LECTURES ON THE

THYROID

BY

J. H. MEANS, M.D.

Jackson Professor of Clinical Medicine Emeritus
Harvard University
Former Chief of Medical Services, Massachusetts General Hospital
Physician, Massachusetts Institute of Technology

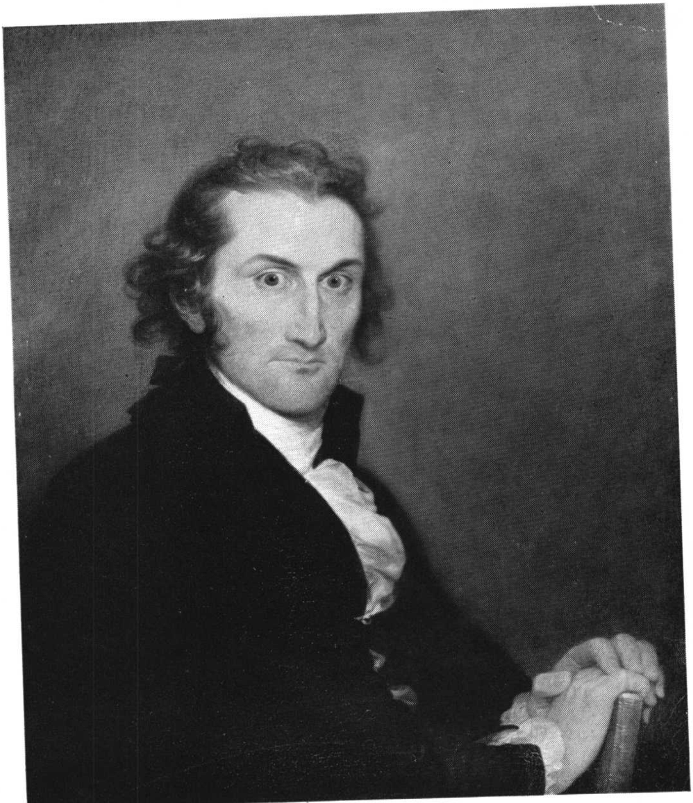
HARVARD UNIVERSITY PRESS · CAMBRIDGE

1954

Distributed in Great Britain by
GEOFFREY CUMBERLEGE
Oxford University Press
London

Library of Congress Catalog Card Number 54–5021

Printed in the United States of America



Portrait of Dr. Lemuel Hopkins (1750–1801), physician of Hartford, by John Trumbull. Dr. Hopkins's eyes show unmistakable evidence of his having, or having had, Graves's disease. (Courtesy of Yale University Art Gallery.)

PREFACE

The lectures collected in this volume were delivered in various places during the period from June 1949 to April 1953. Although not in any way planned as a sequential course, the several lectures yet have some relevancy one to another. The excuse for publishing them in the present form is that, taken together, they epitomize some of the thoughts which I have derived from my own work on the thyroid, together with that of many brilliant colleagues, whose brains I have freely picked. In my own case the experience has extended over some forty years. The collection is a personal account. It is not intended in any sense as a complete coverage of the topics discussed.

The first four lectures, previously published in medical journals, have all been carefully edited and brought up to present knowledge as nearly as possible by means of textual alterations. In the doing of this I have had the invaluable aid and advice of Dr. John B. Stanbury, my successor in the Thyroid Clinic at the Massachusetts General Hospital.

Lecture I was the third annual Harvard Lecture given at the University of Colorado Medical Center, Denver, on December 8, 1950, under the auspices of the Rocky Mountain Harvard Medical Alumni Association.

Lectures II and III were the seventeenth course of lectures under the William Sydney Thayer and Susan Read Thayer Lectureship in Clinical Medicine. They were delivered at the Johns Hopkins Hospital, Baltimore, on April 26 and 27, 1951.

Lecture IV was the Holme Lecture delivered at University College Hospital Medical School, London, on June 23, 1949.

Lecture V was the Hanau W. Loeb Lecture of the Alphi Pi

Chapter of Phi Delta Epsilon, St. Louis University School of Medicine, delivered on March 26, 1953.

