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An Address
ON
**ACROMEGALY FROM A SURGICAL
STANDPOINT.***

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PART I.

ONE of the tiniest of the Virgin Islands, a speck named Little Vandyke, almost too small to be designated on a map, was once given over—and may still be, for all that is known—to the growing of cotton. On this plantation there happened to be born on November 22nd, 1744, of Quaker parents, a boy who six years later was sent to England to get his education. His chief asset appears to have been a negro "shuffle," which he had learned from his father's slaves; and without this chance accomplishment, so the story goes, the attention of the Reverend Samuel Fothergill of Warrington would probably not have been drawn to the inconspicuous lad. As it was, he gave him a halfpenny, ere long became his guardian, and in course of time recommended him to the consideration of his brother, Dr. John Fothergill of London, whose protégé he was destined to become. This, in small compass, was the early story of John Coakley Lettsom, the founder and chief benefactor of the venerable society I have the privilege of addressing.

Being the first of my countrymen, so far as I am aware, to give this Annual Oration, it is fitting that I should call to mind the debt we owe to Fothergill and Lettsom for their unfailing kindness to a succession of American students who in the early days came here to walk the hospitals. Fothergill even found occasion to give a helping hand in starting two of our oldest medical schools—that in Pennsylvania, established shortly before the separation of the colonies, and that in the State of Massachusetts shortly afterwards.

Since I happen to occupy a chair in this latter school, I may recall to you that Benjamin Waterhouse, one of its founders and its first Professor of Medicine, was a relation of Fothergill's—sufficiently close to call him "Uncle"—and also that, through Waterhouse, Lettsom once presented to Harvard a large and valuable collection of minerals to encourage, in our backward land, the study of natural science. Thus do some of the medical traditions of my country become interlocked with those of the Medical Society of London.

Men of the calibre of Fothergill and Lettsom were universalists in medicine, with interests comprehensive and manifold. This was more possible in their time than in ours, and I fear they would have looked askance on the modern tendency to ultra-specialization as something foreign to the best interests of our medical guild. I feel somewhat conscience-stricken over this, since I have chosen to devote my address to a consideration of the surgical aspects of a malady which would have seemed to them, and I fear may to many of you, as small a speck on the medical horizon as is Little Vandyke on the geographer's chart.

Though we begin our professional lives with a general training, we very soon find that there are certain maladies or phenomena of disease that particularly interest us, and from opportunity or force of circumstance come largely to engage our attention. It is in this way, by progression from the general to the particular, that specialization arises, and though in the process the field may narrow, at the same time the point of view may broaden. Concentration on a given subject, however small, makes it loom large to the observer, and as Lettsom's significant life had an obscure beginning, so the speck that I propose to discuss may, if fortune favours, be expanded into something worthy of this occasion.

For those of us whose student days go back to the "nineties," the pituitary body was too inconspicuous an object to attract much notice, or, if noticed, it was brushed aside as a vestigial relic of no recognizable importance. There were glimmerings, to be sure, of its relation to the disorder to which Pierre Marie had recently given a name, but this was about all. Once pointed out, this disorder was unmistakable, and yet acromegaly was looked upon, for long, as little more than a freak of nature which eclipsed understanding, in its extreme forms fit only for the "side-show," to be exhibited with the giant, the dwarf, the bearded woman, and the fat boy whose hypophyseal and cousinly relationship was as yet unrecognized.

Of the manifold functions of the pituitary body and of its relation to the other glands of internal secretion there was then not the slightest conception. How different, by contrast, to-day, when the problems of endocrinology absorb the attention of such a host of investigators that scarcely a month passes without some new light, from one aspect or another, being shed on the kaleidoscopic subject! Not since the early discoveries in bacteriology has there been anything comparable. Nuggets, to be sure, had already been picked up by such as Addison, Graves, Gull, Ord, and many others who were the pioneers. But the rush to the gold-field did not begin until after the discovery of an effective substitution therapy for myxoedema, and the recognition of exophthalmic goitre as its counterposed state. And when, a decade later, the maladies of hypophyseal origin began to be better understood, and the disclosure was made that all the ductless glands were functionally more or less interdependent, not only was the interest of the profession at large finally aroused, but the curiosity of the laity as well, in consequence of which, for popular consumption, much twaddle has come to be written on the subject.

