Disorders of the Pituitary Gland

RETROSPECTIVE AND PROPHETIC

HARVEY CUSHING, M.D.
Professor of Surgery, the Harvard Medical School
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AN ALLEGORY

We find ourselves embarked on the fog-bound and poorly charted sea of endocrinology. It is easy to lose our bearings for we have, most of us, little knowledge of seafaring and only a vague idea of our destination. Our motives are varied. Some unquestionably follow the lure of discovery; some are earnest colonizers; some have the spirit of missionaries and would spread the gospel; some are attracted merely by the prospect of gain and are running full sail before the trade wind. Traders, adventurers, even pirates are certain to follow on the heels of exploration. In every profession, even ours, are to be found those who gather up beads of information of little intrinsic value which are exchanged for the property of credulous people, as gullible as the natives of a new-found land. Thus do discoveries become exploited and there were discreditable chapters in the histories of all the Great Companies of days gone by.

The impulse which launched us in such amazing numbers on our several missions some future historian may have to tell. There is nothing comparable to it, for the development of a specialty is usually a very slow process, but the endocrinologist seems to have generated spontaneously everywhere.

To our present short sight it would appear that this sudden enthusiasm to put to sea under the pennant of the ductless glands was largely influenced by the chance discovery in 1909 that certain hitherto uncharted though easily recognizable disorders are due to a state

* Presidential Address before the Association for the Study of Internal Secretions, Boston, June 6, 1921.
of pituitary insufficiency. There followed a deluge of papers, and soon after, the endocrinologist came into being, with the establishment a few years ago of this association whose official organ represents a sort of mariner's almanac of the subject.

This organization has become, indeed, a sort of geographic society, and though from time to time it may unwittingly foster the publication of supposed discoveries which may long delay progress, these are merely comparable to the errors of the geographer of old, who of pituitary insufficiency. There followed a deluge of papers, and soon after, the endocrinologist came into being, with the establishment a few years ago of this association whose official organ represents a sort of mariner's almanac of the subject.

This organization has become, indeed, a sort of geographic society, and though from time to time it may unwittingly foster the publication of supposed discoveries which may long delay progress, these are merely comparable to the errors of the geographer of old, who, as Parry, Claude Bernard, Addison, Brown-Sequard, Kocher, Marie, von Mering, Gley and others. They made the discoveries. Colonizers followed in their wake. But no one could venture to say whether the lands in this new archipelago were good for much or whether the mainland had even been attained.

The thyroid alone was within easy reach and had been thoroughly surveyed before the beginning of the

1. A plotted chart of the number of articles relating to the pituitary gland published annually during the past two decades shows that in 1907 there were thirty-four papers of which twenty-four dealt solely with acromegaly. In 1913, the year of my monograph, the curve rose so abruptly that the Index Medicus perforce rearranged its headings and for the first time assembled under one heading the publications dealing with the internal secretions. In 1913 there were 298 titles on the subject of the pituitary alone.


HYPOPITUITARISM

It is perhaps of no greater import what particular discovery led to the stampede of which I have spoken. Though my assumption that it was largely related to the pituitary body may be historically incorrect, it nevertheless will be admitted that suddenly before our eyes there was found to exist a large group of individuals whose physical peculiarities, previously regarded as within normal physiologic limits, were due to a disordered function of this obscure gland. As may be recalled, the state of our confusion had been such that, after Marie's acromegaly had been shown to be associated with tumor, many futile attempts had been made to reproduce the condition experimentally by extirpating the gland. Hence when Alfred Fröhlich under the title "Ein Fall von Tumor der Hypophysis cerebri ohne Akromegalie" published his brief paper describing an example of adiposogenital dystrophy with tumor, the observation was utterly mystifying, until it was disclosed some years later, through a series of experiments in the Hunterian Laboratory, that this condition and not acromegaly was the consequence of pituitary insufficiency.

