or not, a confrontation of the corresponding antigens by the Ouchterlony technique was attempted, but so far no precipitation lines have been obtained in this system.

A combined electrophoretic and immunologic analysis is already available in the form of the ingenious immunoelectrophoretic method described by GRABAR and WILLIAMS[44]. The applicability of this method to viruses has not been demonstrated; probably sorption and molecular-sieving effects will cause difficulties. In density gradient electrophoresis, such difficulties are entirely out of question. Consequently, it may be more advantageous for virologists to try a combination of density gradient electrophoresis and the immunoprecipitation technique described by OUCHTERLONY[45] and OUDIN[46].

Density gradient electrophoresis has proved to be of value also for the *purification of viruses*. For poliomyelitis virus, it has been found that the active agent separates well from a fastermoving opalescent zone. For Rous' virus, a first peak of virus activity was found to separate from a faster migrating opalescent zone still containing some virus activity. A separation of the active agent from two opalescent zones has been observed for polyoma virus as well. The study of many viruses, especially cancer viruses, is still seriously hampered by the lack of satisfactorily purified virus preparations. The purification effects obtained for unstable viruses, such as Rous' sarcoma virus, which are not resistant to organic solvents, are of special interest.

It is sometimes desirable to remove not only impurities, but also biologically active material, such as *virus inhibitors*, from a virus preparation. In the case of a masked non-hemagglutinating strain of SE polyoma virus, a definite separation of the hemagglutinin from an inhibitor substance has been achieved (CRAMER and STEWART[36]).

From the above considerations, it is evident that electrophoretic methods are capable of rendering a greatly increased service to virus research. Although this statement refers to all electrophoretic methods in current use, the authors are convinced that the density gradient method offers special advantages to workers in the virological field. The viruses, being excessively large molecular entities, are more susceptible to sorption and molecularsieving disturbances than are smaller molecules of biological interest, when electrophoresis in paper, powders, or gels is tried. The density gradient method rules out these secondary influences altogether. Moreover, a maximum of sampling accuracy is ascertained by this method, and no problems concerning quantitative elution of active material are relevant. The fractions obtainable from density gradient runs can be assayed by a multitude of biological tests, which is very essential for work with viruses.

Résumé. Les avantages de la méthode d'électrophorèse en gradient de densité pour des travaux en virologie sont analysés.

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Renal and Extrarenal Actions of Aldosterone*

By F. GROSS**

The isolation, identification, and the synthesis of aldosterone were accomplished in a situation and under conditions quite different from those existing for other adrenocortical hormones. Already before the genuine hormone became known, there was a steroid – cortexone – isolated from the adrenal cortex, the action of which corresponded quite well to the concept of the rôle which the natural hormone would play in sodium metabolism. Some investigators even went so far as to claim cortexone to be the essential secretory product of the adrenal cortex. Hence, when the natural hormone was recognised, it met a biased situation in so far as it was expected to produce the same effects as its predecessor which was already designated as 'sodium retaining' or, even worse, as 'mineralocorticoid'. The fact that, due to the complicated synthesis, only very small quantities of aldosterone were available for several years had the consequence that the majority of investigations of this hormone concern its excretion in the urine and to a lesser degree its secretion rate in various normal and pathological conditions. It is understandable that in view of the characterisation as a sodium retaining hormone, most efforts in this research were directed towards the detection of an elevated aldosterone secretion in pathological conditions associated with a retention of sodium or with edema formation. The syndrome of primary aldosteronism was

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established by CONN[1,2], and in various pathological states which are accompanied by an elevated aldosterone secretion or excretion, the hormone was suspected of participating in pathogenesis. It has, however, to be mentioned that this overemphasis of a possible pathogenic rôle of aldosterone led to a neglect of its physiological functions and the therapeutic importance which it might have under certain conditions. In our opinion, the present characterisation of aldosterone merits some reconsideration, and to this end, the various activities of the hormone will be discussed from the following points of view:

1. The action on the renal transport of sodium. 2. The restorative effects in the adrenalectomised animal. 3. The consequences of prolonged administration of high doses of aldosterone. 4. The extrarenal effects. 5. The antitoxic effects of aldosterone in comparison with other corticoids.