I am grateful for permission to republish to the *Annals of Internal Medicine* in the case of Lecture I, the *Bulletin of the Johns Hopkins Hospital* in that of Lectures II and III, the *Lancet* for Lecture IV, and the *Medical Bulletin of St. Louis University* in the case of Lecture V.

J. H. MEANS

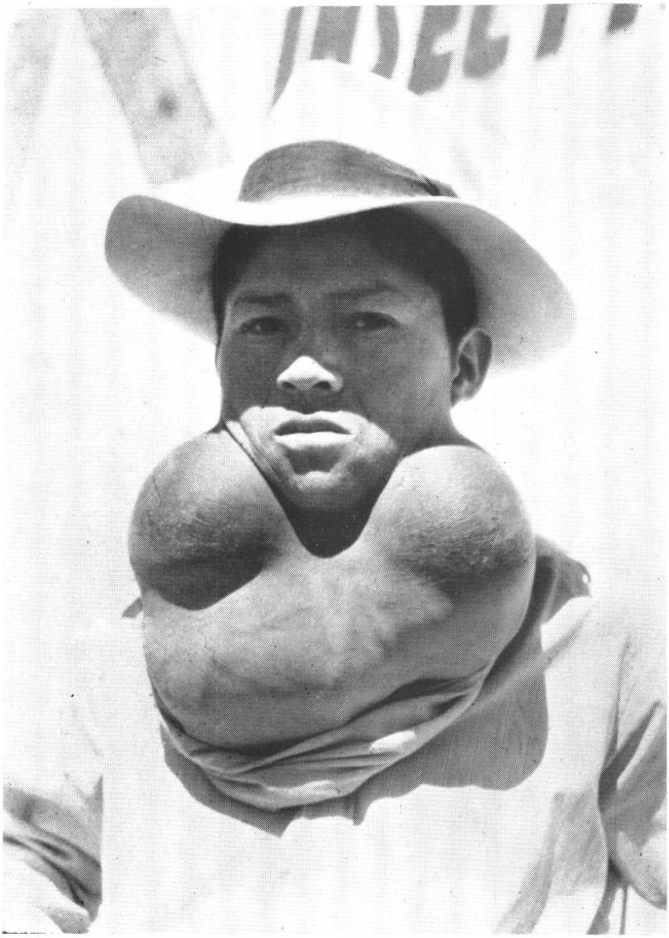


Fig. 8. "Francisco"; endemic goiter from the Peruvian Andes. (Courtesy of Dr. Elwood A. Sharp of Parke, Davis & Company, Detroit, Michigan.)

CONTENTS

1 The integrative action of the endocrine system

For the subject of this lecture I have chosen certain aspects of the fundamental question, "What makes us tick?"

"What makes us tick as human beings" is perhaps relatively easy to answer. We might say the cerebral cortex or, if you prefer, the soul of man. The latter, however, gets us into theology, and I would prefer to stay out of that — at least at this time. "What makes us tick as animals" is a more complicated question. There is involved not only our cerebral cortex but our adrenal cortices as well, to say nothing of the rest, both of our nervous systems and of our endocrine systems.

The great dynamic integrative mechanisms of the animal body are the nervous and circulatory systems and the endocrine system, which employs the circulation as its conveyor. These systems, which are integrated with one another, together play an indispensable role in the integration of the higher animal in its entirety.

But, one may ask, "What of the amoeba?" This lowly being seemingly gets on well without either an endocrine or a nervous system, yet it behaves as a beautifully integrated organism, better perhaps in some respects than man. Who, for example, ever heard of a schizophrenic amoeba? Does the amoeba make substances bearing any resemblance to hormones, or does it get on quite well without them? I suspect that it gets on without them, and that integration in single-celled existence is achieved through regulation of the rate of one enzyme system by the accumulated products of another enzyme system. We may call this enzymatic integration, or the primordial integration of the unicellular, and perhaps look upon it as the most primitive integrating mechanism of the multicellular. I will return to this interesting subject later.