By this demonstration not only was a new light shed on the entire group of pituitary disorders but also on the derangements of the ductless glands in general, for here was another of these structures which, like the thyroid, gave recognizable clinical signs of functional loss which could be contrasted with those assumed to be due to functional excess. Indeed, it soon became apparent that evidences of dyspituitarism, particularly on the side of lowered function, were as common, if not more common than were corresponding states due to functional deficiency of the thyroid which, in this
country at least, are relatively uncommon. What is more, in many disorders showing a polyglandular participation there is an obvious hypophysial influence at work, whereas this is far less, if at all, apparent in those maladies which seemingly originate in the thyroid. Again, the diseases of the pituitary gland immediately interested a much larger public. It included the neurologist, the ophthalmologist, the rhinologist, the obstetrician, the urologist, the dentist, the pediatrician, the psychiatrist, and many others beside the general surgeon and the physician to whom alone the diseases of the thyroid were a matter of special concern.

**THERAPEUTIC EXPLOITATION**

These are but a few of the influences which have led us in such numbers to embark glandward ho! and a good many of us, I fear, have completely lost our bearings in the therapeutic haze eagerly fostered by the many pharmaceutical establishments. For this, however, a credulous profession is largely responsible. An enthusiastic writer says, "We are now in the epoch of pragmatic endocrinology and should make the most of the splendid opportunity." Children are either too short or too tall, too fat or too lean. Their adolescence is too early or too late; they have too little or too much hair. They are intellectually backward or stupid, even defective or epileptic. The sella turcica is too small or too large and its bedposts are of the wrong shape or may even coalesce. The pineal gland casts a shadow and must be causing trouble. The basal metabolism, laboriously calculated, is found to be a little low or a little high. All this needs attention and can be corrected by some whole-gland extract, usually with a pinch of thyroid thrown in.

Pituitary extract is advocated in parturition, shock, baldness, impotence, epilepsy, scleroderma, amenorrhea, dementia praecox and a multitude of other conditions, which hitherto have baffled us, and if it does not suffice by itself you are earnestly recommended, according to the directions in the enclosed folder, to try this or that combination of hormones which contain the active principle of several glands: "In hypertensive conditions use hormotone without post-pituitary," we are advised. Never before has there arisen such an opportunity for polypharmaceutical charlatanism. The subject has fired the imagination of the stay-at-homes as did the Mississippi Company and the South Sea Bubble, and there is likely to be the same final crash and then ridicule when common sense begins to breed a proper skepticism. Here are a few samples taken at random from the hundreds of paragraphs that might be quoted from standard medical journals.

"Speaking in relative terms and in view of its relation to the posterior pituitary it is a male gland just as relatively speaking the thyroid is a female sex gland."

"It is the normal action of the anterior pituitary which is concerned with that cerebral trophic stimulation and with that maturity of mind and with that judgment which in most men act as restraining factors to the coarser instincts."

"As a corollary to the clinical use of pineal gland in accelerating the chemical movement of the brain in the backward child, it has appeared to me justifiable to try it in premature decay of the mental powers in old people. I have found that while it will not make over-hardened arteries of a dilated heart, it will quicken the slowed-down mental processes of old age, improve the memory, and produce a remarkable cheerfulness and sense of well-being. Some of my elderly patients have taken it for years, and decline to be without it."

"We note that we can identify gonadal difficulties by the position, shape, or absence of the lateral incisors; we can detect pituitary compensation in the male and adrenal compensation in the female as a result of these gonadal disturbances."

"The pituitary, we have found, controls all functions based on periodicity-menstruation, the rhythm of poetry and music, punctuality, neatness, order, all of these have their origin in the pituitary. We find clinical corroboration of this in diseased conditions of the gland, when a sudden fondness and aptitude for music make their appearance simultaneously with a new growth which activates certain secretions of the pituitary."

"In diagnosis it is no longer a question of bimanual examination, of listening to the lungs, to the heart, testing the blood-pressure, examining the urine, examining the blood, etc. It is a matter of observation and also of tests to determine what the endocrines have been doing to a patient before she comes to us, and then it is for us to determine what the endocrines are doing at the time the patient consults us; and if the patient suffers from too little of a secretion necessary to her well-being, what is easier than to administer it?"

Certainly nothing is easier, but what buncombe this is for a profession like ours. I know of nothing similar unless it was the furore over phrenology. There was much of value in Gull's early doctrines, but when specu-
lation regarding the cerebral "faculties" and their relation to bumps on the skull was allowed to run away with the subject, it came to be treated with derision and soon passed into oblivion. After the death of Gull thirty-three years elapsed before the rebirth of the topic with Broca's attempt to localize the faculty of speech. Exploitation makes enormously more difficult the task of the serious-minded colonists who realize that the clearing of the land will be a slow and wearisome process before marketable profits can be taken from the soil.

