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Address

THE HYPOPHYSIS CEREBRI

CLINICAL ASPECTS OF HYPERPITUITARISM AND OF HYPOPITUITARISM*

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Few chapters in the history of medicine tell a more creditable story than that which relates our progress toward a better understanding of the thyroid and parathyroid glands. A combination of clinical, experimental and surgical experiences during the past twenty years has served to unveil many of the mysteries which formerly surrounded the function of these structures, whose normal activities prove to be so essential to the maintenance of physiologic equilibrium. Myxedema, cretinisn, exophthalmic goiter, surgical myxedema (cachexia strumipriva) and tetany have come to be understandable maladies, definitely amenable to rational methods of treatment—and organotherapy, when glandular activity is subnormal, or partial surgical removal to correct functional over-activity, is a triumph of the experimental method in medicine, at the hands of Horsley, Kocher, Halsted, Gley, Vassale and Generale, MacCallum and a host of others.

Not the least memorable incident of the entire story was the recognition, first by the Italian investigators, of the important rôle played by the lesser glands—the parathyroid bodies—in occasioning the so-called acute cachexia thyreopriva with tetanoid symptoms; for without this knowledge the condition of myxedema must have remained obscure from inability to produce its experimental counterpart, and actual investigation of the parathyroids might have been long delayed.

No less satisfactory a tale is in the making as regards a hitherto even more obscure member of the family of ductless glands—the pituitary body—and it is my purpose on this occasion to recount briefly some of the steps already taken toward a better knowledge of the normal function and the part played in certain diseases by this peculiar and inaccessible structure—called "l'organe enigmatique" by Van Gehuchten. Our progress, such as it is, would have been much slower without the previous experiences with the cervical glands, for out of the confusion which long reigned in their case from lack of appreciation of the double glandular rôle a lesson has been learned and applied to the pituitary body, for it likewise combines glandular structures of widely differing function.

Not only in view of the general awakening of interest in the subject, but owing to the fact that most of the recent work on the hypophysis has appeared in foreign languages, it has seemed to me that a simple review of our knowledge of the anatomy and physiology of the gland and some discussion necessarily of a more speculative character as to the part it plays in certain diseases would make an appropriate topic for this annual oration.

THE GLANDULAR STRUCTURE

Regarded by the ancients as an organ which discharged *pituita* or mucus into the nose, and by most scientists of the past century as a mere vestigial relic of prehistoric usefulness, our first insight into a possible functional activity of this gland came from the laboratories of the modern comparative anatomists and embryologists, with many of whom it has been a favorite object of research. As a knowledge of its structure, development and morphologic significance is essential to the proper understanding of matters relating to its function, it may not be out of place to briefly recall here some few of the more important facts:

Rathke, in 1838, described an invagination of mucous membrane, supposedly arising from the anterior end of the foregut—since known as Rathke's pouch—and correctly attributed to this origin the epithelial portion of the pituitary body, which before this time was thought to be wholly derived from the brain. It remained for Götte and Balfour and Mihalkovics, in 1874 and 1875, to show that the invagination described by Rathke was derived from the embryonic buccal cavity rather than from the primitive gut, and hence was of ectodermic rather than of entodermic origin.

This ectodermic and epithelial pouch of Rathke, therefore, projecting from the buccal cavity and pressing against the floor of the anterior cerebral vesicle, leads to a downward fold in its wall, which becomes the early infundibulum. The stalk of the epithelial pouch becomes cut off, leaving a closed sac—the hypophyseal sac—which embraces the thickening wall or infundibular body at the tip of the vesicular fold, and the combined epithelial and nervous structure represents the anlage of the adult hypophysis. As the primitive gland develops further the epithelium of the anterior or lower part of the closed sac representing the remains of Rathke's pouch becomes thickened, forming the anterior lobe of the pituitary body. A more or less definite cleft separates this portion of the gland from the so-called posterior lobe, composed of the upper portion of the primitive closed epithelial sac together with the infundibular body to which it has become intimately adherent and with which it remains functionally associated. It is the persistence of this cleft in the mammalian hypophysis which usually permits of an easy, gross anatomic or surgical separation of the two lobes.

Thus the neural portion of the gland (the infundibular body) becomes surrounded by an intimate epithelial investment pos-

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* From an etymological point of view the terms *hyper-*, *hypo-*, *dys-*, and *a-pituitarism* are doubtless of badly mixed parentage, but there are certain obvious objections to such a combination as *hypohypophysism*, and I have therefore concluded to retain the Latin word with its Greek prefix. *Hyperpituitism*, etc., might possibly be less unwieldy.

sessing a different histologic picture in the adult gland from that which characterizes the anterior lobe, though the two are of the same ectodermic origin. In accordance with the terminology proposed by Herring, this epithelial investment of the posterior lobe, together with its upward extension onto the outer walls of the infundibular stalk will be referred to as the *pars intermedia;* the infundibular body itself, as the *pars nervosa*, and the anterior, epithelial portion separated, from these by the persisting cleft, as the *pars anterior.*

The posterior lobe as a whole is scantily vascularized through a single stalk of vessels which enter this part of the gland at its posterior surface; the anterior lobe, on the other hand, is excessively vascular, the vessels of its outer or cortical portion in particular being sinusoidal in character. Apparently, the blood supply to this portion of the gland, from observations made by Dr. G. J. Heuer, comes, at least in the dog, through the infundibular stalk; and at all events separation of this stalk may seriously jeopardize or, according to Paulesco, effectually check the functional activity of the gland. To this I shall return when discussing the operative procedures.

