HORMONAL REGULATION of ENERGY METABOLISM

Compiled and Edited
by

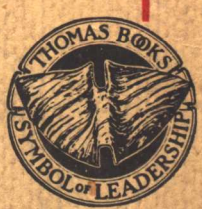
LAURANCE W. KINSELL, M.D.
Institute for Metabolic Research
Highland-Alameda County Hospital
Oakland, California

A CRITICAL EVALUATION OF CURRENT KNOWLEDGE AND CONCEPTS IN A FIELD OF FUNDAMENTAL AND CLINICAL IMPORTANCE

A book of interest to clinicians, clinical investigators, and fundamental scientists.

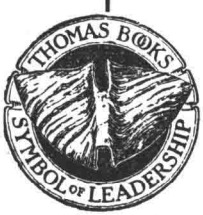
In common with the nervous system, the glands of internal secretion are concerned with the integration of body activities. During the past generation, many of the hormonal substances have been isolated, identified, and synthesized. The physiologic effects of many of the hormones of the pituitary, thyroid, adrenal, Islet cells, and gonads have been well described. The precise mechanism of action of these hormones, with particular reference to effects of specific enzyme systems, is a field which is only now beginning to take form.

CHARLES C THOMAS • PUBLISHER
Springfield, Illinois



HORMONAL REGULATION OF ENERGY METABOLISM

Compiled and Edited by
LAURANCE W. KINSELL, M.D.



CHARLES C THOMAS · PUBLISHER
Springfield · Illinois · U.S.A.

CHARLES C THOMAS · PUBLISHER
BANNERSTONE HOUSE
301-327 EAST LAWRENCE AVENUE, SPRINGFIELD, ILLINOIS, U.S.A.

Published simultaneously in the British Commonwealth of Nations by
BLACKWELL SCIENTIFIC PUBLICATIONS, LTD., OXFORD, ENGLAND

Published simultaneously in Canada by
THE RYERSON PRESS, TORONTO

Library of Congress Catalog Card Number: 57-5600

Printed in the United States of America

PARTICIPANTS

E. B. Astwood, M.D.: *Tufts University Medical School, Boston, Massachusetts.*

Charles H. Best, M.D.: *University of Toronto, Toronto, Canada.*

Walter A. Compton, M.D.: *Elkhart, Indiana.*

Lathan Crandall, Ph.D.: *Elkhart, Indiana.*

Clement A. Finch, M.D.*: *University of Washington, Seattle, Washington.*

Roger W. Friskey, M.D.*: *Institute for Metabolic Research, Highland-Alameda County Hospital, Oakland, California.*

Edgar S. Gordon, M.D.: *University of Wisconsin, Madison, Wisconsin.*

Wendell H. Griffith, Ph.D.*: *University of California, Los Angeles, California.*

Jack Gross, M.D.: *State University of New York College of Medicine, Brooklyn, New York.*

Bernardo A. Houssay, M.D.: *Instituto de Biologia y Medicine Experimental, Buenos Aires, Argentina.*

Elliott P. Joslin, M.D.: *Joslin Clinic, Boston, Massachusetts.*

Laurance W. Kinsell, M.D.:*: *Institute for Metabolic Research, Highland-Alameda County Hospital, Oakland, California.*

Henry A. Lardy, Ph.D.: *University of Wisconsin, Madison, Wisconsin.*

Rachmiel Levine, M.D.: *Department of Metabolic and Endocrine Research, Michael Reese Hospital, Chicago, Illinois.*

John A. Luetscher, Jr., M.D.*: *Stanford University Medical School, San Francisco, California.*

Sidney C. Madden, M.D.*: *University of California, Los Angeles, California.*

George D. Michaels, Ph.D.: *Institute for Metabolic Research, Highland-Alameda County Hospital, Oakland, California.*

Philip J. Randle, M.D.: *University of Cambridge, Cambridge, England.*

Sidney Roberts, Ph.D.: *University of California, Los Angeles, California.*

Howard F. Root, M.D.: *Joslin Clinic, Boston, Massachusetts.*

Leo T. Samuels, Ph.D.: *University of Utah, Salt Lake City, Utah.*

William C. Stadie, M.D.: *University of Pennsylvania, Philadelphia, Pennsylvania.*

* Program Committee

DEWITT STETTEN, JR., M.D.: *National Institutes of Health, Bethesda, Maryland.*

CLARA SZEGO, PH.D.: *University of California, Los Angeles, California.*

ARNE WICK, PH.D.: *Scripps Metabolic Clinic, La Jolla, California.*

ROBERT WILLIAMS, M.D.: *University of Washington, Seattle, Washington.*

FRANK G. YOUNG, D.SC.: *University of Cambridge, England* (in absentio).