SLOW PROGRESS OF KNOWLEDGE

Past experience with the thyroid should be a sufficient lesson, and this was perhaps the simplest problem. Yet how slow has been our progress! Largely by making it subversive to surgical procedures its clinical phenomena have been laboriously disentangled from those of the adjacent parathyroids; its manifestations of inactivity in childhood and adult life have become understood and it has been found that the administration of its extracts will largely counteract the loss of secretion produced by operative removal or disease. Its varied expressions of overactivity have begun to be disentangled and we have found a fairly accurate means of mathematically recording their degree. By slow steps the relation of the gland to iodin has been discovered, and finally its active principle in crystalline form has actually been isolated. The thyroid colony has, in other words, been longest established, and though it has been a far cry from Schiff's experimental thyroidectomy in 1856 to Kendall's synthetic production, in 1914, of thyroxin, yet how little do we really know of the background of thyroid disorders, of their relation to the emotions and the sympathetic nervous system, and their pluriglandular interplay.

With the pituitary gland we are still far behind all this, nor can we profit very greatly by past experiences with the thyroid except that we must avoid certain traps and pitfalls of observation which have been located by our predecessors. We must exercise patience and expect even slower progress, for we are dealing with a far more complicated structure and one whose problems evidently cannot be solved without consideration of their relationship to other glands. Of its great importance to the economy, particularly in its influence upon growth and reproduction, and hence, to quote Arthur Keith, upon the evolutionary processes affecting many of man's racial characteristics, there can be little doubt; but these speculative theories are not for the practicing physician. He must await the tedious accumulation of facts which the experimental laboratory and clinic alone can supply.

The process is somewhat as follows: We first come to recognize an unusual clinical syndrome. This in time is ascribed to the disorder of a particular gland, usually because it is the seat of tumor or enlargement. These tumors exert pressure on neighboring structures and for mechanical reasons have to be removed. Extirpation of the gland whether conducted in laboratory or operating room, reproduces for us in some degree the clinical picture resulting from glandular want. Consequently to secretory excess we venture to ascribe the reverse clinical picture. We in time come to differentiate various modifications of both of these types and endeavor to treat them therapeutically. For states due to oversecretion our only recourse at present is surgery or some form of radiation. The attempt is made to atone for secretory deficiency, on the other hand, by one or another method of glandular administration, awaiting the time when this can be done with greater accuracy after the discovery and synthetization of the active principle.

Still, important as this discovery will be, it will by no means be the last step, for we have had epinephrin for twenty years and yet have made less progress with the disorders of the suprarenal than we have with those of the thyroid in complete ignorance of thyroxin. We will only be approaching the end—as near as one ever is to the end in medicine—when chemical substances come to be known, possibly the active principles of other glands, whose administration will counteract states of functional overactivity. But this time is very remote, and so long as there is tumor formation, giving neighborhood disturbances apart from those attributable to the disorders of internal secretion, so long will the surgeon be needed, and in the interval he should feel it his duty, so far as possible, to blaze a trail which can be easily picked up by those better trained who follow and who in turn will lay the road for all comers.
SIGNIFICANCE OF THE TUMOR

Were it not for the tumor, indeed, clearly indicating the seat of trouble, how little would we now know of the thyroid, for it is only of late years with some knowledge of basal metabolism that we have ventured in its absence to speak, at least with any assurance, of hyperthyroidism. Certainly without the combination of tumor and modern principles of surgery we might still be groping in the wilderness over thyroid insufficiency. But certain goiters pressed on the windpipe and demanded removal. Kocher and Reverdin found the way to do so and the cause of myxedema was disclosed, and then of cretinism and finally of tetany. In the bare statement, this seems simple enough today, but even the technical difficulties of these early thyroidectomies were such that only the boldest operators, whose exciting adventures Professor Halsted has so vividly described, dared to undertake them. Still, formidable as these surgical difficulties appeared to be, they were as nothing when compared with the subsequent intellectual tasks that were necessary for an interpretation of the results.