Histologically, the anterior lobe is seen to be made up of cells with a peculiar staining reaction, the protoplasm of some of them being receptive to eosin, some to hematoxylin, and some barely staining at all. These are thought to represent merely periods of activity in the same type of cells—the eosinophilic cells being generally regarded as representing the functionally mature stage. These active cells seem to distribute themselves in the neighborhood of the thin-walled venous sinuses, into which they doubtless discharge their secretion. Some, indeed, have claimed that the product of cellular activity can be demonstrated under favorable conditions within the lumen of the vessels.

In the pars intermedia, investing the posterior lobe, the cells are of a different type, without eosinophilic granules, and it is here chiefly that one finds a tubular or acinous distribution of cells which have a tendency to secrete colloid resembling in appearance the secretion characteristic of the thyroid gland. These cells also seem, under certain circumstances, actually to invade the pars nervosa, into which the product of their secretion is directly discharged, whence, as Herring first pointed out, it seems to pass through tissue channels toward the infundibular cavity, to find its way ultimately between the ependymal cells into the cerebrospinal cavity of the third ventricle.

We have come fully to accept this view of Herring's, and under certain experimental conditions we have seen the masses of hyaline secretion which stream through the pars nervosa toward the cerebrospinal space enormously increased in amount. In certain animals, as the dog and monkey, the cells of the pars intermedia extend well up over the stalk of the hypophysis and around the infundibulum, and hence in removal of the whole gland it is almost inevitable that some functionally active fraction of the pars intermedia remains attached.

The pars nervosa itself contains no true nerve cells, being made up of ependymal and neuroglial tissue which is so loosely laid down that the spaces which apparently serve as the channels through which this hyaline-like secretion passes toward the third ventricle can be easily detected. Whether the pars nervosa actually has a secretion of its own, whether it serves to modify or merely to transmit the secretion from the pars intermedia, are questions which must await solution.

Anatomical studies, therefore, show us that the pituitary body, present in all vertebrates, is a composite gland with a double source of origin. It is made up (1) of a smaller posterior lobe with a nucleus of neural origin (pars nervosa), which, developing from the infundibular pouch of the thalamencephalon, becomes invested by and intimately fused with a portion of the epithelial sac (pars intermedia) that has arisen from a diverticulum of the buccal epithelium; and (2) of a larger, purely epithelial lobe (pars anterior) arising from the same source as the pars intermedia, from which it remains, however, more or less separated by a cleft—a vestige of the cavity of the original epithelial invagination from the primitive mouth.

THE GLANDULAR FUNCTION

There are a number of ways in which we may approach matters relating to the function of a gland: by laboratory methods of comparative physiology, by the experimental production of pathologic conditions, and by observing the symptomatology of clinical cases and correlating them either with postmortem findings or with the conditions disclosed or brought about by surgical procedures.

Physiologists are accustomed to attack these problems in two ways, by observing, on the one hand, the symptoms brought about by hypersecretion, and, on the other, those consequent on a lessened or hyposecretion, The first—the consequences of over-secretion—must, unfortunately, rest largely with observations on the effects of ingestion or of subcutaneous or intravenous administration of the material extracted from the glands of other animals; for until some hormone can be isolated there seems to be no way by which the pituitary body, or any other ductless gland, may be so over-activated as to give a permanent and pathologic excess of secretion. Transplantations of additional glands from other animals have signally failed in this respect.

Limited, however, as the injection methods are, they have nevertheless taught us certain important facts: first, that the hypophysis of all animals contains a blood-pressure-raising principle, confined, as Howell has proven, to the posterior lobe and restricted, as we believe, to the pars nervosa of this lobe; and second, that an extract or emulsion of this same lobe has a marked diuretic effect on the kidneys (Schäfer)—whether from direct action on the renal epithelium or from the rise in blood pressure and increased volume of the organ seems undecided. The blood-pressure-raising substance, though occasioning a more enduring rise in pressure than that produced by the more familiar extract of the adrenal glands, seems nevertheless to be akin to adrenalin, one striking resemblance being the pupillary dilatation which follows the instillation of either of these substances into the eye.