When I was a medical student I read from cover to cover with rapt attention the work of Sherrington, then professor of physiology at Liverpool, entitled, *The Integrative Action of the Nervous System.*[1] It was his Silliman Lectures, delivered at Yale, and it represented the most authoritative work on the physiology of the nervous system of approximately half a century ago. Investigation since Sherrington's has added much to our understanding of the physiology of the nervous system, as, for example, the whole concept of the conditioned reflex of Pavlov,[2] the chemical mediation of nerve impulse, localization of function in the brain, etc., but I believe there is little, if anything, in Sherrington's conceptual scheme that requires retraction.

This work made a deep impression on me, and through the intervening years, as I have become increasingly interested in endocrinology, I have become more and more conscious of certain similarities between the functions of the nervous and the endocrine systems.

In both systems stimuli are received; signals are sent to distant end-organs which, upon receipt thereof, perform in turn the functions they have been evolved to perform. "The unit mechanism in integration by the nervous system," Sherrington tells us, "is the reflex," and in the reflex there are involved "at least three separable structures": receptors, conductors, and effectors. In the case of the nervous system, receptors are sense organs of one sort or another, conductors are neurones and synapses, and effectors are muscle or gland cells. The same terminology can be applied to the endocrine system. Receptors are the cells of endocrine glands or similar tissues, conductors are hormones, and effectors are the end-organs or targets upon which hormones specifically act. The simplest nervous reflex arc involves at least two neurones, but more complicated reactions require many more. So also in the endocrine system we often find hook-ups in which two or more hormones are involved. An important property of the nervous system also is that action on effectors may in some cases be excitatory, in others, inhibitory. The same is true of the endocrine system. Hormone *A*, for example, provokes the delivery of hormone *B*, but hormone *B* suppresses that of hormone *A*.

I do not wish to belabor the nervous-endocrine analogy unduly — it has, of course, but a limited application — nor do I wish to consider integration by the endocrine system as a thing apart. However, if the limitations of the analogy are recognized (and I hope, if not already obvious, they will emerge as I proceed), it will prove helpful in the development of a concept of total integration of the person, which is what, after all, concerns the physician.

The whole process of living, in its material realm, consists in everlastingly adjusting to environment. Adjustment includes not merely the erection of defenses against hurtful influences of environment, but also the alteration of environment by the organism to make it more suitable for the organism. Good adjustment is health; poor adjustment is illness. Successful adjustment is integration, unsuccessful is disintegration. When adjustment fails completely, life ceases or, if you prefer, death takes place. It is a case of "root, hog, or die." Frustration I should classify as a form of disintegration.

"In the multicellular animal," Sherrington tells us, "especially for those higher reactions which constitute its behaviour as a social unit in the natural economy, it is nervous reaction which par excellence integrates it, welds it together from its components, and constitutes it, from a mere collection of organs, an animal individual."

Sherrington admits that the animal possesses other integrating agencies, for example, "the mechanical combination of the unit cells of the body into a single mass." Also, he speaks of integration resulting from chemical agencies, as, for example, that resulting from the circulation of the blood. But extranervous phenomena were not his concern, and he said nothing further about them.

At approximately the same time that I was reading Sherrington I also had the good fortune to have as teacher of physiology Walter Bradford Cannon. At the time I was a medical student he was beginning his classic studies on the effect of the emotions on bodily processes and the development of his concept of homeostasis.[3] Unlike Sherrington, Cannon was concerned with both nervous and chemical, or endocrine, integrating mechanisms. He was less occupied with external behavior of the organism than with its methods of preserving the constancy of its internal environment, which Claude Bernard had recognized as the price of free and independent life. Therefore, he was more concerned with the vegetative, or autonomic, nervous system, which works inwardly on the viscera and governs internal environment, than with the central, which works outwardly; and of the two divisions of the autonomic nervous system he was more concerned with the sympathetic division, which discharges diffusely to the viscera, including blood vessels, than with the parasympathetic, which is focused more sharply on specific end-organs. In considering the integration of the nervous and the endocrine systems, one with the other, we shall have to take into account all divisions of the former, but in particular the sympathetic.