In the case of pituitary disorders we are not far beyond the stage of tumor. One may recognize outspoken acromegaly without a roentgenogram of the sella, just as one may exophthalmic goiter without seeing the neck. But in the absence of neighboring pressure signs, to say that a child who is undersized, or fat, or whose dentition or adolescence is delayed, or that an adult who has the texture and color of skin, the adiposity, impotence, subnormal temperature, and so on, known to characterize certain individuals with hypophysial adenomas, is really a subject of pituitary want, is purely a matter of guesswork. If this admission must be made regarding these fairly characteristic pituitary syndromes, what is there to say of a pluriglandular complex except to acknowledge an abysmal ignorance?

PITUITARY OPERATIONS

Hence it is that with the therapeutics of hypophysial disorders we are still mired in the crude path-breaking stage of surgery, and progress is necessarily slow.

Indeed, it is only within a few years that such a thing has ever been deemed possible. Yet this need be no occasion for wonderment since only of late with the development of roentgenology and the more extended use of the ophthalmoscope and perimeter can a diagnosis of pituitary disease apart from acromegaly be made with any probability. Unlike the thyroid enlargements, an hypophysial or parahypophysial growth can be determined only by indirect methods, for next to the brain stem itself, the hypophysis lies in possibly the best protected and most inaccessible place in the body—one reason for assuming that it may be a most important member of the endocrine series.

Surgeons have assailed it from below through the nasal cavities, and from above through the skull by elevating the frontal lobe either from in front or the side. It is certain that no one method is applicable for all conditions of pituitary tumor and that for some no satisfactory procedure has been devised. Speaking for myself, I find that I am conducting proportionately fewer rather than more transphenoidal operations, though in favorable cases with a large ballooned sella I believe the latter to be the simplest and easiest method, the one most free from risk and most certain to lead to a rapid restoration of vision. However, in increasing numbers, both in children and adults, suprasellar tumors giving secondary hypophysial symptoms are being recognized, and if the sella is not enlarged an approach from above is necessitated.4

The first thing we must learn to do, therefore, is to recognize and classify the types of pituitary disease which are unmistakable owing to the presence of tumor.

4. At the present time there have been in the writer's series 255 examples of what was regarded as primary pituitary disease. In over 200 of these cases there was unmistakable evidence of tumor, the nature of which has been verified by operation in 190 cases.

Of these 190 patients, 155 were operated on by the transphenoidal route, ten of them on more than one occasion, with a case mortality of 9.7 per cent. Forty of them have been operated upon by the osteoplastic transfrontal route, usually for suprasellar tumors, with a case mortality of 7.5 per cent. In four patients both methods have been used, two of them cases in which a transphenoidal operation was ineffective in restoring vision; of two of these cases in which a transfrontal operation revealed an unperforated glandular capsule and hence an operation from below was preferred.

Only a few of the 190 surgical cases were acromegales. The others showed many and varied forms of hypopituitarism. A great number of these patients have been, induced subsequently to follow out prolonged courses of glandular treatment. I cannot say that I have ever seen any definitely beneficial results of so doing except when there has been some concurrent thyroid want indicating the coincidental use of thyroid extract.

Even this has many difficulties, as is evident from the number of patients referred to the clinic as examples of pituitary disease because the roentgen ray supposedly shows a partially destroyed and distended sella. Though it is well known that the pressure of tumors elsewhere in the cranial chamber may produce secondary hypophysial manifestations, it has not been sufficiently emphasized that these conditions are apt to produce a more or less marked degree of sellar distortion with thinning or actual absorption of the posterior clinoid processes. A still more common pitfall lies in the misinterpretation of plates showing what is supposed to be an abnormally small fossa, and if this finding is regarded as an indication of pituitary insufficiency, a prolonged course of futile glandular therapy is usually instituted. But even in the presence of unmistakable tumor we are as yet little more advanced with our problem than were those, who, in the eighties and early nineties began to operate upon goiter merely for the relief of pressure symptoms. It will be long, I fear, before hyperpituitarism will come to be attacked by operative measures as hyperthyroidism has been, and ere then it is not impossible that some form of therapeutic radiation may prove so effective as to take the matter entirely out of the surgeon’s hands.