My associate, Dr. S. J. Crowe, has corroborated the findings of others that successive injections of posterior lobe extract not only soon fail to cause a rise in blood pressure, but may produce an actual fall, or indeed on several repetitions may even be fatal. It has been shown that extract of the gland when boiled still retains undiminished its evidences of physiologic activity (shown by the blood pressure reaction), so that it is possible to introduce sterile extract. Certain of Crowe's observations have given evidence that repeated daily injections are exceedingly deleterious to the well-being of the animal and lead frequently to extreme tissue alterations, particularly in the liver, a disturbance which apparently is due to posterior lobe secretion rather than of anterior.

Beyond these few properties possessed by an extract of the posterior lobe, the methods of injection have taught us little or nothing indeed regarding the function of the anterior lobe, which histologically would seem to be by far the more important part of the gland. Sandri has observed some apparent thickening of the bones and atheromatous patches in the arteries following intraperitoneal injections in young animals but we have failed as yet to produce any constant disturbances except a definite loss of weight by repeated (over weeks) injections of extracts of pars anterior alone, using the boiled extract or the emulsion of fresh and aseptically removed glands.

All this goes to indicate how far removed we are from a satisfactory organotherapy of the hypophysis, for as yet most of the available preparations contain the extract of both lobes, and so long at least as there is any confusion as to their separate activity, particularly in view of possible injury from excessive posterior lobe administration, we must restrict our studies, as well as their therapeutic application so far as possible to the individual lobes.

The reverse of these experimental observations directed toward the effects of over-activity of one or another part of the gland, concerns the effects of their diminished secretion; and here the problem might be simple were it not for the fact that Nature has placed the pituitary body in one of the best protected and most inaccessible spots in the body. It is here that modern surgical methods have been called on to play their part in furthering knowledge of these matters.

Since the earlier unsuccessful attempts to remove the hypophysis by operation, many investigators have endeavored in divers ways to find some satisfactory approach to the gland in an animal suitable for experimental observation. Frogs, cats, dogs, chickens and monkeys have been used for this purpose at various hands, with the attempt either to extirpate the gland or to destroy it *in situ*. It has been approached from below by numerous transphenoidal routes, the best of which are attended with a great risk of subsequent cerebrospinal infection; numerous intracranial methods of approach have been likewise evolved: through the vertex, with penetration of the cerebrum or separation of its hemispheres; through the forehead with elevation of the frontal lobes; and from the side by a passage under the temporal lobe.

Leaving aside for the time being the question of the preferable approach to the gland under various circumstances in man, and confining ourselves to the experimental problem, there can be no doubt but that the lateral and intracranial approach under the temporal lobe is the only method worth considering in the canine —the animal most suitable for these researches. Paulesco was the first to appreciate the possibilities offered by this operation when coupled with a certain principle of modern cerebral explorations—that of dislocation. The steps of the procedure have already been described by Dr. Lewis L. Reford and myself, and during the past year, in collaboration with Dr. S. J. Crowe and Dr. John Homans, the method has been perfected to such an extent that in our later series—and we have had all told more than one hundred total or partial hypophysectomies—it has been possible, in an hour's time, to carry through an individual operation, treating the gland in the way desired, without any complication whatsoever either from bleeding during the operation or from subsequent infection. A report *in extenso* of our experimental, clinical and pathologic observations on the gland will be forthcoming, but it will not detract from its interest to mention here a few of our results, in order to round out this general review of the entire subject.

Since the brief report of our work of a year ago[1] we have gained further and more conclusive evidence as to the correctness of the view that the pituitary body is essential to the maintenance of life, though the important fact has been brought out by Dr. Crowe that young dogs survive the total loss of the gland for a considerably longer period than do older dogs; and we have been able to prolong life for a time, though not indefinitely, by immediate or antecedent transplantation of the anterior lobe or by postoperative injection of its extract.

Since Paulesco, in 1908, published the results of his investigations, the reports of subsequent researches have appeared which are not confirmatory of his more important contention; but it is our impression, from their careful perusal, that the results are inconclusive, owing to the employment of unsatisfactory surgical methods. The assertion may safely be made that the total removal of the gland leads, in the course of days or at most of a few weeks, to death with a peculiar and characteristic train of symptoms (apituitarism or cachexia hypophyseopriva).

Does this property of maintaining the physiologic equilibrium reside in the anterior or the posterior lobe? The anatomic separation of the posterior from the anterior lobe by a persisting cleft has been mentioned, and this line of cleavage, when facility in the surgical procedure has been acquired, makes possible in the dog the operative separation of the two lobes and the removal of one of them singly—the posterior more easily than the anterior. No particularly characteristic symptoms, if we may possibly exclude some sexual disturbances, appear to follow the loss even of the entire posterior lobe (pars nervosa and its epithelial investment), though it must be confessed that some of the epithelium of the pars intermedia usually remains attached to the tip of the infundibulum after the operation.

Now, it is otherwise with the anterior lobe, for its partial removal, supposedly equivalent to a condition of hyposecretion of this part of the gland, though not incompatible with life nevertheless leads in some cases to profound alterations—notably an increase in the deposition of fat. This condition seems to have occurred in one of the animals of Paulesco's series—a chance observation to which especial attention does not seem to have been paid. We have had a number of similar experiences; and indeed believe that we have succeeded in purposefully producing this condition which we regard as characteristic of lessened secretion. The adiposity has been associated in some cases with polyuria and transient glycosuria, with shedding of hair, occasionally with unmistakable lessening of sexual activities and even with atrophy of testes and ovaries.

