents, has stimulated interest in the similarities, differences, modes and mechanisms of action of diuretic agents. It is the aim of this review to set in perspective some of the current knowledge concerning these agents.

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10) N. U. MELDRUM and F. J. W. ROUGHTON, J. Physiol *75*, 15P (1932).

As an exercise in pure physiology, one might consider first the osmotic diuretics. Such substances as mannitol, urea, sucrose or hypertonic sodium chloride increase the osmotic content of the glomerular ultrafiltrate, thereby decreasing the amount of water and solute that can be reabsorbed in the proximal tubules. Water and solute excretion may thus be increased, without any specific effect on the tubular portion of the nephron. The nonspecific nature of this effect, especially with respect to enhancement of sodium excretion, renders these substances of very limited clinical utility. Countless studies have been recorded utilizing osmotic diuretics, but the fruitfulness of many of these has been sharply limited by exclusive attention to only one component, be it water, chloride, sodium, titratable acid, or 'fixed base' and obfuscated by the juxtaposition of antiquated and modern terminology of acids, bases and ions[11]). In contrast, much useful fundamental information concerning the nephron has come from studies of the newer compounds related to the xanthines, the organomercurial diuretics and mercury complexes, the hormone antagonists such as the spirolactones, and the carbonic anhydrase inhibitors, whether of the conventional type or the newer agents of the chlorothiazide family.

2. Factors That Influence Water and Electrolyte Excretion: Physiologic Considerations

2.1 *Adrenergic Innervation of the Kidney*

The adrenergic innervation of the kidney acutely influences primarily blood flow and secondarily the function of the nephron. Thus, Block *et al.* [12]) have reaffirmed, since the work by Trueta and his associates[13]), that electrical stimulation of the renal nerves caused a sufficient vasoconstriction to produce a cessation of blood flow through the kidney for a few minutes. Interestingly, the effect was not sustained, in spite of continued stimulation of the local nerve supply or a more general continued stimulation as to the sciatic nerve or by tracheal occlusion. Moreover, the constriction was limited to the vessels of the cortex, including the juxtamedullary region. Before describing the effects of renal vasoconstriction on functions of the kidney, it should be pointed out that there is no discernible renal sympathetic nervous system activity in the normal dog. Although the denervated kidney may be somewhat more sensitive to stimuli, such as epinephrine, both the normal and the denervated kidney respond similarly[14]).

Renal arterial constriction, as by stimulation, by partially clamping the renal artery or by the injection of epinephrine or norepinephrine, causes a decrease in the excretion of salt and water. In the instance of reduced blood

11) J. A. Owen and J. S. Robson, Scottish med. J. *1*, 294 (1956).
12) M. A. Block, K. G. Wakim and F. C. Mann, Amer. J. Physiol. *169*, 659 (1952).
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flow, as induced by minimal arterial constriction, the reduction in sodium excretion and urine can take place without an obvious reduction in glomerular filtration rate, according to BLAKE *et al.*[15]). MUELLER and his associates[16]) made the same observation, but were not certain that a minimal reduction in glomerular filtration rate did not exist. Certainly, where a reduction in glomerular filtration rate was noted there was a more marked diminution in sodium excretion. In general, when filtration was reduced without a commensurate decrease in tubular functional capacity, there was an increased percentage reabsorption of the filtered sodium[17, 18]).

As compared to the influence of adrenergic stimulation, physiologic dosages of epinephrine or norepinephrine induce a renal vasoconstriction and cause a decrease in renal blood flow without necessarily an attendant reduction in glomerular filtration. The site of the vasoconstriction has been placed in the postglomerular vascular bed by SMITH *et al.*[19]) and in the venular bed by GOMEZ[20]). Either explanation would account for the swelling that RICHARDS and PLANT[21, 22]) noted when kidneys were perfused with adrenal extracts. SMYTHE *et al.*[23]) found that the increased filtration fraction that resulted from the efferent arteriolar constriction resulted usually in no change or an increased urine flow, but that there was an attendant increased reabsorption of sodium and potassium. There was no effect on the tubular functional capacity for glucose reabsorption or diodrast secretion in man. BERNE *et al.*[24]) found a reduction in sodium excretion and urine flow to attend the same inhibitory effects of epinephrine and norepinephrine on the renal blood flow in dogs, even when glomerular filtration and the sodium load presented for reabsorption increased. The cause of the increased sodium reabsorption is not obvious, since denervated kidneys respond as do the normally innervated organ and since norepinephrine is not thought to induce reflex production of adrenal or posterior pituitary hormones[25]). Actually, the effects of epinephrine on renal function are similar to those that BLAKE *et al.*[26]) found to attend an increased renal venous pressure.