**Diabetes Insipidus**

That we are not far on our way is evidenced by the present discussion concerning diabetes insipidus. We were long misled by the early experiments which appeared to indicate that posterior lobe extracts were diuretic in their action—an error due to the brevity of the usual physiologic experiment. Until Motzfeldt’s studies which showed that these extracts were really anti-diuretic in action it was difficult to understand why diabetes insipidus was so often an accompaniment of pituitary insufficiency rather than of its counter state. This observation gave us for the first time a rational basis for the treatment of the disorder, but unhappily posterior lobe extracts appear to be ineffective when given by mouth, as so many glandular extracts are, and there are limits to daily hypodermic injections of a substance such as pituitary extract. Again, no sooner do we appear to have a clear understanding of the cause of diabetes insipidus than we are confronted by the old contention that it is not hypophysial in origin after all, but is due to a lesion of the tuber cinereum, and the view has even been advanced that the somnolence and adiposity assumed to be hypophysial are also of like origin.

In short, does a suprasellar tumor so affect the hypophysis as to cause adiposity, tardiness of adolescence, diabetes insipidus and the like, or are these symptoms attributable to an adjacent cerebral lesion? We may of course have suprasellar tumors which produce none of these effects; but when they occur, what is the explanation? Roussy and Camus, Houssay and others have revived this subject in favor of the nuclear origin, and Percival Bailey and F. Bremer by very exact surgical methods have succeeded repeatedly during the past year in making under direct vision a minute lesion in the tuber cinereum of the dog which results in the permanent establishment of a polyuria of high degree. This is a brilliant achievement; but, nevertheless, since they have found that injections of pituitary extract will temporarily abolish the experimental polyuria of their animals just as it does the diabetes insipidus of man, we are left in some doubt as to whether the function of the hypophysis may not after all be affected even by this procedure.

Of these matters all that can be safely said at present is that many pituitary disorders, like those of the thyroid, probably have some neurogenic background of which we know little. It was with this in mind that some years ago the attempt was made with Weed and Jacobson to trace the pathway of fibers influencing the gland from the fourth ventricle by way of the cer...

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5. Under these circumstances the ophthalmoscope will usually make the diagnosis, but this is not invariable, for a choked disk rather than primary atrophy may occasionally accompany an intrasellar tumor. We have recently had three striking examples of this. But with the combination of ophthalmoscope, perimeter and roentgen ray there should rarely be room for differential doubt.

vical sympathetics.\(^7\) When there was available glycogen stimulation of this pathway provoked glycosuria even though impulses could not reach other ductless glands, and we were led to believe that through a chemical messenger the pituitary had a definite influence upon the utilization of glycogen.

**METABOLISM STUDIES**

These particular experiments were the outcome of studies made largely by Conrad Jacobson and incorporated in my monograph of twelve years ago, regarding the sugar tolerance of our experimental animals and of pituitary patients. It was observed that in states of insufficiency there was often an enormous increase in the animal's or patient's sugar-holding capacity, and we hoped that the estimation of sugar tolerance might prove to be as reliable a measure of the individual's degree of hypopituitarism as it is of hypothyroidism—in short, a measure of his food combustion. The method in the end proved far too cumbersome and inaccurate for clinical purposes:

7. Efforts to reproduce experimentally the clinical states assumed to be due to glandular overactivity, like hyperthyroidism or acromegaly, have so far been unavailing. When some method of accomplishing this is finally discovered it will act as a star shell in the night, to illuminate the entanglements among which we are groping. It was a brilliant conception of Cannon's that one might stimulate a gland by shunting into its governing nerve supply the rhythmic impulses which pass along the phrenic to the diaphragm. He endeavored to overstimulate the thyroid in this way by anastomosing the phrenic and cervical sympathetic of the cat and in some cases a state resulted which bore a certain resemblance to hyperthyroidism. These experiments, however, were repeated the following year by Gilbert Horrax with the difference that in the animals of his series a preliminary excision was made of the thyroid on the side of the anastomosis. In a few animals the same phenomena was observed that Cannon had described. Some other interpretation than his, therefore, must be forthcoming. One might argue that the impulses must have primarily affected the hypophysis and secondarily, if at all, the thyroid. This most ingenious method deserves further employment.

Of late Cannon has been engaged in perfecting a method of registering the functional activity of a gland by electrical measurement, a difference of electrical potential being regarded as an evidence of secretory activity. All such experiments directed toward the underlying neurogenic influences of glandular action, if capable of development, promise the greatest reward.