1. *Rôle of Aldosterone in the Tubular Transport of Sodium.* As was shown by PITTS[3], removal of the adrenals diminishes the tubular reabsorption of sodium by only about 2%, indicating that the responsible hormones play but a modifying part in the fundamental process of sodium conservation. By administering aldosterone directly into one renal artery of the normal unanesthetised dog, no definite effect on sodium excretion can be demonstrated, while potassium elimination increases after one hour's infusion. In the adrenalectomised animal, however, a definite diminution of the elevated sodium excretion was obtained, first in the infused and, later on, also in the contralateral kidney, being followed, after a certain delay, by a kaliuresis (BARGER et al.[4]). These results have been confirmed in principle by other investigators who also found a delay in the onset of sodium retention in the adrenalectomised animal, indicating that aldosterone, like cortexone[5], takes time to influence the tubular function, contrary, for example, to the effect of ADH which is already manifest a few minutes after the beginning of an intrarenal infusion[4]. The delayed onset of action of either aldosterone or cortexone cannot be explained on the basis of the data available, but it can only be assumed that it may be due to a slow adaptation of the enzymes involved in the tubular cation exchange[6], or that the change is so small that it needs a cumulative effect in order to become manifest.

Contradictory findings were reported about the site of action of aldosterone in the nephron[7–13], but with the aid of the stop-flow technique, it was possible to decide that the hormone influences sodium absorption mainly in the distal tubules (VANDER et al.[11]). In the adrenalectomised dog, aldosterone restores the capacity of the distal tubules to almost complete reabsorption of sodium, while it does not influence sodium concentration in the proximal tubules[13,14]. Aldosterone also restores the reduced sodium concentration gradient between the tubular cells and the lumen which in the adrenalectomised animal depends to a certain degree on the plasma sodium concentration, while in the presence of aldosterone, sodium concentration in the distal tubular urine is lowered, regardless of the plasma sodium concentration (VANDER et al.[13]).

Aldosterone favours tubular potassium and hydrion (titratable acid) excretion and differs in this respect from cortisol which only stimulates potassium elimination[7,15–18]. This different effect on potassium excretion also becomes evident from investigations on combined administration of corticosterone or cortisol and aldosterone, from which it was found that both hormones together lead to a more pronounced kaliuria than aldosterone alone, whilst its sodium retaining effect is diminished[19]. In patients with Addison's disease, infusion of aldosterone may rather lead to a more pronounced decrease of sodium excretion than to an increase in potassium loss[20,21]. Under a low sodium diet, or in patients with secondary aldosteronism, either due to congestive heart failure or liver cirrhosis, further administration of aldosterone causes almost complete sodium reabsorption but does not necessarily increase potassium excretion, indicating that sodium is not exclusively reabsorbed by direct exchange against potassium[8,22]. In this connection, the attractive hypothesis of VÉSIN[23] has to be mentioned, according to which the site where aldosterone influences sodium re-

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absorption is situated in the collecting duct where ammonium ion is simultaneously secreted, and also in the distal tubules where potassium secretion is favoured. Hence, the mechanism of tubular cation exchange seems to be more complex than supposed so far, but further experiments are necessary to evaluate the modifying rôle aldosterone plays in the conservation of sodium and the maintenance of ionic equilibrium by the kidney.

Antagonism against the Effect of Aldosterone on Sodium Reabsorption in the Kidney. Recently, various steroids of the spirolactone type were found to produce natriuresis without influencing or even lowering the excretion of potassium, differing in this respect from the benzothiazide derivatives which stimulate the elimination of both cations[24, 25]. The spirolactones have only a natriuretic effect in the presence of sodium retaining steroids and act as competitive antagonists to aldosterone at the site in the distal tubule, where the hormone favours the reabsorption of sodium. Simultaneously with the decrease of potassium elimination, the spirolactones also diminish the excretion of titratable acid and of ammonia, confirming by this that aldosterone stimulates the excretion of hydrion as well as of potassium[26, 27]. In rats as well as in man, spirolactones do not necessarily increase aldosterone secretion if a normal diet containing adequate salt is given, but it was found in rats that with a low salt diet, spirolactone markedly stimulates aldosterone secretion[28]. This observation underlines the importance of preexisting conditions in this and other types of experiment on the secretion and function of aldosterone.

Whether progesterone possesses a similar type of competitive antagonism to the sodium conserving effect of aldosterone, and if the natriuretic effect of high doses of progesterone is the consequence of a peripheral inhibition of endogenous aldosterone, remains to be settled[29].