There are certain general principles on which, right or wrong, we have come to base our conception of the way in which the ductless gland disorders affect the body. The first of these is grounded on the presumption that there are counterposed states of primary underfunction and of primary overfunction for every individual member of the so-called endocrine series. It is assumed, moreover, that each of these states, in the case of every gland, will evoke its own peculiar clinical syndrome, some of which we already recognize, and some few of which, more particularly the deprivation states like myxoedema, diabetes mellitus, eunuchoidism, tetany, and so on, may be experimentally reproduced in animals. This view, at least, has long served as our working hypothesis, even though in its support the experimental reproduction of states of glandular overactivity has so far largely baffled us.

* The Annual Oration before the Medical Society of London on June 13th, 1927.

This hypothesis has been largely the outgrowth of our experiences with thyroid disorders, and surgery has played no small part in its elaboration. I need recall only a few incidents in the well known story. That Gull's myxoedema was really due to thyroid deprivation, Kocher's experiences with post-operative "cachexia strumipriva" served to make probable; and the success of Horsley's and Murray's substitution therapy left no doubts in the matter. On the other hand, the view advanced by Moebius and Greenfield that exophthalmic goitre was possibly due to glandular overactivity, first suggested by the disclosure that thyroid extracts exaggerated the syndrome, was finally substantiated by Halsted's discovery that experimental hypertrophy of the thyroid is characterized by the same histological alterations that are found in the goitre of Graves and Basedow. Thereby it was shown why extirpation of the thyroid in this peculiar form of goitre would serve to ameliorate its symptoms. We accordingly have come, with a good deal of confidence, to speak of hyperthyroidism as opposed to hypothyroidism, of which states the basal metabolic rate now gives us a fairly reliable measure.

This, briefly, is the first principle; and on this basis it might well enough have been anticipated that for each of the other glands, acting more or less independently of one another, a clinical syndrome of overactivity and underactivity would by this time have come to be recognizable. However, in the case of the hypophysis alone has this anticipation finally been realized; and though clues serviceable in partially solving the thyroid riddle were persistently followed, even this has been a most complicated task.

An enlargement of the thyroid is for all to see, and in regions where goitre is endemic the surgeon was primarily induced to operate upon cases in which life was endangered or made insufferable from pressure of the enlarged gland on the trachea. Hazardous procedures they proved to be. They were critical enough in themselves, without the unforeseen dangers that lurked in the background of convalescence until, through experience and experiment, it slowly dawned on men's minds that a residuum of thyroid tissue must be left and that the parathyroid glands must be spared if subsequent health—even life itself—was to be maintained.

In comparison, even to get a start in untangling the pituitary problem was far more difficult. Not until roentgenology came to be sufficiently perfected as a diagnostic aid could we really tell with any assurance when the gland was actually tumefied, and its inaccessibility long served to remove it from surgical temptation. Even its experimental removal in animals was difficult to accomplish and gave contradictory results, due in large measure, as we now know, to coincidental lesions of nervous centres adjacent to, and which possibly preside over, the activity of the neuro-hypophysis. In short, hypothalamic injuries long led to as much confusion in the interpretation of the results of experimental hypophysectomy as did the removal of the parathyroids in interpreting the consequences of thyroidectomy.

One of the first questions to be raised in regard to acromegaly concerned its possible relation to the pituitary tumour found in some of the first cases submitted to autopsy; and the acromegalic skeletons in pathological museums the world over were being examined to see whether they showed an enlargement of the sella turcica, which most of them did. However, from time to time examples of acromegaly came to be described in which there was no demonstrable tumefaction of the gland; and, to make the confusion worse, examples of undoubted pituitary tumour, to judge from the syndrome of an enlarged sella combined with a primary optic atrophy and bitemporal hemianopsia, were being put on record which showed no trace whatsoever of acromegalic overgrowth. Quite the contrary, these patients exhibited a medley of inexplicable symptoms, such as dwarfism, sexual dystrophy or infantilism, diabetes insipidus, adiposity, amenorrhoea, myxoedematous atrophies, and so on.

But out of this chaotic jumble order has begun to shape itself, and we are at least coming to close quarters with the riddle. To its partial solution countless persons have made contributions, which piece by piece have been fitted together. The physiologists and biochemists have chiefly

centred their attention on the active substance discovered in extracts of the neuro-hypophysis. The pathologists have, with some measure of success, come to differentiate certain of the hyperplasias and other tumefactions which affect the gland. The morphologists have shown how, in the development of Rathke's pouch, the epithelial *anlage* of certain of the congenital tumours may arise. The experimentalists have laboriously undertaken to determine the secondary effects of ablation of the gland or of portions of it, the amphibian embryo no less than the adult mammalian animal having been called upon for the purpose. As a combined result of these many disconnected studies, the obscurities of the past are here and there sufficiently clarified, so that we begin to have a partial explanation at least of some of the constitutional effects of deranged pituitary function. Curiously enough, it was not acromegaly, but the reverse condition, that had its first experimental counterpart brought to light.