LOUIS J. ZELDIS, M.D.: *University of California School of Medicine, Los Angeles, California.*

FOREWORD

IN A DAY of bigness, the need emerges for round table, small group discussion of certain problems.

The Conference on Hormonal Regulation of Energy Metabolism was arranged by the Program Committee on the premise that such a need existed in this field. The Proceedings are presented in this volume.

The remarks of Dr. Joslin, the Dean of diabetologists, for several reasons are removed from their strict chronological sequence, and, like Abou ben Adhem's name, lead all the rest. The central focus of the Conference was not, officially, diabetes. Yet the disturbed metabolism found in the disease, and the known and suspected physiologic effects of insulin, found their way into most of the discussions. Throughout the Conference, Dr. Joslin's wisdom served as a warm and strong cement to bring together the various disciplines represented.

The Chairman takes this opportunity to acknowledge the invaluable assistance of many members of the Conference in the organization and editing of the Proceedings, particularly Drs. Friskey and Gordon.

THE ROAD AHEAD

By ELLIOTT P. JOSLIN

ALL OF US TODAY, concerned with the treatment of diabetes look forward with hope in our hearts. Think how much hope one gathers from a meeting such as this.

This book which I hold in my hand was the first treatise on the treatment of diabetes.* Rollo wrote it only a few years ago—1796, actually but four years before my grandfather was born. When you read it and compare the training to which he was exposed with that which you before me have had, one cannot help gathering hope. Dr. Root always emphasizes one of Josiah Royce's dicta, namely, "the fecundity of the aggregation." What an aggregation is assembled in this room!

Just a word about the status of diabetes as I see it today. It is quite real to me. I was born in the little New England town of Oxford, Massachusetts. On its Main Street there were three large and commodious houses, and of the six heads of families in those houses, five came down with diabetes. The one who did not was not obese. That made quite an impression upon me. Also, another impression was created, because across the street from our home lived Mr. George Fred Daniels, who never went to college and yet was an educated man with a scientific spirit. He wrote one of the best histories of New England towns. Oxford was settled just after the revocation of the Edict of Nantes in 1687. Six years later occurred a massacre by the Indians of the Johnson family in the town. Mr. George F. Daniels, as a boy, walking back and forth to school, was taught by his father to lay down a stone on the site of the massacre. The stones grew to a cairn and later were replaced by a monument. From that example, I began laying down stone after stone or, rather, recording one by one my diabetics who died.

* Rollo, John: Cases of the Diabetes Mellitus, with the Results of the Trials of Certain Acids, and other Substances, in *Cure of the Lues Venerea,* 2nd Ed. London, T. Gillet for C. Dilly, 1798.

The data have been compiled by the Metropolitan Life Insurance Company. During the period from 1897 to 1914, the average patient I treated lived 4.9 years. Those with onset under 10 years lived 1.2 years. Today, the average patient lives 16 years and those with onset in the first decade of life who have died have averaged 20 years. Those with onset between 40 and 59 years live 16 years, and those with onset from 60 onwards, instead of living 4 years as formerly, now live 10. Meantime a great change in the age at death of diabetics has taken place. Thus, up to 1914, those in our series who died were on the average 44 years old, but now the average is 65 years.

Years ago one of my patients gave me a thousand dollars and with it, through the kindness of Miss Amelia Peabody, a life expectancy medal was created which we give to those patients who live longer with their diabetes than they were expected to live without it. As a matter of fact, Case 8 of my series, who lived in one of those Oxford houses, completed her full span of life with the Naunyn treatment. Through the years we have given many of these medals, possibly 2000, and only yesterday I was impressed by the gratitude shown by a patient who received one, and how he was using it to encourage another diabetic to take heart for a long life. The distribution of these medals became so common that later the Quarter Century Victory Medal was created. There are now 63 who, after 25 years, have passed the tests of ophthalmologists, roentgenologists and internists by being free from degenerative stigmata in the eyes, the blood vessels and the kidneys.

If one looks for the greatest common divisor in these patients who have done unusually well, it will be found to be the meticulous care which these patients have received. The first case had almost everything at his disposal—wonderful parents, one of our best nurses, who remained with him 7 years, funds sufficient to supply his needs and even allow him and his nurse alone to fly in his airplane from New Jersey to Cape Cod; and finally his marriage to a girl who spent months learning how to take care of diabetics. He had diet, exercise and insulin, plus what is needed today, namely, opportunity and a zeal to follow treatment. His life has stimulated us to build the Hospital Teaching Clinic, where teaching will take precedence over nursing. In this way,

money can be saved, and at reduced costs we can invite back our patients so that they, too, will have an opportunity to learn how to be medal cases. We hope that the results we obtain in the Hospital Teaching Clinic will be so good that it will lead to similar opportunities being created for diabetic patients in every hospital in the world. Until now the young diabetic has carried on his back the expense for the care of the old and seriously complicated diabetic, whose future holds little chance for rehabilitation. Today there exists no discrimination in hospitals between the cost for the care of the young and ambulatory diabetic with years of possible activity ahead, requiring chiefly teaching, and the old, pathetic patient whose life is nearly at an end, for whom almost hourly nursing is necessary.