Inhibition of the sodium reabsorption effected by aldosterone has also been reported in the rat for vasopressin and oxytocin, leading to sodium excretion in this animal species[30]. There are, however, no indications that the two polypeptides act as physiological antagonists to aldosterone in controlling renal tubular function.

2. *Restorative Effects in the Adrenalectomised Animal.* In a series of experiments, SWINGLE et al.[31] found that in the adrenalectomised dog showing distinct symptoms of adrenal insufficiency, corticoids, such as prednisone and particularly 2-α-methyl-9α-fluoro-cortisol, were capable of alleviating rapidly the condition of the animal which was kept without food and water, and of restoring in part, but not completely, the plasma electrolyte pattern. Aldosterone, however, like cortexone, revealed itself to be without effect under these conditions, although given repeatedly at intervals of only a few hours in doses as high as 4 mg.

Under similar conditions, we compared prednisolone and aldosterone administered intravenously to adrenal insufficient dogs in single doses of 10 mg (prednisolone in the form of the sodium salt of the tetrahydrophthalate, aldosterone as unesterified racemate), but gave the animals free access to food and water. While prednisolone had an almost immediate effect on the general condition of the animal, which became alert, less atactic and began to eat, a delay of about 6 h occurred before the same effects were apparent in the dogs treated with aldosterone. This delayed response to aldosterone was also evident in the changes in various parameters in the plasma (Fig. 1).

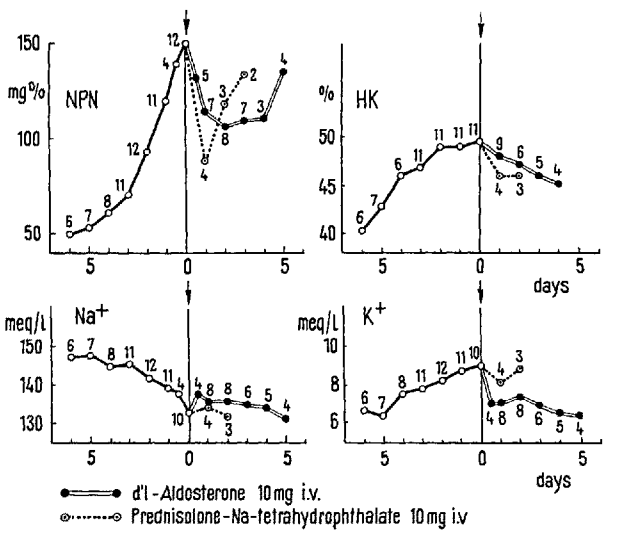

Fig. 1. Effect of a single dose of aldosterone and Prednisolone in the adrenal insufficient dog.

While under prednisolone, the non-protein nitrogen concentration fell markedly within 24 h, it took about twice this time with aldosterone, but the effect lasted also about twice as long as with prednisolone. The general condition of the animals treated with a single dose of aldosterone was definitely improved for 4–5 days, while after prednisolone, the effect lasted only 2–3 days. Neither plasma sodium nor potassium concentration was restored to normal with either hormone, but aldosterone produced the more marked effects, particularly in lowering elevated potassium concentra-

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tion, which even as long as 5 days after the single dose was still definitely lower than at the time of injection. Similar variations were found in the hematocrit values which were also definitely lowered over 5 days by a single aldosterone injection.

It can thus be stated that, by treatment with a single dose of aldosterone, a severe state of adrenal insufficiency in the dog can be partly abolished, but that the hormone acts with a certain delay and less dramatically than prednisolone or similar corticoids. This retarded response observed by us in the dog is in contrast to findings reported by FRIEDMAN[32], who found in the adrenalectomised rat within 30–60 min after the injection of aldosterone not only a return of the low blood pressure to normal values, but also a restoration of the pressor response to pitressin.

Effect of Aldosterone on the Excretion of Water and Salt Load. COLE[33,34] has demonstrated that the intact rat loses sodium in response to infusions of isotonic saline and that aldosterone as well as cortexone in a dosage range which approximately corresponds to normal secretion rates reduce the sodium loss in part but not completely. It remains to be investigated if by larger amounts of aldosterone, this increase of the tubular rejection fraction may be completely abolished.