The problems relating to bodily growth and to organs of sex are especially difficult ones, requiring as they do months of observation; and concerning them our data is as yet very insufficient, though in all probability they are matters which are associated with the function of the anterior rather than of the posterior lobe. To correlate fully our experimental with the clinical conditions to be described, a long series of partial removals of the anterior lobe in animals of different ages and of both sexes will be required.

In all these observations, not only on the hypophysis cerebri, but on any other of the ductless glands, there is one vitally important matter that is not to be disregarded—namely, the close physiologic interrelation of all of these structures[2]. It is impossible to remove—probably partially to remove—the hypophysis without producing marked alterations in all the other glands—

1. Johns Hopkins Hosp. Bull., 1909, xx, p. 105.

2. Though the hypophyseal question was not considered by them, an article by Eppinger, Falta and Rudinger (Ueber die Wechselwirkungen der Drüsen mit innerer Sekretion. Ztschr. f. klin. Med., 1908, lxvi, 1-52) is of interest in this connection. Cf. also: Rénon, Delille and Monier-Vinard: Syndrome polyglandulaire par dyshypophyse et par insuffisance thyro-testiculaire, Bull. et mém. Soc. méd. des Hôp. de Paris, 1909, series 3, xxvi, 204-211.

thyroid, parathyroid, adrenal, testicle, ovaries, islands of Langerhans, and thymus. Changes in the hypophysis consequent on thyroidectomy or castration have long been known, and after an hypophysectomy we have found the reverse to be true—the simplest example being an acute hypertrophy of the thyroid.

This interrelation of the ductless glands makes the problem the more interesting and at the same time increasingly difficult. Does the adiposity following partial hypophysectomy hold any possible relation to the secondary lesions in the ovaries or testes, or the glycosuria to alterations in the islands of Langerhans or thyroid? Answers to these and other similar questions must await further investigation. Then, too, it must be borne in mind that the various ductless glands not only give evidence of adaptation to a pathologic process affecting one or another member of their family, but respond to an unusual physiologic process likewise, as is illustrated by the recognizable functional alterations in the thyroid and hypophysis which accompany pregnancy.

Thus, it would appear, from these various investigations on the physiology of the hypophysis that the extract of the physiologically active posterior lobe, supposedly the most important part of the gland, may be actually harmful when injected, and yet after this portion of the gland has been removed there is no apparent disturbance with the physiologic balance of the body. On the other hand, the supposedly inactive anterior lobe can not be removed in its entirety (leading to a condition of apituitarism) and life be long maintained. This portion of the gland, furthermore, seems primarily to be associated with the growth of the body, with the metabolism of fat, with sexual activities, and to be bound up in ways which as yet are symptomatically obscure with the function probably of all the other ductless glands of the body.

CLINICAL SYMPTOMATOLOGY

Let us pass from these scant observations on the anatomy and physiology of the gland to see in how far they may be applied not only to the few maladies which are under the suspicion of being primarily hypophyseal diseases, but also to other conditions which may show secondary symptoms possibly of hypophyseal origin. Among the primary diseases acromegaly and gigantism naturally deserve the first mention.

Since Pierre Marie, in 1886, gave the name acromegaly to the peculiar and unmistakable malady characterized by striking deformities due to skeletal overgrowth, and in 1889 called attention to the fact that an hypophyseal enlargement (adenoma or hyperplasia) was a frequent accompaniment of the condition, there has been an active dispute in regard to the part, if any, which the gland actually plays in the disease. Many cases of acromegaly have been recorded in which, in agreement with Marie, glandular enlargements or tumors of the pituitary body, with the characteristic deformation of the sella turcica, have been demonstrated after death.[3] On the other hand, there have been a still larger number of carefully studied cases in which a tumor of the hypophysis or of its neighborhood has been unaccompanied by these symptoms. Finally, a few cases of undoubted acromegaly have been described in which the hypophysis on postmortem examination is said to have been normal in every respect.