The endocrine system, like the nervous system, can be separated into certain divisions. On the one hand we have such organs as the adrenal medulla and the posterior pituitary (or neurohypophysis), which are clearly under direct neural control, and which even bear strong resemblances histologically to nervous tissue; while on the other we have the remaining, more obviously glandular, endocrine organs, which have not been proved to be under any direct neural control. I have been tempted to call the first category the para-endocrine system, to set it apart in our minds from all the rest of the endocrine system. The hormones of the para-endocrines — adrenalin and pituitrin — are quick acting and have widespread effects. They are secreted in response to stimuli reaching their parent cells directly over autonomic nervous pathways. The hormones of the remaining endocrines are more sharply focused on their targets. They are secreted in response to humoral, not neural, stimulation.

In the organizational pattern of the endocrine system in its present state of evolution in vertebrates, we find what I have called the para-endocrine system, occupying an intermediary position between the nervous and the endocrine systems proper. All impulses — at least so it appears — that pass from the nervous system to the endocrine — and we know beyond all possible doubt that such passages occur — must pass by way of the para-endocrines, reaching the para-endocrine glands neurally; they continue humorally (or, if you prefer, hormonally), seemingly only via the anterior lobe of the pituitary. From the anterior pituitary the organizational pattern may be described, in part at least, as a congeries of two-way hormonic pathways (or axes) radiating from the anterior lobe to one of the peripheral endocrine organs. In each case the two-way pathway is traversed on the outward journey by a tropic hormone of the anterior pituitary which stimulates the peripheral gland to make its hormone (or hormones), and on the return journey by the peripheral hormone, which in turn inhibits the pituitary with respect to that particular tropic function. This type of balanced reaction, which I shall call the axial principle, is semiautomatic, but not, as we shall see presently, completely independent unless it becomes so in disease. It may be looked upon as a functional unit of the endocrine system, analogous in some respects to the reflex arc of the nervous system. That the secretion by the pituitary of adenotropic hormones (that is, hormones whose targets are other endocrines) is controlled by the blood level of the hormones of the peripheral gland that is stimulated seems to be a fundamental law of the endocrine system. Knowledge of this law was first gained from the so-called castration phenomenon, that is to say, hypertrophy of the pituitary and increased secretion of the hormone tropic to the gonads that have been removed or destroyed. The phenomenon is well exemplified by the physiologic castration of the menopause, causing a great increase in secretion by the pituitary of gonadotropic hormone.

The axial principle is known to apply to the pituitary in its relation to the gonads, the thyroid, and the adrenal cortices. So far as I have discovered, there is no convincing evidence that the pituitary exercises any tropic action over the parathyroids or pancreatic islands. It also should be noted that the anterior pituitary makes certain hormones which act directly on nonendocrine end-organs, as, for example, prolactin and the growth hormone.

The ascendancy which the anterior pituitary has gained over the endocrine system may be likened to that of the cerebral cortex over the nervous system. As the cerebral cortex signals various parts of the soma over pathways of varying numbers of neurones, so does the pituitary at times send a hormone to impinge directly on an effector target — a melanophore, for example, or a mammary gland — while at others, the ultimate somatic target is reached via an intermediary endocrine, as pituitary to gonad to uterus, or pituitary to thyroid to muscle. In other words, the endocrines and their hormones may be coupled up as are neurones.

Whether there are important direct humoral balance relations between peripheral endocrines, one with another, not routed through or mediated by the anterior pituitary, I think is not known. Presumably there are what we may call nonspecific effects, as when an increasing output of thyroid hormone directly causes an increase in metabolic activity of other endocrines, along with the other cells of the body. For example, we have seen certain patients with far advanced athyreotic myxedema and evidences of reduced pituitary function in whom these evidences have vanished with restoration of the normal thyroid state. Premenopausal patients with severe myxedema often show oligomenorrhea and amenorrhea, and studies of the nature of these disorders have disclosed that the endometrium, via the ovary, may be under the influence of a diminshed pituitary secretion of follicle-stimulating hormone, and that there may be no evidence of any leutinizing hormone whatsoever. The normal functional gonadal hormonal balance is restored when thyroid is given to the patient. Some of our myxedematous patients have also shown some evidences of hypoadrenocorticism, and these abnormalities have also vanished when thyroid has been administered. It is a common observation of the gynecologists that fertility, either of the sterile male or female, can often be restored by dessicated thyroid, although the precise way in which this comes about is not yet clear. But action of this sort would not be in the same category as the specific balanced relations between the anterior lobe and the peripheral gland. The latter may be likened to a nervous reaction originating in and requiring the presence of the higher nerve centers, the former to reflex nervous phenomena which remain intact in the spinal animal. One pertinent fact is that in the case of the thyroid, at least, it can be shown that the gland's own hormone inhibits the gland directly. I have wondered if, phylogenetically speaking, this type of control of thyroid function represents a more ancient one than that mediated through the pituitary.