In earlier experiments, we observed that the adrenalectomised dog under maintenance doses of aldosterone is not able to eliminate a given load of water or salt in the same way as the intact animal[35]. Similar findings have been reported about the effect of aldosterone on water intoxication in the adrenalectomised rat[36] and on salt load in the adrenalectomised dog[37]. Pursuing these investigations, we have now found that by increasing the daily dose of aldosterone to 1000 γ in the form of the racemate, the capacity of the adrenalectomised dog to eliminate a load of salt (1 g/kg) is definitely better than under the influence of the minimum maintenance dose (Fig. 2). For a water load (90 ml/kg), the improvement in excretion as a result of increasing the doses of aldosterone was less marked. This is in contrast to observations with cortexone which, if given in doses of 20–30 mg daily, leads to a more delayed excretion of a given salt load, if compared with the effect of a maintenance dose. A water load, however, is more rapidly eliminated under high doses of cortexone than under the influence of a maintenance dose of this corticoid. These observations led us to

3. *Prolonged Administration of High Doses of Aldosterone.* The scarcity of supplies had the consequence that the effects of exogenous overdosage with aldosterone were not studied to the same extent as the results of endogenous overproduction. On the basis of our own observations of continuous overdosage in the rat[38], in the rabbit[39], and in the dog[40], we may, however, state that the syndrome which develops under high doses of aldosterone and salt is in various respects qualitatively similar to that occurring under high doses of cortexone, although quantitatively definitely less pronounced. In the rabbit, symptoms of increased capillary permeability and of potassium loss prevail, leading to effusions and to paralysis of skeletal as well as of involuntary muscle (Fig. 3), but not to an increase of blood pressure[39].

In rats, the average daily secretion rate of aldosterone was found to be 0.4γ/kg/adrenal/h under normal conditions[41]. This corresponds to nearly 20 γ/kg during 24 h, provided that this secretion rate were to continue during the whole day. An animal of 150 g body weight

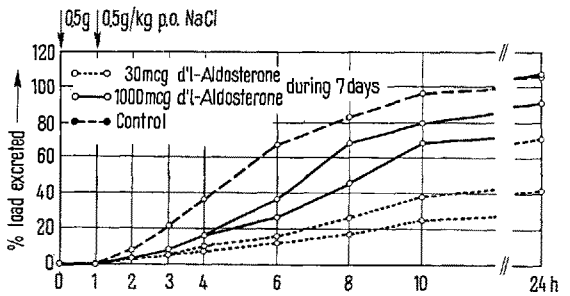

Fig. 2. Effect of a low and a high dose of aldosterone on the excretion of a salt load in the adrenalectomized dog. Pretreatment with aldosterone in the doses indicated on the graph 7 days before loading.

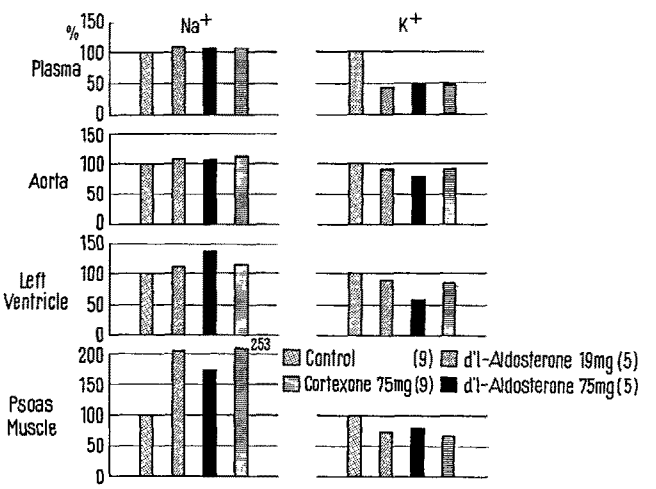

Fig. 3. Overdosage of aldosterone and cortexone in the rabbit. Relative concentration of sodium and of potassium in various tissues under high dosage of aldosterone and of cortexone administered in the form of pellets. Data taken from GROSS and SCHMIDT[39].