Now these apparently conflicting observations are possibly not difficult of explanation in the light of our somewhat more definite knowledge as to whether the underlying condition is one of glandular hypersecretion or hyposecretion—a far more important matter than the mere association, or otherwise, with a tumor. In glands affected by an adenomatous growth, as well as in those the subject of simple hyperplasia, it is a natural conjecture that there may be some excess of glandular secretion. However, in view of the many instances of hypophyseal tumor occurring without acromegaly, Massalongo's supposition that the disease represents a condition of hyperfunction—hyperpituitarism—has been widely discredited. It is believed by Benda and others that an excess of large cells in the eosinophilic stage indicates an overactive gland, but as this supposition has not been widely accepted it is easily understood how a pathologic overactivity in glands not macroscopically enlarged may have escaped recognition, so that the supposed finding of actually normal glands in association with acromegaly must be open to grave doubt.[4]

It has remained for surgical measures to cast the deciding vote in favor of the hypersecretion theory, for there have been two fairly conclusive cases. One of them was a case of Hochenegg's in which a successful effort was made to remove the gland completely, and the other an unpublished case of my own, in which, purposely, a partial hypophysectomy only of the anterior lobe was performed. In the latter case the tissues resemble histologically what we regard as a simple hypertrophy, and the patient has been not only completely relieved of the pressure symptoms, but there has been an actual measurable postoperative reduction in the size of the hands. In Hochenegg's patient there was a measurable diminution of the bony overgrowth, shown first by a narrowing of the spaces between the teeth. Even a tendency toward subsidence of the disease after a partial hypophysectomy—equivalent to the partial thyroidectomy for exophthalmic goiter—would seem to speak conclusively in favor of the hyperpituitarism theory.

That tumors of the gland or of its vicinity may be found unaccompanied by symptoms of acromegaly is precisely what would be expected. Indeed, if there is a resultant interference with the normal secretory activity of the gland one would expect the reverse condition, but this will be considered more appropriately under the heading of hyposecretion.

The relation of gigantism to acromegaly and of both of these to a possible lesion of the hypophysis has been much discussed, and the generalization of Massalongo, that acromegaly is nothing but delayed or abnormal gigantism, has been endorsed by Meige, Woods Hutchinson and Bassoe, who have made the most thorough studies of the question. Thus in Meige's formula, when hypophyseal disease—an evidence as we believe of over-

3. Marie and Marinesco (Sur l'anatomie pathologique de l'acromégalie. Arch. de méd. expér. et d'anat. path., 1891, p. 539) considered acromegaly as a dystrophy analogous to myxedema due to a diminution or an abolition of the functions of the hypophysis. Vessale and others go so far as to regard the hypophyseal hyperplasia, acknowledged to be present in a large percentage of acromegalics, not as the primary process but as one secondary to the general nutritional disorder.

4. The matter has been fully discussed in an able study by Dean Lewis (Hyperplasia of the Chromophile Cells of the Hypophysis as the Cause of Acromegaly. Johns Hopkins Hosp. Bull., 1905, xvi, p. 157) of a case of acromegaly with an hypophysis which appeared normal in its gross appearance but showed, in confirmation of Benda's view a definite hyperplasia of the chromophile cells.

activity of the anterior lobe—commences in youth, gigantism occurs; when in adult life, acromegaly; when commencing in youth and continuing into adult life, a combination of the two is seen. The important fact is that an enlargement of the pituitary body is found in a large majority of cases of both acromegaly and gigantism, and it is a natural conclusion that they are merely different expressions of one and the same morbid condition.

What now are the clinical manifestations, if any, of diminished activity of the gland? There occurs a remarkable physical state characterized by sexual infantilism and adiposity—*dystrophia adiposo-genitalis*—a syndrome to which a paper by Fröhlich[5] first attracted general attention in Vienna, where most of these cases have subsequently been observed. The condition is probably far from an infrequent one, though it has received but tardy recognition in English and American writings.

These patients, in addition to the local pressure symptoms of a growth in the hypophyseal neighborhood show small stature, infantile genitalia, hypotrichosis and an excessive deposition of fat. The title of Fröhlich's paper—and there have been many other articles similarly entitled as "cases of hypophyseal tumor without acromegaly"—indicates a widespread misconception as to the cause not only of these symptoms, but of those described by Marie as well. It is equivalent to describing the goiter which may accompany cretinism or myxedema as "cases of tumor of the thyroid without exophthalmic goiter." This confusion clears away on better knowledge of the effects of hyposecretion, for it is my opinion that in these cases the pressure from the tumor has led to a considerable lessening of the normal glandular activity. In this light, they become equivalent to the canine partial hypophysectomies after which, as I have described, an excessive deposition of fat may occur (with the accretion in some cases of over one-third the former weight within a few weeks after the operation), accompanied at times by a definite atrophy of the genitalia.

One must acknowledge that not only the anterior, but the posterior lobe also, is in all probability affected by such a pressure disturbance from a neighboring tumor, so that the whole picture perhaps can not be ascribed to diminished activity of the anterior lobe alone. It is safe to say, however, that the small stature and the adiposity can be thus accounted for, and further investigations will doubtless reveal the cause for the sexual infantilism. This, indeed, may only be indirectly due to pituitary body alteration, the lessened secretion from which has failed in some way to activate the testicular or ovarian secretions.

It is important to note that among the earliest successful operations on the hypophysis have been those performed by v. Eiselsberg on patients exhibiting the symptoms described by Fröhlich, either with the removal of solid tumors or the evacuation of cystic growths. Striking improvement in the condition, shown by a lessening of fat and rapid appearance of sexual adolescence, has followed these operations, but I am unaware that this was ascribed to reawakening of functional activity in the previously compressed hypophysis, nor that especial care was taken to avoid its removal with the tumor.