For a complete understanding of the modus operandi of the endocrine system as it exists in man and his nearer relatives in the animal scale, I have long believed that more knowledge of the evolutionary process is needed. From what primitive form did it evolve? Early in the multicellular story, enzymatic or, as I called it earlier, primordial integration may have sufficed, but only for very simple organisms living in very simple environments. As the struggle for survival has driven organisms into ever tougher environments, such superstructures as nervous and endocrine systems have of necessity been evolved in order to increase efficiency to the point where such environments can successfully be mastered.

In considering the nervous system, Sherrington discusses the nerve-cell network of the jellyfish Medusa. Here is a nervous system which receives stimuli and promotes coördinated movement of the whole organism, yet is without polarity or centralization. There is neither head nor tail to such a system, yet it adequately brings about adjustment of this particular organism to its particular environment. As we ascend the animal scale, the nervous system develops a linear and segmental arrangement — a head end gains dominance, culminating in the brain of man. Similarly, may not the endocrine system have begun without the segregation of endocrine tissues into specific glands, and, when glands were first evolved, may they not have been in more or less equal partnership, one with the others, without any one member being dominant in the sense that the anterior pituitary is now dominant? As a matter of fact, when I was a medical student that is about the way the endocrine system was visualized. We spoke of the ductless glands, not of the endocrine system, and we visualized them as operating pretty much as individuals. The present concept of what I have called the axial organization was quite unknown. The pituitary-thyroid axis, for example, did not enter our thinking on thyroid problems until after 1930, and then for some years we were rather inclined to conceive it as working pretty much as a self-regulating gadget, not much influenced from higher up.

Now, however, great interest is focused on the neuro-endocrine bridge, of which the anterior pituitary seems to be the keystone — particularly, on the question as to what is the approach to this bridge from the nervous system side. As yet the evidence bearing on this question is, on the whole, rather scant. To be sure, as early as 1914 Cannon showed that stimulation of the splanchnic nerves of the sympathetic nervous system caused a discharge of adrenalin from the adrenal medulla; also it seems likely, though the evidence is less clear cut, that the neurohypophysis is stimulated to secretory activity by nervous impulses reaching it via the stalk from the hypothalamus; but when we search for evidence of a direct pathway, either neural or humoral, between the neurohypophysis and the adenohypophysis, we end up in confusion. It is true that various forms of psychic activity are followed by alteration in function of the peripheral endocrines, but by what route is far from clear. Indeed, one cannot be sure that the intimate proximity of the neurohypophysis to the adenohypophysis, or of the adrenal medulla to the adrenal cortex, has any functional significance at all. It is possible that these juxtapositions are purely adventitious. Since evidence of direct secretory innervation of endocrines, except adrenal medulla and neurohypophysis, is unconvincing, we may postulate that for stimulation of the other glands a neurohumoral pathway is requisite. In the case of one of them — the adrenal cortex — the pathway, thanks largely to the work of Long and his collaborators, has been elucidated. With evidence now available, this pathway may be traced as follows:

Afferent impulses from the outside world and the muscular system impinge, through sense organs, upon the thalamus. Thence they are relayed to the higher levels of the brain, where they give rise to processes of cerebration, the emotional component of which activates the hypothalamus, which in turn excites the sympathetic nervous system, and with it, the adrenal medulla, with resulting discharge of adrenalin. Adrenalin, of course, has many and varied actions and a multiplicity of targets, among which, so Long's work suggests, is the adenohypophysis, which is stimulated to discharge adrenocorticotropic hormone or, as it is now universally called, ACTH. Thus one might refer to adrenalin, in this particular one of its roles, as a pituitary tropic hormone, or perhaps as adrenocorticotropic-tropic hormone. The next event in the chain of events is, of course, the stimulation of