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would accordingly secrete about 3–4 γ of aldosterone per day (Table). Considering these figures, one wonders how GORNALL et al.[49,50] could provoke hypertension and other pathological changes by giving less than the daily amount of endogenously produced aldosterone to intact rats, even if one takes into account the long duration of their experiments, lasting 3–6 months. Hence it is not surprising that these results could not be confirmed by other investigators[51,52]. In order to provoke hypertension in the rat, in our own experiments, it was necessary to give about 50 times larger amounts than those secreted by the gland, together with free access to saline[38]. It has, moreover, to be stated that within the period of observation, the degree of blood pressure elevation as well as the morphological alterations in kidney, heart, and arteries were definitely less pronounced – if detectable at all – than after giving cortexone in a five times higher dose. In our opinion, it is not justified to draw any conclusion from these experimental results on the rôle which aldosterone may possibly play in the pathogenesis of essential hypertension. The finding of an elevated secretion or excretion of aldosterone in various forms of human hypertension, recently reported, does not give enough evidence for establishing a primary pathogenic rôle for aldosterone, but may be a consequence rather than the cause of this disease (LAUGH et al.[53]).

Secretion rate of aldosterone in γ/kg/day

	normal		low salt intake	high salt intake
rat	19,7 [41]		27,7 [41]	6,4 [41]
	14,7 [42]			
dog	4,7 [43]		8,5 [43]	
	2,1 [44]			
	5,1 [360] [45]		8,0 [45]	
human	♀3,2 [192] [46]		11,0 [46]	
	3,4 [240] [47]		13,6 [47]	0,7 [47]
	♀1,3 [77] [48]			

[ ] = total secretion in γ/day.

In the human being, PETERSON[45], by developing his ingenious tracer dilution technique, has determined average values for 24 h secretions which, according to dietary conditions, are in the range of 200–400 γ. TAIT et al.[46], having formerly reported figures only somewhat lower, give just now an average secretion rate of only 77 γ/day[48] (Table). Studies on the prolonged administration of high doses revealed that in normal subjects, as well as in patients with Addison's disease, after an initial retention of sodium and weight gain, values turn towards normal despite further administration of aldosterone (AUGUST et al.[54–58]. This escape phenomenon, known also from long term experiments with cortexone, indicates that a continuous endogenous secretion or exogenous administration of aldosterone does not necessarily lead to sodium retention and edema formation[59]. If the normal sodium excretion often observed in patients with primary aldosteronism can be explained as a consequence of the escape phenomenon, or whether it is even justified to try to provoke such an extreme reaction in cases of secondary aldosteronism by administering exogenous hormone[60] needs further investigation. It can, however, be assumed that, even in Addison's disease, the dangers from aldosterone overdosage are not great, even during prolonged administration[53,54], although further experience of long courses of treatment under various conditions is necessary.

The speculative statements made a few years ago, ascribing a pathogenic rôle to absolute or relative overproduction of cortexone or substance S in inflammatory diseases, hypertension, or other diseases of adaptation were subsequently refuted by experimental and clinical facts. This sequence of events should at least have the one beneficial consequence for aldosterone that similar mistakes are avoided to-day and that one becomes more careful in assuming a causative relationship to be the basis of variations which happen to occur simultaneously.

4. *The Extrarenal Effects of Aldosterone.* It cannot yet be decided whether the amelioration of the symptoms of adrenal insufficiency produced by aldosterone can mainly be ascribed to the normalisation of renal function. This is certainly the case for the decrease in the plasma non-protein nitrogen, although it is not fully understood whether it is the reduced glomerular filtration rate alone, developing during adrenal in-

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sufficiency, which is responsible for the impaired kidney function or whether other mechanisms may be involved. Very little, however, is known about the influence of aldosterone and other cortical hormones on electrolyte, especially cationic exchange outside the tubular cells of the kidney. Numerous attempts have been made to demonstrate a direct action of aldosterone on various tissues, especially on functions in which an electrolyte exchange may be involved, but the results available are not yet very convincing, perhaps because of the delayed action which the hormone exerts. In erythrocytes, active cation transport is inhibited by cardiac glycosides[61], leading to a diminished potassium influx and an increase of extracellular potassium concentration. Aldosterone was said partially to antagonise this effect of strophanthin[62], but other investigators did not observe any influence on the effect of digoxin on cation transport in isolated red cells nor was the cation movement across the erythrocyte membrane affected by aldosterone itself[63,64], although here, too, the results are contradictory[65]. The significance of an increased sodium/potassium ratio in the erythrocytes of patients with secondary aldosteronism due to cardiac failure still has to be evaluated[66].