It is noteworthy that a frequent early symptom of acromegaly or of gigantism associated with tumor is amenorrhea in women and impotence in men—though this need not apply to those adult cases which show a simple hypertrophy of the anterior lobe without tumor formation—and it is quite probable that here we see an overlap in the symptoms occasioned by hypersecretion of one part of the gland and diminished secretion of another. It must be kept in mind also that in the condition of "adiposo-genital degeneration" described by Fröhlich, which in the light of our experimental observations we consider to be due to hyposecretion, the malady begins to show itself before adolescence, and it is quite probable that the clinical picture, when the disease originates later in life, has a somewhat different aspect, just as gigantism differs from acromegaly. As an analogous condition in the case of the thyroid I may mention cretinism as the result of thyroid deficiency dating from childhood, and myxedema as the result of a similar deficit occurring in adult life.

One somewhat characteristic symptom of hyposecretion of the anterior lobe, not only after partial experimental ablations, but also evident in clinical conditions is polyuria, sometimes associated with glycosuria. This symptom, in our animals, we might possibly have attributed to a temporary activation of the retained posterior lobe, the secretion of which, as Schäfer has shown, possesses diuretic properties when injected, had it not been for the fact that it occurs in animals with a partial anterior and total posterior lobe removal. In some of our dogs in which there had been an increase of fat, these urinary symptoms persisted over months.

Clinical instances of hyposecretion are doubtless far from uncommon and probably many will recall illustrative cases in their own experience. I have heretofore recorded a typical case of the infantile type associated with a congenital teratoma of the hypophyseal region, and the following may serve as an instance of the adult condition—the patient having been under Dr. Heuer's and my observation this past winter:

A single woman, aged 36, had suffered from severe bitemporal headache for seven months, during which time there was a gain of 69 pounds (from 118 to 187 pounds) in weight. Polyuria was constant and sugar had been present in the urine from time to time. The hair had become thin and scanty. Evidences of the local lesion were shown by a primary optic atrophy unassociated with a choked disc, and by a homonomous hemianopsia. Amenorrhea had been present from the onset. The *x*-ray showed no enlargement of the sella turcica, and a lateral intracranial exploration (subtemporal) was performed, in the hope of exposing the growth so as to determine how it could best be attacked. It was not possible to dislocate the tense temporal lobe sufficiently to disclose the lesion. A transphenoidal operation was refused. The patient's condition remains unaltered.

Another history of considerable interest is:

The patient, a man aged 40, exhibited characteristic symptoms of intracranial pressure, thought to be due to tumor or to the edema of arteriosclerosis. A subtemporal decompression was performed, with complete relief for a year, during which time he became very fat. Subsequently, polyuria occurred with intermittent traces of sugar in the urine; he became somnolent, with a persistent subnormal temperature and slow pulse, and finally succumbed. A primary tubercle of the hypophysis (pars anterior) was found postmortem, in addition to a marked degree of cerebral arteriosclerosis.

5. Fröhlich's paper (Ein Fall von Tumor der Hypophysis Cerebri ohne Akromegalie. Wiener klin. Rundsch., 1901, 47, u. 48), describing two of these cases, preceded by several years an article of my own (Sexual Infantilism with Optic Atrophy in Cases of Tumor Affecting the Hypophysis Cerebri. Jour. Nerv. and Ment. Dis., November, 1906) in which two further cases were described, though insufficient emphasis was laid on the peculiar adiposity which was present in each. Both of these reports were made before a safe method of operative approach to the gland has been evolved.
Compare also, Berger's paper, Ein Fall von Tumor des Hypophysengegend mit obduktionsbefund. Ztschr. für klin. Med., 1904, liv, p. 448.

Whether the adiposis dolorosa of Dercum is akin to hypophyseal adiposis is not assured, though there are many features of the condition which lend support to such a conjecture. G. E. Price, in a recent article, describes the changes in the gland, but they are possibly no more marked than in the average adult gland; and from a histologic standpoint we are still groping for the characteristic cellular picture of lessened hypophyseal activity. Gross lesions of the pituitary body (tumors, etc.) have been found in at least four of the few reported cases that have come to autopsy; and there have been certain features of their symptomatology also which suggest a close relationship.

Symptoms of hypophyseal origin doubtless occur in association with many diseases in which they are overlooked, for we have found, in the examination of over a hundred glands taken at random from autopsy material, that histologic alterations are very common. It is not always possible to interpret the effect of these lesions, particularly since, on the clinical side, we are far from being on the alert for them. Certain hypophyseal symptoms, nevertheless, even in the state of our present knowledge, are capable of interpretation. This is particularly true of the glandular lesions which occur secondary to injuries and to intracranial tumors which are provocative of hydrocephalus.

