PRESIDENTIAL ADDRESS AT THIRTIETH ANNUAL MEETING OF THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS

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Members of the Association and their guests, ladies and gentlemen:

The constitution of the Association contains no provision that the President should address the members at their annual meeting, nor for that matter does it compel the membership to listen to him, yet the custom of our society has always been that this occasion is one at which the President is privileged to speak on matters pertaining to our common interest in endocrinology. In recent years your President's responsibility has been lightened by the fact that the address is usually delivered after the annual dinner and after a preliminary gathering which is nicely calculated to bring his audience into its most receptive mood. This adroit timing of the address not only enables the listeners to endure what is to follow but is in sharp contrast to the custom of another eminent medical society, which also once honored me with their presidency. Their barbarous custom was and is to compel the incumbent to address his unfortunate colleagues immediately after an early breakfast. For all concerned it was and is a chilling and disheartening experience. Indeed its effects are such as to remind me of the classical reply of the eminent British scientist who was invited to speak at a scientific meeting in this country. On his arrival he was informed by the secretary of the society concerned that his paper was scheduled for 7 A.M. the next day. Without a pause he replied "Young man I never stay up as late as that."

However, before I begin to speak on a more serious note I want to take this opportunity to convey to the members of the Association my sincere appreciation of the privilege that it has been to serve as your President during the past year. The presidency of this association is not only an honor but a responsibility. The honor is one I shall always cherish; the responsibility could not have been met had it not been for the cooperation of your Council and above all the hard work and tireless enthusiasm of the Secretary-Treasurer. The Association owes a deep debt of gratitude to Dr. Henry Turner and one that I consider it a privilege to acknowledge this evening. It is also

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proper at this time to extend the appreciation and thanks of the Society to Dr. Willard Thompson and the other members of the local committee for the work they have done to make this meeting such a pleasant occasion for us all.

The question as to what I should devote the main body of my address this evening has given me no little concern. Judging from past years there were many possibilities ranging all the way from an interesting travelogue by one past president to rather detailed scientific papers by others. Since my peregrinations are of little interest and since we have a very full program of papers this year, it seemed more appropriate that I should spend a little time to discuss with you the past, present and, so far as one man can see, the future developments of endocrinology.

It is now thirty-one years since the first volume of ENDOCRINOLOGY was published and it is a salutary experience to re-read the papers presented in it, particularly if this is followed by a perusal of the volumes which were published in 1947. In volume I there appeared eighteen original articles, in the two volumes for 1947 a total of 126 original papers, to say nothing of those appearing in the Journal of Clinical Endocrinology. Yet these figures give a most inadequate picture of the changing character of this science. Among the sixteen papers in the first volume we note one by Brailsford Robertson on "Tethelin," the growth controlling constituent of the anterior pituitary, a principle stated to be active by mouth and stable at 80° C., a paper that drew cautious and guarded comment from Dr. Goetsch, for in those days the discussion of papers given at the Association meeting was printed in the journal. We also find in this first number the classical paper by Kendall on the isolation of thyroxine and its effects on human cretinism and myxoedema. But aside from these articles which have a flavor of modern experimental endocrinology, the remainder are essentially of a descriptive character. By this I mean they report the over-all effects of certain types of endocrine hypo- or hyperfunction in man and in reality represent the emergence of endocrinology from the world of giants, dwarfs, bearded ladies and the other oddities produced by extreme degrees of endocrine dys-function with which it had for so long been identified.

I choose the term "emergence of endocrinology" with deliberation since it is my belief that we have now reached the stage when the functions of the endocrine glands are well enough understood to appreciate that they constitute a bodily system of which it is more important to know the basic knowledge of their mode of action and the minor aberrations of such function than it is to consider them only when they present themselves in such usually rare forms as Addison's disease, Cushing's syndrome, etc.