The antagonism to acetylcholine which various corticoids exert is not specific but may only be the expression of a change of the membrane properties by steroids which lead to a partial inhibition of depolarisation (Fig. 4). The promptness of this effect also indicates its non-specific nature, as well as the fact that aldosterone acts less markedly than does cortexone.

In the nephrectomised rat, aldosterone was said to increase extracellular fluid volume and extracellular sodium concentration, acting thus in the opposite sense to adrenalectomy[32]. The data available, however, are contradictory, as other investigators did not find in the nephrectomised and simultaneously adrenalectomised animal a normalisation of the increased extracellular concentration of potassium[67].

RONDELL[68] found that isolated rings of rabbit aorta under the influence of relatively high concentrations of aldosterone (10^{-5}) develop an increased sensitivity to either nor-adrenaline or angiotensin (Fig. 5). Under similar conditions but exposed to much lower concentrations of aldosterone, the isolated heart of the rat works not only longer but is also more efficient than without the addition of the hormone which, in these experiments, has an influence on heart muscle qualitatively similar to that of the cardiac glycosides[69].

A direct effect of aldosterone on cation exchange was demonstrated in the isolated bladder of the toad in which, after a latent period of 1 h, the net sodium transport across the bladder wall was, under the influence of low hormone concentrations (2×10^{-7}), more than twice that of the controls[70]. This effect could be blocked by spironolactone in 100 times higher concentrations, which indicates that the competitive antagonism between these two steroids, assumed to occur in the distal tubular cells, may exist also in other tissues.

In the brain and in the skeletal muscle of intact mice, the intra-extracellular concentration gradients of sodium and of potassium are both found to be influenced by aldosterone, indicating that the hormone may act directly on cation exchange in various tissues[71]. Recently it was claimed that the distribution of other cations, such as magnesium and calcium, may be influenced in skeletal muscle and that excess aldosterone

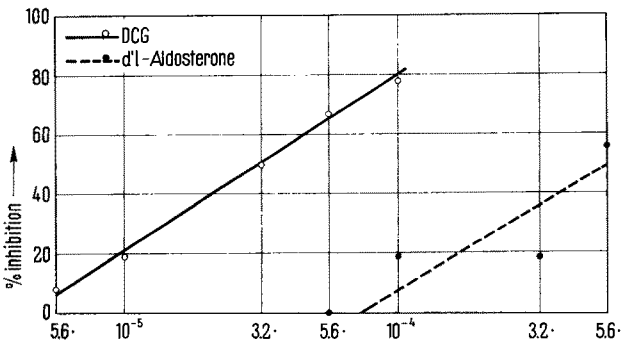

Fig. 4. Inhibition of ACh action on frog heart. Dose response curve for the inhibitory effect of cortexone-glucoside (DCG) and aldosterone on acetylcholine action in the frog heart.

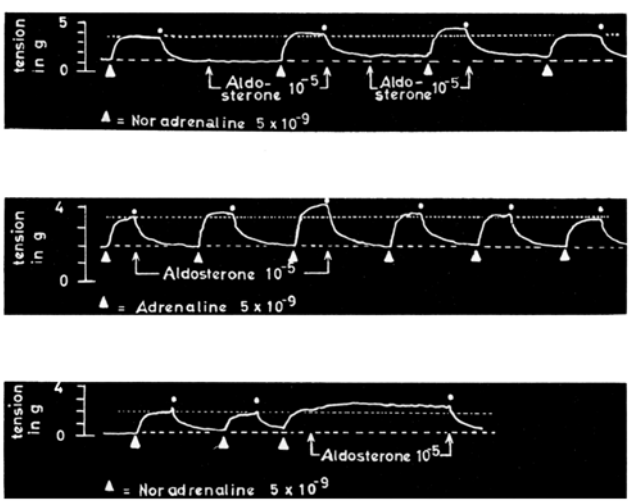

Fig. 5. Tension development in isolated rabbit aortic rings.

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leads to magnesium depletion[72,73]. Much more work, however, has to be done in this direction, especially with various doses of aldosterone under different conditions, before assumptions regarding extrarenal activities become established.