In most of the cases of brain tumor which we have examined, Dr. G. J. Heuer and I have found characteristic gross alterations of the gland, which is often cup-shaped, flattened or otherwise deformed. This is particularly true of the cases in which there has been an associated internal hydrocephalus, in which one sees evidences of the damming back of the hyaline secretion of the posterior lobe, which often accumulates as a large hyaline cyst. This is what would be expected from Herring's observation. It is not inconceivable, therefore, that many of these patients would actually show symptoms of altered hypophyseal function were our attention more definitely centered on the activities of this gland. These symptoms would be more likely to fall in the group due to hyposecretion than that of hypersecretion, and may account for the occasional marked increase in weight, the amenorrhea and somnolence not infrequently seen in company with cerebral neoplasms.

These may be considered as secondary hypophyseal symptoms in contradistinction to the primary manifestations which occur when the gland is directly implicated by a growth in its immediate neighborhood—a state of things betrayed by the well-known local symptoms.

I have here endeavored to postulate in simple form some clinical conditions which we may safely regard as evidences of hypersecretion of the anterior lobe, as shown by overgrowth, and others which may equally well be taken as evidences of hyposecretion, shown by undergrowth or infantilism accompanied by a tendency toward an excessive deposition of fat. As we have seen, it is possible to simulate the latter condition by experimental methods. A condition corresponding to the clinical state due to hypersecretion still remains to be reproduced in the laboratory.

This simple subdivision must be taken merely as the suggestion for a working basis. It may in time prove to be wrong, and it signally fails to take into consideration not only the possible lesions of the other portions of the pituitary body (pars intermedia and pars nervosa), but also of the other correlated ductless glands. This fact, however, holds equally true for the condition of the other ductless glands in the analogous diseases of the thyroid—the hyperthyroidism of Graves' disease and the hypothyroidism of myxedema. Still, it gives us a certain hold on the maladies of the pituitary body which heretofore we seem not to have possessed.

There is every reason to suppose that functional irregularities of the hypophysis are at least as common as those of the thyroid gland, though heretofore only when a local neoplasm has clearly pointed the way to the hypophyseal region have the symptoms due to these irregularities been given the attention they deserve.

THERAPY

If such a subdivision of these conditions as our experimental observations have tempted us to make shall prove to be practicable, with a grouping of clinical cases into those suffering from excessive secretion (hyperpituitarism), *versus* those with diminished secretion (hypopituitarism), can we safely draw any conclusions therefrom which will hold out some promise of their future rational treatment?

It is far from utopian to look forward to the day when organotherapy, or, better, the administration of the isolated active principle of one or another part of the gland, will accomplish, at least for conditions of hyposecretion, what thyroid extract does for cretinism or myxedema. We can even now with reasonable certainty anticipate the results of anterior lobe administration for the adiposity associated with the conditions of hypopituitarism, and it is not improbable that many of the cases of adiposity of diverse origin which have been benefited in the past by thyroid administration have been so benefited in consequence of the indirect reawakening of activity in the hypophysis (and possibly with a secondary activation of the generative organs) resultant to this treatment.

Possibly less can be expected in the near future from glandular therapy for the conditions of hyperactivity, though it is conceivable that physiologic chemists may succeed in elaborating substances which will counteract the excessive secretion of any one of the ductless glands which may be under investigation.

At present, as is the case with hyperthyroidism, the cruder measures of surgery must be resorted to—namely, the partial removal of the hypertrophied or overactive gland. This, as I have stated, has been carried out with promising results in certain cases of acromegaly—a disease supposedly representing the effects of overaction of the gland in adult life. Our experimental observations, largely confirmatory of those of Paulesco, have shown that the procedure must be limited solely to a *partial* removal of the anterior lobe with careful avoidance of *total* removal, which leads to a condition of cachexia hypophyseopriva as definitely as does a complete thyroidectomy to one of cachexia strumipriva. In view of the experimental results, one would naturally apprehend serious consequences in man, as well as in animals, if the whole anterior lobe, or indeed of its major portion, be removed, though proper glandular administration of extract of this lobe would doubtless do for such a condition what thyroid extract does for the hypothyroidism following too extensive a removal of the thyroid.

Glandular therapy, as I have said, would be the natural therapeutic resource in the conditions which we have described as due in all probability to a diminished hypophyseal activity; but as yet no clinical cases of this sort have been recorded as consequent on a simple primary incompetence from atrophy of the gland, though such a condition doubtless occurs. As a matter of fact,

they have only been described as an accompaniment of tumors in its neighborhood with secondary implication of the hypophysis through compression. Hence in many of these conditions of hypopituitarism, as well as in those of hyperpituitarism, there are definite indications for surgical intervention, and fortunately in many of the cases, especially those with delayed adolescence of the Fröhlich type, the damaging growth is a benign one, favorable for operation.