The emergence of endocrinology from the age of curiosities to a full fledged basic and clinical science has depended on three main
pathways of research. The first of these is the identification and isolation of the hormones themselves. In 1917 two hormones were clearly recognized and only one chemically identified. They were of course epinephrine and thyroxine; to these may be added the recognition of the activity of posterior lobe extracts. Today there has been isolated practically every known hormone, the majority in pure form. This phase of endocrinology may well be said to have been begun by the isolation of insulin in 1921, followed by the synthesis of thyroxine in 1926, the isolation of estrone in 1929, of testosterone and androsterone in 1935, the identification of the active adrenal cortical hormones as steroids in the early 1930's. The recognition that a protein, insulin, could also be a hormone led to a sustained attack on the other protein hormones, notably those of the anterior pituitary. Such success has now been achieved that the adrenotrophic, lactogenic, growth and gonadotrophic hormones have all been obtained in substantially pure form leaving only the thyrotrophic and possible other at present unidentified pituitary factors to the wiles of the protein chemist. Among the other protein hormones work still remains to be done on that of the parathyroid and certain gastrointestinal hormones.

These achievements carried out in several countries and by many different investigators have not only presented the physician with a remarkable armament of therapeutic agents but have led the way for the dissection of function of the endocrine system that is so essential for our understanding of its extraordinary effects on bodily processes. Their potency has also compelled a degree of caution in their use which is wholly desirable for medicine, for while our colleagues of thirty years ago may have fed anterior pituitary extracts with reckless abandon, no physician should, after what we have heard this afternoon, inject adrenotrophic hormone without careful consideration of its potent diabetogenic qualities. Indeed, I like to think that one of the important contributions of our meetings is to emphasize these qualities of present day endocrine preparations as much as to record our success in their isolation.

Therefore, so far as the isolation of the active principles of the known endocrine glands is concerned, it may be said to be substantially complete. The chemical structure of all except the protein hormones is rather exactly known; synthetic methods have been developed for epinephrine, thyroxine and many steroid hormones and are being continually increased. The contributions of the chemist to endocrinology in the last thirty years are perhaps the most outstanding event of this period.

The second line of endeavor that has enormously broadened our concept of endocrinology has been the parallel advances in our understanding of the intermediary metabolism of cells. This has included not only an analysis of the chemical steps involved but also the isolation and identification of the enzymes themselves. Not only have...
we learned much about these but also the mechanism by which the chemical energy released by their action is made available for cellular function. In doing so, we have found the reason why certain vitamins are needed for the well being of the organism, for it is now known that these substances are necessary since they form parts of the enzyme systems whose activity underlies the whole of the processes of cellular activity. Since we are now agreed that the normal function of the hormones is to divert cellular processes to meet the circumstances imposed by changing conditions within or without the organism, the obvious next line of advance is to find the points of cellular metabolism upon which the hormones exert their characteristic effects.

In this regard, the belief has long been held that the hormones act only on intact cellular structures and were perhaps more in the nature of organisms of cellular activity than direct participants in cellular metabolic processes. Such a belief has now been shaken by the demonstration by Dr. and Mrs. Cori and their colleagues that one of the most important enzymes of carbohydrate metabolism—hexokinase—is inhibited by an anterior pituitary hormone and that this inhibition is removed by insulin; a demonstration of hormone action in an isolated system which gives at least a partial understanding of the effects of hypophysectomy in pancreatic diabetes and the production of diabetes by anterior lobe extracts.

We may expect within the next few decades or even sooner that the intimate relationship of hormones to cellular function will be as well understood as that of certain vitamins is today.