Without any basis of experimental control clinicians have from time to time evolved speculative hypotheses regarding the relation of the nervous system to the endocrine series. Findeis was among the first to discuss the matter; but, as he once told me, it is difficult to tell whether the sympathetic nervous system is the performer that plays on the ductless glands, particularly the suprarenal, thyroid and pancreas, or whether, on the contrary, the secretion of the ductless glands twangs the strings of the nervous system and sometimes makes agreeable sounds, sometimes discordos.

The views of the Vienna school as expressed by Eppinger, Falta and Rudinger are well known, but whether we will get very far with the analysis of sympathicotonic versus vegetative states without a better understanding of normal function is somewhat doubtful and the subject has become almost too complicated for ordinary understanding.

We at the same time were led, rightly or wrongly, to see resemblances in our experimental animals to certain hibernating states, and knowing that the basal metabolism in hibernation had been shown to be exceedingly low, one of my co-workers, John Homans, subsequently made some metabolism studies in Dr. Benedict's laboratory on hypophysectomized animals, with results sufficiently encouraging to make us pursue the subject into the clinic. With this in view, W. M. Boothby installed in the Brigham Hospital the first laboratory, to my knowledge, for the methodical study of the metabolism of ductless gland disorders. He soon observed that deviations in the normal respiratory exchange were more extreme in thyroid than in pituitary disorders, but nevertheless it has continued to be a hospital routine since 1912 to determine whenever possible the basal metabolism of our hypophysial as well as of our thyroid cases. Before Dr. Boothby's departure, ninety patients with unquestionable pituitary disease were studied, and since then estimations have been made on almost as many others by Miss Tompkins and Dr. Sturgis. The results have never been published, but in brief it may be said that in the early stages of acromegaly there is a definite increase in metabolism though it rarely exceeds +28, whereas in the reverse states, those showing a slow pulse, subnormal temperature, lethargy, adiposity, and so on, the rate, as would be anticipated, averages at least 20 points below normal.

The observations are of greater physiologic interest than of practical application, and there is no reason why every one should feel that a metabolism estimation is needed for every patient showing a pituitary dystrophy. One can make a diagnosis of valvular disease of the heart without the employment of the electrocardiogram, and, after all, these elaborate instruments of precision are more suitable for the research laboratory than for the clinic. One finds advertised that a metabolimeter has been perfected which requires no calculation, the accuracy of which is guaranteed and which does its work in five minutes. The difficulty is to know what we are to do with the information when we get it, and I have heard Dr. Benedict say that any fool can make a basal analysis but few can interpret it.

In this connection, too, it should be recalled that even in normal individuals the estimation of the respira-
tory exchange is a matter of considerable difficulty and uncertainty. It is very easy to say that when the metabolism is low give thyroid extract, and when high give a counter extract, possibly some lutein. This is a good deal like the hypertension bugaboo, the outcome of the blood pressure apparatus which encourages the attempt to lower tension if it is too high or to raise it if it is too low. We ought to be beyond this variety of pure symptomatic treatment, for hypertension is not a disease any more than is tachycardia or bradycardia, discussions of which flooded the literature after the introduction of the pulse watch. When our clinical tests get too far in advance of our powers of interpretation, theory is apt to elope with practice.

INSTRUMENTS OF PRECISION

The profession perennially aspires to make diagnosis and therapy less of an art and more of an exact science. The introduction of instruments of precision unquestionably has enabled us to substitute some degree of numerical exactitude in place of the more or less rough methods of estimating and recording certain clinical phenomena, but our tendency is to become so dependent upon these accessories to bedside clinical observation that we are prone to lose sight of the patient as a whole while investigating in detail a single symptom of his disease. If overdone it has a particularly bad effect on our students, who, relying too little on their special sense organs and too much on the laboratory, come to feel that there is little use in ever trying to arrive at a diagnosis without these aids which are but subsidiary ones.

The introduction of instruments of precision is by no means a new idea. Galileo and Kepler had it, for in the sixteenth century they played with the thermometer and pulse counting, while Sanctorius undertook primitive metabolism experiments. Unquestionably many of our seemingly elaborate instruments of the present day may in time become simplified and put to routine use, for it is to be remembered that three centuries elapsed before the profession, after coquetting with the clinical thermometer, passionately adopted it after Wunderlich's classical studies in 1868 on animal heat in disease. I am far from wishing to belittle, therefore, the utilization of instruments permitting exactitude of measurement, but merely wish to distinguish between instruments which in their present form are useful for research, like the caloriometer and electrocardiogram, and those really necessary for a diagnosis.

