International Symposium

Hypophyseal Growth Hormone, Nature and Actions

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The Hypophyseal Growth Hormone, Nature and Actions

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Introduction

In this volume are recorded the complete proceedings of an international symposium, *The Hypophyseal Growth Hormone, Nature and Actions*. The symposium was held at the Henry Ford Hospital on October 27, 28, and 29, 1954 and was sponsored jointly by the Hospital and the Edsel B. Ford Institute for Medical Research with their respective staffs. It was the second in a series of such meetings inaugurated by Dr. Robin Buerki, Executive Director, as an impetus to progress in the basic medical sciences. The first of these was held in 1953 and its proceedings were published by The Blakiston Company, Inc. in 1954 under the title of *The Dynamics of Virus and Rickettsial Infections*. For the 1955 meeting the subject *Enzymes: Units of Biological Structure and Function* has been selected by the joint staffs of the Institute and Hospital.

The symposium on the growth hormone was attended by 300 persons from laboratories and institutions in Europe, England, South America, Canada, and throughout the United States. Among them were representatives of many scientific disciplines including anatomists, physiologists, biochemists, pharmacologists, zoologists and investigators in endocrinology, animal husbandry, and clinical medicine, not to name them all. This broad representation had much to do with the unquestioned success of the meeting.

Regardless of its ultimate value the symposium was, in certain respects, a notable occasion. This was apparent to those who realized that the enigmatic pituitary growth hormone had been under study by one full generation of investigators and that present at the symposium were all the scientists, with few exceptions, who had been intimately concerned at one time or other with this most elusive of the pituitary hormones. It was 33 years ago that J. A. Long and H. M. Evans detected growth-promoting activity in crude extracts of the anterior hypophysis. Shortly thereafter, the series of experiments by P. E. Smith began defining the various functions of the anterior pituitary, and the pursuit of the growth-promoting factor had begun. Closely following these developments was the first of the many important observations of Houssay on the relation of anterior pituitary action to diabetes. This is not the place to review the history of anterior lobe physiology, nor is it adequate to highlight just certain milestones along the 30-year road of scientific effort. However, for those who were familiar with the historical background it was a memorable experience to have witnessed the joint participation of such eminent investigators. As is apparent from the list of participants on page v of this volume, two scientists were conspicuously absent. The reader, undoubtedly, will have identified them as Herbert M.

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Evans and F. G. Young. Dr. Evans was to have addressed the symposium following the dinner on the first evening and to have reminisced on the past 30 years or more of investigation in the field of the pituitary hormones. A temporary illness forced him from participating. Dr. Young was fulfilling long-standing commitments in South Africa at the time of the meeting, but his laboratory and philosophies were ably represented by his associate, P. J. Randle. At this point it is appropriate to mention the contribution to the symposium by Alfred H. Washburn, who addressed the symposium members and many of the hospital staff following the dinner on the second night. He summarized certain of the impressive number of observations on patterns of human growth that he has accumulated over the past 20 years.

A few comments about the programming and symposium operations are warranted inasmuch as these are reflected closely in the format of the present volume. As will be noted, the symposium was divided into 5 Parts, and between some of these there is an apparent overlapping of headings as, for example, in the subject designations of Part II and IV. Each is concerned with the growth hormone effects on certain structures; yet it should be apparent that effects on morphology is, for the most part, the essential topic of Part II, while the mechanism of action is the main theme of Part IV. Another reason for the apparent arbitrariness of subject grouping was the desire of the Program Committee to devote one full day to the extensive material on the major metabolic actions of growth hormone (Part III). This meant some division of other areas of study which might have been grouped under one heading. It will be apparent to the reader that the large amount of research concerning the action of growth hormone on the mammary gland warranted assigning this material to a part which would permit an uninterrupted consideration. Inasmuch as the data on growth hormone effects in man were quite limited and since much of the work, both in this area and in respect to the mammary gland, was applied or clinical research, it was decided to combine these into Part V.

This volume was prepared for publication with the view that the recorded data, methods, and speculations pertaining to this accelerating field of research should be passed on without delay to the many readers anticipating its release. In order to accomplish this, it was decided that all contributions to the symposium, having been carefully recorded, would be revised by one editor and that the material would not be submitted to the respective speaker or discussor for his own revisions. Obviously, this introduced the considerable hazard of misinterpreting the thought or data which the contributor actually intended to present, particularly in the designated and general discussion periods. This is mentioned in order to free the participants of any responsibility for the misinterpretations which may have resulted. Likewise, proofreading was the sole responsibility of the editors, and the authors should be relieved of criticism for any errors in the publication of the manuscripts.