Now while the chemist has been supplying us with the information as to the chemical nature of the hormones and the students of metabolism have been uncovering the cellular mechanisms upon which they act, a third group of workers have been engaged upon another phase of endocrinology of no less importance that the former. This I choose to call the "integrative action of the endocrine system," paraphrasing the classical work of Sherrington on the nervous system. Such a term is of course more than a mere plagiarism since the endocrine system is the oldest correlating mechanism found in the higher forms of life. While it is true that the adrenal medulla and posterior pituitary are to be regarded as extensions of the autonomic nervous system, the remainder of the endocrine glands have so far as has been shown up to the present time only a slight dependence on the nervous system for the regulation and integration of their activity. The extensive research of the last thirty years has shown that such regulation and integration is largely achieved in two main ways. The first of these is the dependence of the gonads, the thyroid and the adrenal cortex on the anterior pituitary not only for the maintenance of their normal structural integrity but for their capacity to vary their characteristic secretions according to the needs of the body. This is
achieved as we all know by the elaboration and release of the specific trophic hormones from the anterior pituitary. There is in addition an inverse relationship between the activity of the target glands and their trophic hormones, inasmuch as a rise in the blood level of the hormone released from the target organ brings about a suppression of the secretion of its trophic hormone by the anterior pituitary. Such a delicately poised system while capable of rapid adjustment to bodily needs also offers many opportunities for the development of minor aberrations in function which if long continued may necessitate major alterations in the whole endocrine system and the processes they control. Such an example would be a decreased sensitivity of the anterior pituitary cells to the blood concentration of the target hormone, allowing in consequence abnormally high concentrations of the latter to reach the receptive cells for long periods.

The secretory activity of other endocrine glands notably the islets of Langerhans does not depend on the prior liberation of a trophic hormone but rather on the changing blood concentration of a metabolite. In the case of insulin this appears to be glucose and in the case of the parathyroids may be the plasma level of inorganic phosphate.

Thus the regulation and integration of the endocrine system involves at least three basic types of mechanism. First, a secretion that is a consequence of an increased degree of activity of the nervous system including both the voluntary and involuntary elements; second, one in which secretion is regulated by a delicate balance between the blood levels of the trophic and target gland hormones and, lastly, a simpler one in which the concentration of certain metabolites in the blood perfusing the gland are the regulatory factors. It is possible that various combinations of all these three may be involved in the operation of a single endocrine organ, particularly in the case of the anterior pituitary.

This then is a rough outline of our present understanding of the integration of the endocrine system. It is perhaps the most difficult problem in endocrinology but its complete understanding would enormously advance our ability to deal with endocrine disorders in man.

I would like to conclude my remarks this evening by some reference to what I consider to be the most important future lines for investigation in both experimental and clinical endocrinology. These are of course a personal selection but one I believe that would find the agreement of most endocrinologists.

The central position of the anterior pituitary both as a source of trophic hormones and those acting directly on the tissues makes it urgent that we should acquire much more information then we possess on the regulation of the secretory elements of this organ. There is as I have already indicated some evidence in the case of the trophic hormones that it is the blood level of the target hormone that is a
major factor. There is also some evidence in the case of the adrenotropic hormone that the release of epinephrine by activation of the autonomic nervous system is a preliminary event. Yet we do not know the role, if any, of nerve elements that may reach these cells nor do we know how the selective discharge of pituitary hormones is affected. It appears unlikely at first sight that the release of F.S.H. and L. H. or of growth hormone and adrenotropic hormone would occur simultaneously. Rather it would appear that the time sequence of discharge is adjusted in some manner to the circumstances prevailing in the body. Furthermore, we do not know whether in the period of rapid growth if the presumed excess of growth hormone in the blood is due to an increased secretion by the gland or a lowering of the rate of release of adrenotropic hormone while maintaining a constant output of growth hormone. There are dozens of such questions relating to the function of the thyroid, gonads and adrenal cortex that require information about the regulation of anterior lobe secretion for their solution.

I have spoken several times of the importance of the blood levels of certain hormones as a determinant of endocrine activity. We are greatly handicapped in clinical endocrinology by our inability to find methods that will enable us to analyze or assay for such blood concentrations. Dependence on urine levels for the assessment of the secretory activity of an organ places us in the same position as were the clinicians of thirty years ago who had only urinary glucose measurements to guide their diagnosis and treatment of diabetes mellitus. We can anticipate an equally great increase in our ability to diagnose and treat endocrine disorders were we in a position to follow the blood levels of the various hormones.