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15) W. D. BLAKE, R. WEGRIA, H. P. WARD and C. W. FRANK, Amer. J. Physiol. *163*, 422 (1950).
16) C. B. MUELLER, A. SURTSHIN, M. R. CARLIN and H. L. WHITE, Amer. J. Physiol. *165*, 411 (1951).
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They showed in dogs that moderate increases in venous pressure caused a reduction in salt excretion and urine volume without a change in renal blood flow, glomerular filtration or tubular capacity to reabsorb glucose or secrete diodrast. Still greater elevation of venous pressure reduced renal blood flow and glomerular filtration rate.

Probably the principal neurogenic or adrenergic effect on salt and water retention is reflected in acute or subacute adjustments to environment or circumstance rather than to an altered steady state. As mentioned in a foregoing paragraph, the continuous stimulation of renal vasomotion does not result in a sustained vasoconstriction[13]). The patient whose hypertension is attributable to a pheochromocytoma does not retain sodium [27]), although short-term injections of norepinephrine evoke such retention [23]). On the other hand, the decreased excretion of salt and water that attends exercise [28]) or the change from recumbent to standing position may be mediated by increased renal vasomotor tonus. KATTUS *et al.* [29]) pointed out that such factors probably account for the beneficial effects of bed rest for the moderately decompensated cardiac patient.

2.2 *Anterior Pituitary (Adenohypophysis)*

The anterior pituitary gland exerts a renotropic effect through the intermediation of the thyroid, the adrenal cortex and by the elaboration of a growth hormone. In turn, its renotropic effect seems to be influenced (stimulated) by androgens.

If one kidney is removed or irradiated, there occur an hypertrophy and an increase in the functional capacity of the opposite organ[30–32]). This same effect of increased glomerular filtration rate, size and tubular functional capacity to secrete *p*-aminohippurate can be induced in the normal dog by the administration of growth hormone, according to WHITE and his associates[33]). Consistent with the finding of WHITE, acromegaly is reported to be attended by an increase in clearance values[34]). Conversely, if the adenohypophysis is removed prior to nephrectomy, there is no compensatory hypertrophy of the contralateral kidney according to WINTERNITZ and WATERS[35]).

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[27]) A. J. BARNETT, R. B. BLACKET, A. E. DEPOORTER, P. H. SANDERSON and G. M. WILSON, Clin. Sci. *9*, 151 (1950).

[28]) H. BUCHT, J. EK, H. ELIASCH, A. HOLMGREN, B. JOSEPHSON and L. WERKO, Acta physiol. Scand. *28*, 95 (1953).

[29]) A. A. KATTUS, B. SINCLAIR-SMITH, J. GENEST and E. V. NEWMAN, Bull. Johns Hopkins Hosp. *84*, 344 (1949).

[30]) A. L. DEAN and J. C. ABELS, J. Urol. *52*, 467 (1944).

[31]) E. M. MAC KAY, Proc. Soc. exptl. Biol. Med. *45*, 216 (1940).

[32]) C. A. WELCH, I. WELLEN and H. C. TAYLOR, JR., J. clin. Invest. *23*, 750 (1944).

[33]) H. L. WHITE, P. HEINBECKER and D. ROLF, Amer. J. Physiol. *157*, 47 (1949).

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[35]) M. C. WINTERNITZ and L. L. WATERS, Yale J. Biol. Med. *12*, 705 (1940).

If the anterior hypophysis is removed from the dog[36–39]) or its function is decreased in man[40]), there is an attendant reduction in glomerular filtration rate, renal plasma flow and in the capacity of the tubules to secrete *p*-aminohippurate. Under these conditions, the study is the more complex because of the absence of the thyrotropic and adrenocorticotropic effects of the anterior pituitary, which, in turn, influence renal function. WHITE and his associates[36, 37]) felt that the reduction in glomerular filtration rate and renal blood flow following adenohypophysectomy was not secondary to thyroid or adrenal cortical atrophy, but was attributable to the loss of the renotropic effect of growth hormone. ZECKWER[40]) reported the compensatory growth of the kidney after unilateral nephrectomy in thyroidectomized rats, which seemed to be consistent with the above views. On the other hand, LUFT and SJÖGREN[38]) were able to increase the glomerular filtration rate of some cases of pituitary insufficiency with the aid of deoxycorticosterone and to return renal blood flow essentially to normal as thyroxine was administered to the point that basal metabolic rate returned to normal. Hypophysectomized patients can be maintained on a sodium intake of 10 meq per day, if they are administered cortisone[41]). Certainly, the adrenocortical hormones have a profound effect on renal hemodynamics, as will be discussed in the next section. Thus, the adenohypophysis seems to influence salt and water metabolism through its general trophic effect rather than specifically.