CONTENTS

HORMONAL REGULATION
OF
ENERGY METABOLISM

I

CERTAIN ASPECTS OF HORMONAL REGULATION OF CARBOHYDRATE METABOLISM

By DEWITT STETTEN, JR.

I DO NOT PLAN to present original or new contribution, but rather to consider certain problems, certain areas of ignorance, possibly to provoke a few arguments.

We may start out with the idea that certain endocrines operate in the organism by controlling the rates of specific enzyme catalysts. This may not be universally true, but I believe it is foremost in the thoughts of many workers in the field. Right away we are up against an overwhelming difficulty. As was pointed out by some of the speakers at a recent meeting, there is not a single enzyme-catalyzed reaction for which we can today write a mechanism that is satisfactory to the organic chemist. In other words, we are talking about the regulation of reactions that we don't understand. One of the obvious reasons we cannot write mechanisms for enzyme-catalyzed reactions is that, thus far, we do not know the structure of the enzyme. Before the organic chemist can write a mechanism for a reaction, he must obviously know in some detail, the structures of the reactants. It follows almost necessarily, that since we don't know the mechanism of any enzyme-catalyzed reactions, we do not know the mechanism of the endocrine control of such a reaction. As a matter of fact I believe there is no endocrine-regulated phenomenon about which one would find even a reasonable degree of concordance as to how it operates.

In contrast to the situation of the enzymologists, the endocrinologist has made considerable progress in elucidating the structures of the compounds in which he is predominantly interested. The structures of epinephrine, thyroxin and insulin can today be written, but even with these compounds there are large areas of ignorance. The structures that have been established are those of compounds which have been extracted from the endocrine

glands after more or less vigorous treatment. There is I believe, no assurance in any single case that the product whose structure is written in the text book is indeed that of the native product that occurs in the gland from which it is extracted. There is also, in most cases, no assurance that the product which circulates in the blood is identical chemically with the product which is isolated from the gland. In this area the thyroid physiologists have perhaps progressed further than the insulin physiologists.

Insulin, generated in the pancreas, must, in all probability, pass through the liver before it gets to its most important target organ, the skeletal muscle. There is no clear evidence that the material that goes into the liver is the same as that which comes out of the liver. As a matter of fact, much of the recent speculation and experimentation would suggest that insulin is altered in the course of its passage through the liver. Unfortunately most of the therapeutic and experimental applications of insulin have involved its administration not into the portal blood, but into peripheral blood. It is therefore difficult to ascertain that the insulin we are injecting is arriving in the same condition as is the insulin which arrives at the muscle after intrinsic production in the pancreas.

Then there is another problem, namely, whatever the form in which the hormone travels in the blood, what is the form in which it operates on the target organ? Here again thyroid physiologists, I think, have led the way. I have no doubt that we will hear something about this from Dr. Gross before the meeting is over. I believe that there is no assurance that the material which produces the actual effect on the target organ, is chemically identical with the material which travels to the target organ through the vascular tree.

Whereas we cannot say much about intimate mechanisms of most hormonal effects, there has been considerable speculation and experimentation designed to determine the sites of action of several of the endocrine agents.

The site of action, or at least a major site of action of insulin is generally believed today to be early in the course of utilization of glucose, and possibly other sugars. Attention was focused upon this by the work in the St. Louis laboratories. Over the past few years there has been an impressive accumulation of evidence from

Levine's laboratory; also in Parks and other laboratories, suggesting that the action of insulin is related to the transport of glucose, chemically unaltered or minimally altered, from the extra-cellular to the intra-cellular compartment. I believe this latter to be the best working hypothesis of insulin action that we have today. I would point out however that it fails to explain certain data in the literature. As an example I might mention a report from Burk's laboratory, dealing with a response to insulin in the homogenate of a mouse sarcoma, in which no cells and no cell membranes were present. This insulin response is similar, though perhaps not identical, to the effect of insulin that might be anticipated in an intact tissue. It is therefore possible that the hypothesis from the beautifully executed experiments of Dr. Levine and his colleagues may not explain *all* of the manifestations of insulin action. In any event, I believe that we can focus on the entry of glucose, and its initial phosphorylation, as the *areas* in which insulin acts. I would repeat that the *mechanism* of insulin action is today, as far as I am aware, completely unknown; this despite the fact that in this particular case we do know the structure of the hormone in question.