Considerable importance has been attached to the discussion periods which followed each group of papers. With few exceptions, a designated speaker initiated the discussion period, either presenting data and observations from his own experience or discussing the previous presentations. All invited guests were encouraged to contribute in the general discussion period and all comments were fully recorded. It is hoped that the reader will devote equal attention to the portions of the volume devoted to the general discussions. Only certain brief remarks of the chairmen which concerned the mechanics of running the symposium have been deleted.

Finally, it might be said that the symposium on the growth hormone did not arise from circumstances which have led to many of the valuable conferences we have witnessed in the past few years. Growth homone, to date, has shown discouragingly little clinical promise and the symposium was primarily a meeting of investigators working in the basic biological and medical sciences. Possibly the status of the pituitary growth hormone is about where corticotropin quietly rested in 1946, 1947, and 1948 prior to the notable observations of Hench, Kendall, and others which opened the floodgates to applied research and clinical trials with corticotropin. Although, as this conference revealed, there is little at the present time to encourage the idea that growth hormone will be of similar usefulness in clinical medicine, nevertheless this possibility is one that cannot be ignored. For the moment it will be rewarding enough to convince ourselves that there is a specific pituitary growth hormone, that it can be isolated intact and in amounts which will permit extensive experimentation, and that it does manifest anabolic properties in man. Perhaps our thinking has become conditioned to the rapid metabolic actions of corticotropin and we expect, unreasonably, that growth hormone will induce immediate and readily measured changes. If we consider the growth process, we will appreciate that, even under optimal circumstances, it proceeds at limited rates. Broadly characterized, normal growth is a subliminal, steady and, usually, proportionate phenomenon. The limits of our yardsticks must be heeded and it would be artless science to expect in short-term experiments quantitative, or even qualitative, duplications of naturally occurring growth. This symposium was held to sift over the rapidly accumulating data, to compare techniques of study, to attempt a resolution of disturbing differences, and to stimulate new approaches which someday may bring usefulness to this most intriguing pituitary substance.

We wish to gratefully acknowedge the splendid secretarial assistance rendered by Miss Dorothy Reid and Mrs. Nancy Hasegawa and the enthusiastic support given to the Program Committee by the administrative and service departments of the hospital.

Detroit, Michigan
February, 1955

RICHMOND W. SMITH, JR.
OLIVER H. GAEBLER
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What is Growth?*

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The invitation to give an introductory address to this meeting is a distinct honor; it also carries a mandate to set the phenomenon of growth in proper perspective before discussing "growth" hormone. Unfortunately, "growth" itself has received much less critical attention than have the agents for which it serves as indicator and assay. To put it bluntly, "growth" is a term as vague, ambiguous and fuzzy as everyday language has ever produced. Adopted into scientific language without precise and consistent meaning, it may be passable for crude description, but is ill-fitted to analytical application. Hence, if you ask: "Just what is Growth?", the correct answer is: "A word that covers, like a blanket, a multitude of various things and meanings." To know "growth" for what it really is, rather than what we are wont to call it, we must remove that blanket and uncover the underlying facts it has concealed. This I propose to do in rudimentary sample form as time permits. A close look at the facts will do far more for clarification than would a host of academic definitions and circumlocutions.

Our notions about growth have been shaped more by usage than by incisive study; they form a sort of scientific folklore. As a result, we find that various groups, while they all just plainly speak of "growth," do not all mean and talk about the same thing. Thus growth has come to connote any and all of these: reproduction, increase in dimensions, linear increase, gain in weight, gain in organic mass, cell multiplication, mitosis, cell migration, protein synthesis, and perhaps more. It would seem inconsistent to apply the most exacting standards of precision to our research data and then proceed to mix into their description and interpretation such vague ter-

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minology as this. The mixture can be no more precise than its vaguest ingredient.[1]

Then, what is wrong? Why such diversity of views and versions? The reasons lie in our unfounded expectation that growth is a single, simple, measurable entity. In this conviction, each of us has tended to deal with his own limited aspect of the problem as if it were a representative sample of the total perspective. Yet, far from being a single, simple and unitary phenomenon, growth is conglomerate, complex and intricate, and this is why it defies formulation in simple terms. What usually deceives us is the simplicity of our tools and terms of measurement, which all too easily produce the illusion of similar simplicity of the measured systems.