2.3 *Adrenal Cortex — Aldosterone*

The adrenal cortex has been associated with electrolyte and water excretion at least since 1933 in dogs[42]) and in man[43]). Three years later, it was shown that adrenal extracts would cause sodium retention in dogs[44]) and in both normal and Addisonian patients[45]). In 1937, STEIGER and REICHSTEIN[46]) reported the synthesis of deoxycorticosterone. The compound was found to negate the signs and symptoms of adrenalectomy or Addison's disease, and has remained the prototype of adrenal mineralocorticoids in studies on the adrenal cortex and

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water metabolism[47]), although it has only been recently shown to be present at all in the adrenal gland. FARRELL *et al.*[48]) found the amounts secreted by the gland to be so small as to be biologically unimportant.

The adenohypophysis exerts a trophic effect on the adrenal cortex which, in turn, is modulated by the blood level of adrenocorticoids[49–51]). However, GREEP and DEANE[52]) coupled the observation that less salt was required to maintain the hypophysectomized rat than the adrenalectomized rat with the persistence of the adrenal zona glomerulosa following hypophysectomy. From this synthesis of concept they proposed that a salt-retaining hormone was secreted by the zona glomerulosa and that its elaboration was less dependent on pituitary adrenocorticotropin than were the 17-hydroxycorticoids. The isolation of the salt-retaining factor yielded to the research of SIMPSON *et al.*[53, 54]), who joined effort with WETTSTEIN and his collaborators[55]) to establish the chemical structure of this substance as the 18-aldehyde of corticosterone, aldosterone.

It seems established that aldosterone is produced by the zona glomerulosa, hydrocortisone is elaborated by the zona fasciculata and corticosterone is secreted by both areas[56]). The quasi-independence of the two areas is illustrated by the relative insensitivity of aldosterone secretion to stimulation by adrenocorticotropin[57]) or depression by hydrocortisone[58]). It is less sensitive than hydrocortisone production to hypophysectomy[59]), but it is relatively more responsive to sodium and potassium metabolic adjustments, to changes in extracellular volume, and to certain crude posterior pituitary antidiuretic extracts. RAUSCHKOLB and FARRELL[60]) concluded from a series of ablation experiments that a hypothalamic regulation of aldosterone secretion exists.

Reduction in extracellular volume[61, 62]), salt restriction[63]) or hyperkalemia increases aldosterone production[64]), whereas decreased extracellular volume,

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48) G. L. FARRELL, E. W. RAUSCHKOLB, P. C. ROYCE and H. HIRSCHMANN, Proc. Soc. exptl. Biol. Med. *87*, 587 (1954).
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diminished potassium intake or excessive salt intake tends to depress its elaboration and excretion. Presumably, the salt and water retention (edema formation) attending cirrhosis, nephrosis and certain instances of hypertensive heart disease is associated with a 'secondary' increase in aldosterone production [65–67]. On the other hand, primary hyperaldosteronism is characterized by hypertension, polyuria that does not respond to posterior pituitary preparations, hypochloremic alkalosis, hypokalemia and the signs of weakness associated with potassium loss. CONN [68], who first described this syndrome, also noted that hyperaldosteronism is not attended by edema, although the administration of aldosterone to the Addisonian patient causes an avid retention of salt and water [69].

There is no question that aldosterone is the most potent of the adrenal salt-retaining hormones [70]. This fact has given impetus to the search for compounds that either block the formation of or the renotropic effect of the steroid, with the hope that such agents, if safe and specific, might be important diuretic compounds. Whether such will be the case will depend on the unanimity with which the impact of factors that influence electrolytes is mediated through or modified by fine adjustments in aldosterone (corticosteroid) elaboration or effect, and the success with which chemist and biologist combine to attain their objective. The present status of such research will be discussed in the sections on Amphenone and Spirolactones.

2.4 *Posterior Pituitary (Neurohypophysis)*

Whereas the adrenal cortex influences predominantly electrolyte reabsorption and renal hemodynamics, the neurohypophysis modulates the facultative reabsorption of water. More properly, the source of the antidiuretic hormone may be traced to its release from the supraoptic and paraventricular nuclei of the hypothalamus in association with a neurosecretory carrier material. According to the hypothesis initially proposed by SCHARRER and SCHARRER [71], the bound hormone flows down the supraopticohypophyseal tract to the posterior pituitary, which serves as a reservoir from which the active antidiuretic principle is released. Substantial support for this thesis has evolved from both histomorphic and histochemical evidence [72–75].

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