UNSOLVED PROBLEMS

But I am permitting myself to digress too far from the main topic of this address—the pituitary body and its derangements, in furthering our knowledge of which every possible agency must be brought to bear and all must take a part—the experimental zoologist, the comparative anatomist, the biochemist, the histologist, and many others besides the clinician. From whatever side the problem is approached the rewards are likely to be great. Studies such as those of Phillip E. Smith on the pigmented and growth alterations in tadpoles deprived of the epithelial rudiment of the hypophysis are an example. The physiologist will perfect new methods to replace the simple observation on the kymography of the blood pressure raising quality or otherwise of ductless gland extracts. The pathologist has by no means as yet done his share. The pituitary gland in disease has been insufficiently studied by histologic methods, and we have as yet nothing in any way comparable to Halsted's compensatory thyroid hypertrophy, which for so many years has been the basis of our interpretation of hyperthyroidism. There has been as yet no serious attempt toward a histologic classification of the pituitary adenomas, and this is hardly possible until we have learned more regarding the stages of activity of the normal anterior lobe cells; for there is still doubt as to whether the basophilic and acidophilic cells differ in function or represent different stages of activity of the same cell. Neither can we as yet by staining methods clearly differentiate the secretory granules and mitochondria.

GLANDULAR THERAPY

The physician or surgeon, meanwhile, even if incapable of participating in these underlying studies, must do the best he can with the mere recognition and classification of clinical types, and should he venture to try glandular therapy he must be slow to draw conclusions from the apparent effect of glandular extracts given by mouth, particularly when more than one is given at a
time. It has been claimed that the body picks out the substance it needs and will discard the others, but this has the familiar sound of the gunshot doses of earlier days. The experience with pituitary extract in diabetes insipidus shows that the substance only acts when given hypodermically, and we have very little evidence that other glandular extracts have any action when given by mouth.

It has been the experience of all time that the less one knows of a disease the more enthusiastically are certain therapeutic agents advocated for its cure, and I know of nothing comparable to the present furor regarding the administration of glandular extracts unless it be the plant pharmacology of the middle ages, based on the "doctrine of signatures." A patient is bilious—therefore he has some disease of the liver. The leaves of a certain plant resemble in their color and appearance the surface of the liver—therefore a concoction of these leaves is good for biliousness, and the plant comes to be called hepatica. But then, lest it may not really do this, we will add several other things to the concoction as well. This is about the basis on which glandular extracts are administered today. And it will be noted that most of them contain a certain amount of thyroid extract, which possibly is the only one of these substances having any definite action when given by mouth.

And so, if I may return again to my underlying allegory, if this society wishes to play a useful role in furthering advances in endocrinology, it must, so far as possible, through the pages of its journal, keep such an exact almanac that those pursuing the subject in the proper spirit may be able to avoid unfavorable winds, currents and counter currents. It must discountenance the exploitation of the few discoveries which have already been made by those who recklessly under full sail plow through a fog bank of therapeutics, their horns tooting.

Surely nothing will discredit the subject in which we have a common interest so effectively as pseudoscientific reports which find their way from the medical press into advertising leaflets, where cleverly intermixed with abstracts from researches of actual value the administration of pluriglandular compounds is promiscuously advocated for a multitude of symptoms, real and fictitious. The Lewis Carroll of today would have Alice nibble from a pituitary mushroom in her left hand and a lutein one in her right and presto! she is any height desired.

Endocrinology as a special subject, if it wishes to survive and come to be a factor in medical practice, must look out for the character of its clinical advance agents lest it come to be utterly discredited. We have nothing as yet, in the treatment of pituitary insufficiency, comparable to what Victor Horsley and his pupil Murray accomplished for myxedema, and we are still further behind in the case of the other glands. Indeed, no Magellan or Balboa for ductless gland therapeutics in general has yet appeared, though let us hope he may be on the way. Meanwhile there is many an imitator of Cortez or Pizarro to trade on the superstitious awe of the natives, who will soon come to be fully disillusioned.