In searching for an interpretation of all the different findings, we become aware that too many gaps and contradictions militate against this attempt. It has to be stressed that cells of different tissues may react quite differently to aldosterone under physiological conditions and differently again when isolated. Hence all generalisations based on single observations should be avoided. The greatest obstacle is the fact that aldosterone, like other corticoids, exerts – if any – only modifying influences on various tissue functions and that a deficit leads to changes which are only just within the limits of accuracy of most of the methods available to us. Furthermore, it cannot be expected that an excess of an agent with a permissive or modifying influence, when added to an intact organism, will improve a function beyond normal.

5. *Antitoxic Effects of Aldosterone.* Although, soon after its isolation, aldosterone was shown to have some cortisol-like activity as regards glycogen fixation in the liver[74] and diminution of the circulating eosinophils[75,76], these actions were only demonstrable with doses much higher than those necessary for the effects on electrolyte excretion. Furthermore, even with such high doses of aldosterone, no cortisone-like effect on the formation of foreign body granuloma or other anti-inflammatory activity was observed[77]. It was therefore surprising to find that under certain experimental conditions, aldosterone may exert antitoxic effects which are in the same range or even more pronounced than those of the glucocorticoids. These investigations started with an observation made by MEIER and BEIN[78] that, in the adrenalectomised cat, the impaired reaction to adrenaline could only be restored by the administration of aldosterone but not by cortexone or by other corticoids. However, this is not the case in the dog, whose response to nor-adrenaline is not influenced by adrenalectomy[79]. A partial protective effect of aldosterone against Brucella toxin was observed in mice[80]. Recently, BEIN and JAQUES[81] found that the shock-like stage which develops in cats, rats, or guinea pigs after administration of bacterial endotoxins can be avoided or markedly improved by giving aldosterone. In these experiments, aldosterone was about 30 times more active than either prednisone or cortisol (Fig. 6). Not only the toxic symptoms produced by lipopolysaccharides, but also those elicited by other toxins, such as snake venom, or the shock induced by trypsin were reduced in intensity by aldosterone. Furthermore, aldosterone restored the pressor response to adrenaline and to nor-adrenaline, which after the injection of polysaccharides may be reversed or markedly diminished.

In addition, it was possible to demonstrate an antitoxic effect of aldosterone against endotoxins in quite a different experimental set-up. In the embryonated egg, bacterial polysaccharides are highly toxic and lead to the death of the chick embryo in concentrations as low as 10^{-10}. By giving aldosterone simultaneously in concentrations of 10^{-6}, the toxicity of the polysaccharide is definitely reduced to the same extent as by cortisone (Fig. 7), while dexamethasone shows the same

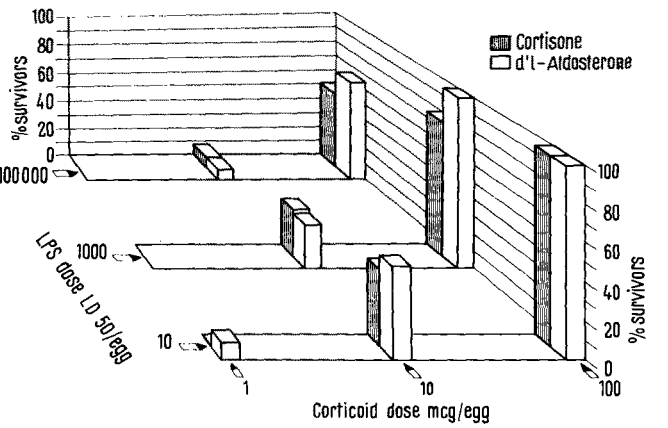

Fig. 6. Protection against bacterial endotoxins by corticoids in the cat. BEIN and JAQUES[81].

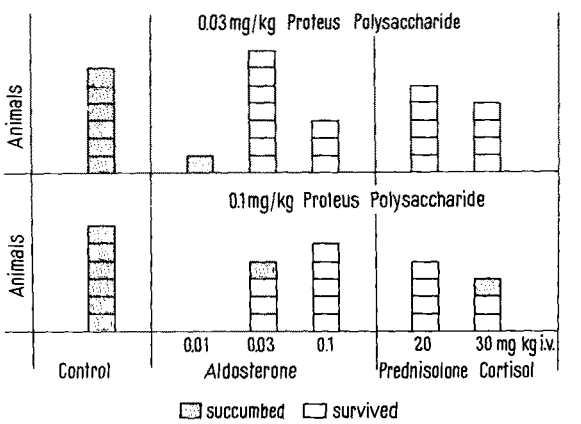

Fig. 7. Protection of corticoids against bacterial endotoxins in the embryonated egg. WYLER, KRADOLFER and GROSS[82].