We must realize, too, that there may be a double reason for operating, in view of this frequent association of a local neoplasm with both of the conditions which we are considering. I have purposely refrained from making particular mention of the well-recognized local symptomatology of these growths in the infundibular region, for it is their effect on the hypophysis that I wish to emphasize, unobscured by other symptoms. Headache, of course, is often extreme in these cases—a form of cephalalgia produced by distention of the dural pocket enclosing the gland and consequently not relieved by the usual decompressive measures, as I have found to my discomfiture. Amblyopia from an optic atrophy which usually is primary—not secondary to a choked disc—is a still more serious and equally frequent manifestation of the local lesion. It appears in its most characteristic form as a bitemporal hemianopsia, though this is far from the most common type of partial blindness, inasmuch as one nerve is apt to be more seriously implicated than the other. Enlargement of the sella turcica is another valuable sign, one which need be expected, however, only in those cases in which the growth originates in or invades the glandular dural pocket. There are a number of additional signs of less moment.

Though these manifestations of a local tumor, whether primarily originating in the gland or secondarily involving it from pressure, have possibly been absent more often with hyperpituitarism (acromegaly) than with the reverse condition, we must remember that they may be common to both of them. These local tension symptoms may be completely relieved, as we have found to be the case with our acromegalic patient, by the simple incision of the dural pocket encasing the enlarged gland.

These things, of course, are quite apart from the treatment of the hypophyseal symptoms themselves, in regard to which the matter must likewise remain at present largely a surgical problem. This resolves itself, on the one hand, into partial removal of the hypertrophied gland or the glandular tumor when there are clinical manifestations of over-activity (acromegaly and gigantism); on the other hand, when there are evidences of under-activity (adiposity, either with infantilism or sexual degeneracy) into removal, if possible, of the tumor causing the compression, with supplementary organotherapy (anterior lobe administration) should the gland prove to have been injured by the operation or for other reason fail to resume its normal activity.

As has been the case with operations on the thyroid, we may expect a rapid perfection of the surgical methods of approach even to this far more inaccessible structure—the pituitary body; and depending on whether the growth largely occupies a distended sella turcica or lies above it in the interpeduncular region, the transphenoidal route, successfully followed in our case of acromegaly, or an intracranial route comparable to that employed by Horsley and used in our animal experiments, will prove to be the preferable one to follow.

SUMMARY

Two conditions, one due to a pathologically increased activity of the pars anterior of the hypophysis (hyperpituitarism), the other to a diminished activity of the same epithelial structure (hypopituitarism), seem capable of clinical differentiation.

The former expresses itself chiefly as a process of overgrowth—gigantism, when originating in youth, acromegaly when originating in adult life. The latter expresses itself chiefly as an excessive, often a rapid, deposition of fat with persistence of infantile sexual characteristics when the process dates from youth, and a tendency toward a loss of the acquired signs of adolescence when it first appears in adult life.

Experimental observations show not only that the anterior lobe of the hypophysis is a structure of such importance that a condition of apituitarism is incompatible with the long maintenance of life, but also that its partial removal leads to symptoms comparable to those which we regard as characteristic of lessened secretion (hypopituitarism) in man.

A tumor of the gland itself, or one arising in its neighborhood and implicating the gland by pressure, is naturally the lesion to which one or the other of these conditions has heretofore been attributed, though it is probable that over-secretion from simple hypertrophy, or under-secretion from atrophy, will be found to occur irrespective of tumor growth when examination of the pituitary body becomes a routine measure in the postmortem examination of all cases in which the conditions suggest one or the other of the symptoms-complex described.

When due to tumor, surgery is the treatment that these conditions demand, and at present there are reasonably satisfactory ways of approaching the gland; but clinicians and surgeons must clearly distinguish between the local manifestations of the neoplasm due to involvement of structures in its neighborhood other than hypophysis, and those of a general character from disturbances of metabolism due to alterations of the hypophysis itself.

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Penetrating Injury of the Brain.—W. A. Gills, in the *Virginia Medical Semi-Monthly*, May 7, 1909, reports the case of a man, aged 30, who shot himself with a 32-caliber revolver, the ball entering the right side of the head two inches behind the upper temporal ridge and one inch above the zygoma, traversing the frontal region, passing entirely through the bone of the opposite side (but not through the skin) at a point midway between the frontal eminence and the superciliary ridge, an inch to the outer side, a skin incision being necessary to remove it. About one hour after the shooting the patient was almost pulseless, with breathing very shallow, but conscious—recognizing voices. His eyes were so badly swollen that one was unable to recognize him; and because of the swelling, it could not be determined if there were any ocular changes present. Gills noted the presence of brain substance on the cheek. An incision of about an inch and a half was made through the skin and the ball removed without any trouble. Treatment was tentative and conservative. On removal of the dressing it was found that each wound extended to the brain. Drainage was put in each, an ice cap applied to the head, a mercurial purge given and the patient placed in a dark room under the care of a competent nurse. The head of the bed was elevated; a saline solution four ounces every fourth hour per rectum, ordered; the eyes cleansed with boric acid solution; the ears and nose irrigated with saline solution, and morphin given to induce sleep. No probing was done. The patient made a complete recovery except for slight impairment of the sense of smell.