Just bear in mind how we get to know about growth: by taking measurements at different times, comparing them and noting a net gain—of size or mass or numbers. These serial measurements then define a growth curve, as descriptive of the particular system as, let us say, a fingerprint—and equally empirical. This is the blanket under which a host of disparate events lie hidden; events, moreover, of opposite signs, some adding to, others subtracting from, the measured body. Since they are not all of one kind and their shares are unequal, growth can be recorded, but it cannot be understood, without identifying these tributaries and determining their respective contributions.

Let me phrase this in terms of an analogy. The body is a community of cells; each cell a community of smaller particles; and each particle an assemblage of molecular species. Thus, the proper analogue of biological growth is the growth of a human community; for example, of a city. Here we rate as growth, for instance, any increase in population over a given interval. But a simple tally will not tell us how the increase has come about. It takes census data to give a more detailed accounting. They reveal that additions come from two different sources: reproduction from within, and immigration from without; losses, likewise, from death as well as emigration. The results would be altogether different if instead of just counting noses, we chose to include in our considerations the physical wealth of the community, that is, the net gain in goods and estates produced by the members of the population. To understand its sources would require running inventories of raw materials, production, conversion, consumption, imports, exports, storage and wastage. Moreover, in either reckoning, the data can have meaning only in reference to fixed boundaries which divide what we count as "within" from that which we count as "without."

Now, as we apply this simile to biological growth, the whole indefiniteness of our customary position becomes obvious. First, let us consider the matter on the tissue level. Suppose we note an increase in the number of cells of a given organ. What does this really tell us? As in the human population, some cells have reproduced, others have immigrated, still others have been lost by shedding or disintegration, the proportions and rates of these

component events varying from tissue to tissue. The final tally—no more than a crude balance sheet—discloses none of these details. According to Hamburger and Levi-Montalcini,[2] for instance, abnormal enlargements in the early central nervous system, formerly ascribed simply to "hyperplasia," that is, overproduction, are partly due to the fact that fewer cells degenerate, rather than that more are being proliferated, and partly to the fact that the cell group being counted has received additions from an indifferent pool outside the counted area. Another shortcoming of plain cell counts is that they ignore all growth of individual cells (e.g., hypertrophy) not followed by division.

If, then, we turn from cell counts to over-all dimensions or total mass, we are on even weaker ground. In terms of our community analogy, we first have to agree as to what is, and what is not, real property of the system we measure, or what has been acquired and what discarded during the measured period. Food in the alimentary tract is still distinctly out-of-bounds; even if stored for weeks, as in a hamster's pouch. But what of this mass once it has passed into the blood and lymph stream? Though strictly on the inside, it still has not become converted into substance of the body proper. Then, what about the food stuffs stored in modified form, for instance, as glycogen or fat in liver or fat bodies? Their fluctuations up and down are not conventionally considered growth and degrowth. Why? Because we sense that growth connotes some *permanent* addition, and merely temporary physiological variations do not qualify under this title.

Then, what about the wastes not yet eliminated? And the products manufactured by our organs? Take hair or nails or even red cells—terminal products destined to be shed or otherwise eliminated. In counting bodily productions, is it fair to include just those fractions which happen to be present on the measured body when we take our measurements, and leave out all the unknown mass that has been similarly produced in the interim but irretrievably lost? Evidently, we ought to be consistent and either count it all in or all out, neither of which is practicable. We certainly would not collect secretions, such as slime, urine, sweat and sebum, over a measured period and add them to the growth record. Yet, we do customarily include the bulk of cartilage and bone and other connective tissues, which consists of residues of cellular secretions, just like those other ones, but incidentally deposited, instead of extruded, hence accruing to the measured mass. Thus what we measure, is related not so much to the process of production as to the accident of the disposal of the products. If they persist, we count them; if they drop out, we miss them.

The arbitrariness attached to our measurements is about the same, whether we use total mass, dry weight, nitrogen content, volume, length, or what not, as reference system. It is even worse when we turn from the body to its component cells. The cell is bounded by a surface, and we are in the habit of ascribing any increase in the volume thus enclosed to "growth." But

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