The *phosphorylase* reaction appears to be under rather elaborate endocrine control. At least two materials, *epinephrine* and *glucagon* have been implicated by Sutherland as affecting the activity of phosphorylase in certain tissues. Epinephrine seems to favor the reactivation of inactive phosphorylase in liver and in muscle. Glucagon apparently does something similar, but most workers feel that its activity is entirely or almost entirely restricted to the liver. It seems odd that the body should go to the trouble of making two hormones, one of which acts in two places, the other acting in the same fashion only in one place. It is worth noting that whereas the normal venous drainage of the adrenal is into the systemic blood, the normal venous drainage of the pancreas is via the portal vein into the liver. Bornstein has stated that glucagon is quantitatively removed by one passage through the perfused liver. Apparently glucagon not only does not affect phosphorylase in muscle; it probably never gets there. The differences in phosphorylase in liver and muscle are also of interest to us.

Another reaction which has recently attracted attention is the

glucose-6-phosphatase reaction. This enzyme has been shown by several workers to increase in activity, and presumably in abundance, in the diabetic state. A difficulty in which the diabetic necessarily finds himself, stems from the fact that the reaction from glucose to glucose-6-phosphate is resricted, while the reaction from glucose-6-phosphate to glucose is exaggerated. It is quite obvious that the diabetic is hard put to generate everything which derives from glucose-6-phosphate.

So much for some of the more obvious relationships. The relationship of some other endocrines appear to be more subtle.

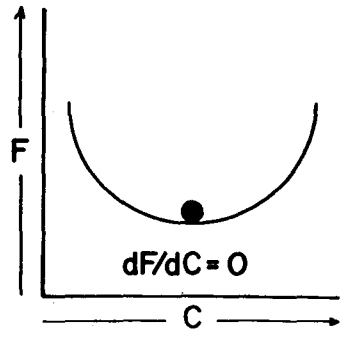


FIG. 1. Thermodynamic equilibrium.

In trying to give "background" to (I hope) future discussion, I would like for a moment to consider one of the more baffling problems in biochemistry namely, why does the composition of the normal adult organism tend to remain constant? This is a problem which has intrigued physiologists since Claude Bernard's day. One frequently hears the word equilibrium used to explain such constancy. "Equilibrium" is a word which is completely respectable, and is well and precisely defined by the physical chemist. It is the condition of minimal free energy. It is the condition from which there is no escape unless work is done on a system. It is often represented by a diagram of a ball resting in the bottom of a valley. The ball cannot possibly escape unless outside work is caused to drive the ball out of the point of maximum stability (Fig. 1). Equilibrium is the first thought that the chemist will have when he encounters a system of invarient composition. He will say, "Let us see whether this system is in equilibrium." If it is in equilibrium, this will explain why its composition is invariant, and there are certain tests by which the existence of equilibrium may be established. I shall not trouble you with these tests. I will only point out that in the body of the mammal there are, probably, certain situations in which the constancy of composition is contributed to by equilibrium considerations. For

instance, it is held that the concentration of the ions which are represented in the bone mineral in the body fluid is at least in part a reflection of equilibration, in the physical chemical sense, of a solution in contact with a solid phase, the solution being essentially saturated with the constituent of the solid phase. However, in most of the situations which one explores biochemically, he finds that in the living organism operations are running quite remote from equilibrium. Thus the phrase that one hears so frequently: "The amino acids of the body are in equilibrium with the proteins of the body" is anathema to some of us. This is quite obviously not true. Most of the nitrogen of the body is in the form of polypeptide or protein. If polypeptide is exposed to water it is hydrolized spontaneously. If one takes a mixture of amino acids in water, no matter how long one waits he does not get an appreciable yield of polypeptides. The equilibrium here is entirely in favor of hydrolytic products. Therefore, the relationship of the amino acids of the body and the proteins of the body is certainly not a reflection of equilibrium forces.

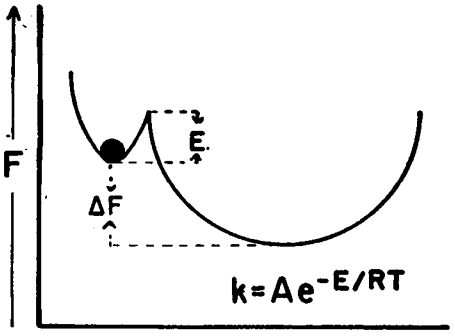


FIG. 2. Kinetic stability.

The second situation that one considers when one wishes to explain constancy of composition is something which has been called "Kinetic stability." The ball in this case has been trapped in a crevasse and cannot readily roll to its position of maximum stability at the bottom of the valley (Fig. 2). It must overcome a certain energy "hump" which we call the energy of activation, before it can roll down. This model breaks down when we consider the situation in chemistry, because, instead of dealing with a single ball, we are dealing with a statistical population of molecules whose energies are not uniform but are distributed. However, in this population there will always be a fraction of molecules having energy in excess of E and the magnitude of that fraction will determine the rate in which the balls can escape from