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CONCLUDING REMARKS ALDOSTERONE SYMPOSIUM

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IT IS MY special pleasure and privilege to close this Symposium with a few observations on the state of the art. Although the Symposium was devoted largely to effects of aldosterone on transporting epithelia, it was a unique opportunity for many of us to hear Professors Reichstein and Wettstein describe for us the excitement of the discovery of aldosterone and the events which culminated in this important finding. These events are very much a part of modern medical history, but for me, at least, it was my first opportunity to see and hear these participants, and I thank the organizers of the Symposium, as well as Professors Reichstein and Wettstein, for this privilege.

It is not surprising that the studies on the mechanism of action of aldosterone have been pursued primarily by a group of investigators interested in transepithelial transport of sodium and other ions. There has been the realization by such workers that any agent which will affect the transport process can be used as a probe by which to study the details of the process itself. If in the course of such studies the mechanism of action of a hormone is elucidated, this in itself would constitute no mean bonus. In spite of the double stimulus for studying the mode of action of aldosterone, it remains clear at the end of this Symposium that Mother Nature still retains sole possession of both secrets.

Most of us present owe to Professor Ussing a large intellectual debt for providing us with an appropriate and simple biological preparation for our studies with aldosterone. I think the impetus for this Symposium can be traced back to 1961 when Dr. Crabbé demonstrated an effect of aldosterone *in vitro* on the toad bladder preparation. Much has happened since then, as we have been hearing.

There are two investigative approaches generally available once a hormone has been shown to affect a physiologic response in an isolated tissue. How the hormone modifies the observable physiologic response, i.e. the final effect of the hormone on the tissue or cells, may serve as one focus for study. The problem can be attacked, on the other hand, from a study of the initial interaction of the hormone with the responsive cells. Hopefully by pursuing the latter forward and the former backward the two lines of investigation will meet to reach our ultimate goal, which is the understanding both of the transport process and its hormonal regulation.

From what we have been hearing, we can congratulate Dr. Edelman and his associates on the steady progress they are making in elucidating the initial interactions of aldosterone with its physiologic receptor sites in the cytosol and nuclei of responsive cells. This approach is clearly a fundamental one.

What the final effect of the hormone is that enhances sodium transport remains an unsettled question. I would be only revealing my bias in stating that the existing evidence favors an increased entry of sodium across the apical surface of the transporting cells as the means by which the hormonal effect is produced. But there are many questions which remain unanswered: How does an increase in sodium content or concentration within some intracellular compartment effect an

increase in tissue metabolism? What is the route across the epithelial cells through which sodium moves as it is actively transported? What are the major permeability barriers which the sodium ion must cross during active transepithelial transport? At which barrier or barriers is there an energy requirement for transport? How is energy coupled to the transport process? What is the efficiency of this coupling and does the hormone affect this efficiency? What is the significance of the increase in activity of several enzymes which occurs with the hormonal effect? Are these primary or secondary hormone effects? Is it valid to distinguish "glucocorticoid" from "mineralocorticoid" effects of aldosterone in the transporting cells? If so, is there an entire set of changes induced by aldosterone in the responsive tissue which do not relate to its effect on sodium transport? What are the steps which link the primary binding of aldosterone to its physiologic receptors to the ultimate expression of the hormonal effect in a stimulation of sodium transport? (It seems noteworthy that not a single report has been presented at these meetings providing direct evidence for a stimulation of either RNA or protein synthesis. This attractive hypothesis is still based on analogy with the effects of other steroid hormones and on the effects of inhibitors of protein and RNA synthesis on the action of aldosterone. Failure to date to provide convincing direct evidence of new RNA or protein synthesis may only indicate that our techniques are still insufficiently sensitive to pick up the small quantities of RNA or protein needed to effect the hormonal response or, more seriously, may be indicative of a major flaw in the hypothesis.).

These are some of the questions and problems which remain to be resolved. Clearly the surface has hardly been scratched. But on this note we should find encouragement that time and opportunity for further Symposia on Aldosterone shall be forthcoming. I would like to express the thanks of all of us to Professor H. Thölen and Dr. Voûte and their associates who have organized this initial Symposium and hope that our research productivity may merit meeting soon again under as gracious auspices and agreeable circumstances as we have experienced here in Basel.

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