Mention of diabetes mellitus calls to mind that perhaps with the exception of gonadal disturbances in the female that this is the most prevalent endocrine disorder encountered in man. Possibly two million people in this country suffer from an absolute or relative insufficiency of insulin secretion. While the isolation of insulin has enabled us to control the disease once it has presented itself, we are still largely in the dark as to the reasons for its onset. In no endocrine disorder is the collaboration of the student of intermediary metabolism and the endocrinologist more essential for the solution of the etiology of this disease. Much the same can be said for human hyperthyroidism. The advances in our understanding of thyroid physiology have been of a spectacular character and have led to the development of agents that can control hyperthyroidism by blocking out enzyme reactions essential for the formation of the hormone, yet here again little is known of the chain of events that lead to the clinical picture that ultimately presents itself for our relief.

A whole evening could be devoted to the shortcomings in our knowledge of gonadal dysfunction, particularly in the female. Replacement therapy at times brings spectacular results; in many others
it is quite incapable of re-initiating the normal sequence of events. Here perhaps as in no other situation is the coordinated and integrated activity of several endocrine glands an essential feature of normal physiological activity. A measure of our distance from the goal is to be seen in our failure to re-establish normal reproductive function in hypophysectomized animals.

I have always been interested in the comparatively small amount of attention that has been paid to the endocrinology and intermediary metabolism of pregnancy. Here is a physiological event quite evidently associated with widespread adjustments in the endocrine system and a sustained and additional burden on the processes of metabolism and yet I think it is fair to say that we know more of some rare endocrine disorders than we do of these events. Of equal interest, at least to me is the participation of certain hormones in the production of lactation. The mammary gland forms in its cells a unique protein, casein, a unique carbohydrate, lactose and fats of a type found only in milk. All these synthetic processes depend upon an adequate supply of the lactogenic hormone of the anterior pituitary and we would dearly like to know not only more about these unique metabolic reactions but also the relation of this hormone to them.

The present age finds the scientists of this country engaged in the most broad attack on the problems of malignancy that has yet been undertaken. Among the many fields that are being given particular attention is the relation of the steroid hormones, both to the genesis and treatment of certain types of malignancy. Promising results have been obtained by applying our knowledge of endocrinology to the treatment of malignancies arising in tissues that are known to be under hormonal control such as the breast and prostate. Others are investigating the hypothesis that aberrations of normal steroid metabolism may be the etiological basis of malignancy—a hypothesis that will not only require long and painstaking experimentation but most certainly necessitates an understanding of the effects of age, nutritive factors and the mechanism of normal hormone metabolism before decisive answers can be obtained.

I could continue to remind you for some time of the scantiness of our knowledge both in experimental and clinical endocrinology and one might despair of our ability to answer such questions were it not that contemplation of the advances in the thirty years since the establishment of the Association revives our hopes for the future. Thirty years ago endocrinology was struggling to be regarded as a respectable field of research; today this Association and its journals represent only a small part of the individuals who are working in this field, not perhaps calling themselves endocrinologists but appreciative of the fact that the capacity of the organism to regulate its function to its needs by means of hormones is vital to our understanding of normal and abnormal physiology.

In conclusion, I would like to say a few words to those physicians
whose problems lie in clinical endocrinology as it presents itself in their daily practice. Many have expressed to me their sense of frustration that the vast volume of experimental work appears at first sight to bear so little relation to human disease. I can only reply that these basic studies are essential, contradictory as they may often appear, yet the physicians should not forget that the contributions of the clinician have been and may be just as important as those from the laboratory. The names of Addison, Graves, Pierre Marie should remind us that careful observation and controlled studies in man are just as pertinent today as they were in their time. I regard it a privilege to have been the President of a society in which there is such a happy mingling of the laboratory worker and the clinician and I hope that the Association both in its membership and in its program will continue to reflect our joint interest in the problems of the function of the endocrine organs in health and disease.