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degree of protection even at concentrations 1000 times lower[82]. Some degree of antagonism against polysaccharides may also be seen in cultures of chicken leucocytes, where the enhancement of leucotaxis produced by bacterial endotoxins is reduced by aldosterone, although not to the same extent as it is by cortisol-like compounds[83]. Whether the stimulating effect of aldosterone on leucocyte agglutination and its inhibition by cortisol are of a specific nature, is however, doubtful[84].

The mechanism of action by which aldosterone may influence toxic reactions provoked by bacterial lipopolysaccharides is not elucidated so far, but it cannot be excluded that disturbances of cell permeability leading to altered distribution of sodium and potassium in the extra- and intracellular compartment of various tissues may be involved. In spite of the lack of a satisfactory explanation for this new effect of aldosterone, on the basis of the experimental data available to-day, it seems to be justified to try aldosterone in conditions of severe shock, especially if toxins are involved in the etiology and if the response to blood pressure elevating substances is reduced or abolished.

This brings us back to the introductory remark that the current characterisation of aldosterone, limiting its function to partial control of tubular cation exchange, needs reconsideration and that other aspects of its importance to the organism under physiological and pathological conditions are worth studying with greater intensity. This not only holds true for experimental but also for clinical medicine.

Zusammenfassung. Es wird eine Übersicht über die Wirkungen von Aldosteron unter physiologischen und verschiedenen experimentellen Bedingungen gegeben und gezeigt, dass das Hormon nicht nur die tubuläre Nierenfunktion, sondern auch extrarenale Vorgänge beeinflusst.

1. Aldosteron fördert die Rückresorption von Natrium in den distalen Tubuli der Niere sowie die Ausscheidung von Kalium und Wasserstoffionen, wobei eine gewisse Latenzzeit bis zum Eintreten eines signifikanten Effektes charakteristisch ist.

2. Am adrenalektomierten Tier gelingt es, durch einmalige Gabe hoher Dosen einen Zustand von schwerer Nebenniereninsuffizienz während mehrerer Tage zu unterdrücken.

3. Längerdauernde Anwendung hoher Dosen von Aldosteron führt beim Menschen oder beim Hund zu einem «escape»-Phänomen in bezug auf Natrium- und Wasserretention.

Zur Erzielung einer Blutdrucksteigerung an der Ratte sind unter gleichen Versuchsbedingungen relativ höhere Dosen von Aldosteron als von Cortexon notwendig.

4. An isolierten Geweben oder Organen (Erythrocyten, Harnblase, Froschherz, Kaninchenaorta) lassen sich erst mit relativ hohen Konzentrationen identische Effekte hervorrufen.

5. Aldosteron besitzt antitoxische Wirkungen gegenüber Polysacchariden bakteriellen Ursprungs, die mit Hilfe verschiedener Versuchsanordnungen nachweisbar sind und teilweise die für Cortisol oder Prednison bekannten ähnlichen Effekte übertreffen.

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Brèves communications – Kurze Mitteilungen – Brevi comunicazioni – Brief Reports

6-Azacytidine - A New Antimetabolite

In the course of a programme of study of antimetabolites of the principal components of the nucleic acids[1], we have now synthesised 6-azacytidine by the following procedure: 6-Azauridine[2] was converted into the tribenzoyl derivative (I), and this, on treatment with phosphorus pentasulphide in dry pyridine, directly afforded the 4-thioderivative (II), which on ammonolysis gave 6-azacytidine (III) m.p. 215°. The same product was obtained when the de-benzoylated thiocompound (IV) was ammonolysed.

6-Azacytidine has been found to be an antimetabolite of the pyrimidine components of the nucleic acids. Its antibacterial activity against *E. coli* has been shown to be superior to that of 6-azauridine and it has also been found to inhibit the growth of some experimental tumours. The toxicity of 6-azacytidine, like that of 6-azauridine, is very low.

A more detailed account of these findings will be published in due course in Collection of Czech. Chem. Commun.

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