Following the grudging acceptance of the view that the syndrome of Marie was usually associated with, if not positively due to, a pituitary tumour, it was a natural assumption that the normal function of the gland, whatever it might be, had been abolished, and consequently that its experimental ablation ought to reproduce the symptoms of acromegaly. But those who undertook to corroborate this assumption reported most conflicting results, some claiming that the removal of the gland had no effect whatsoever on the organism, others that its removal led to cachexia and death. No one claimed to have produced anything suggestive of acromegaly; but it was finally observed that certain incomplete extirpations on adult animals led to adiposity and sexual dystrophy, symptoms quite comparable to those which had been seen in clinical cases; and ere long it was found that similar procedures in young animals led to skeletal dwarfism and prevented sexual development. Here, then, were experimental states due so obviously to lessening or deprivation of function as to force the conclusion that acromegaly must be ascribable to a counterposed state—namely, to glandular overactivity.

Reduced to simple terms, these early experiments showed that the hypophysis secretes a substance or substances which not only influence growth, but which have a marked effect upon the activity of the reproductive organs. Just what portion of the gland possessed these properties was long a matter of uncertainty. A physiologically active principle had been found only in extracts of the posterior lobe; but most physiological experiments deal with acute reactions, and it was not until an experimental morphologist took the matter in hand that the growth-stimulating principle was convincingly shown to be the property of extracts of the anterior lobe alone.

Since the time of Galvani the frog has been hailed as the chief contributor to physiology. No less in these present days does the domesticated rat, the biometrical standards of whose life-history have been accurately established promise to play this important role in experimental morphology. And it is to the rat in the hands of certain investigators that our thanks are due for giving the first wholly dependable and clear-cut results in the hypophyseal problem.

We have learned that menstrual disturbances characterize all forms of pituitary disease in the female; and strangely enough it was primarily through his studies of the oestrous cycle in rats that Professor H. M. Evans of the University of California first came to investigate the effects of injecting pituitary extracts into these animals. He found that fresh anterior lobe extracts would not only interrupt oestrus in adult female rats but would prevent its onset when given to pre-adolescent animals. He found, further, that when intraperitoneal injections of these extracts were continued over a long period the growth of the animals was greatly accelerated, and that experimental gigantism could thereby be produced.

How excited Lettsom's friend John Hunter, who so ardently sought for an explanation of growth, would have been in these disclosures, whose fundamental importance can hardly be overstated! Not only have they served to lay the growth principle exclusively at the door of the anterior hypophysis, but, for the first time, in the case of any member of the ductless gland series, there has been

reproduced in the laboratory what heretofore has only been theoretically assumed to be a clinical state, due to excessive rather than to a perverted glandular secretion. Dr. Evans's observations have been confirmed in my laboratory by Tracy J. Putnam, who has succeeded in producing some gigantic animals; and I may show (Fig. 1) the roentgenogram of one of them with its control.

The large female rat on the right was born on October 28th, 1925, of a thoroughbred stock. On January 21st, 1926, when she weighed 163 grams, intraperitoneal injections of a neutral filtered aqueous extract of anterior lobe beef hypophysis in amounts equivalent to about one-tenth of a beef gland daily were begun. The x ray was taken on August 5th, 1926, at which time she weighed 500 grams.

The small (control) rat on the left, also a female of the same stock, was born on November 2nd, 1925. On January 21st, 1926, she weighed 165 grams. She was given injections of commercial anterior lobe extract, which proved to be without effect. At the time the x ray was taken she weighed 260 grams.

The chief difficulty in the way of success in these experiments lies in the securing of an active extract, for the bovine glands which serve as the usual source of supply seem to vary to a great extent in the amount of the somewhat unstable principle they contain; and it has been my impression for some years that cattle have a seasonal wave of relative pituitary inactivity. Much labour will have to be expended before we have at our command a reliable extract, which can be standardized and kept sterile so that it may be employed for clinical purposes; but the discovery that the pars anterior actually contains a growth-stimulating principle will doubtless spur the biochemist to run it down. And when this substance comes to be isolated, as it almost certainly will be, there will be a different story to tell.

To be sure, these experiments have not reproduced acromegaly, but only gigantism. They nevertheless bring support to the view, long held, that these two clinical conditions are closely related, are both hypophyseal in origin, are both ascribable to an excessive secretion of the anterior lobe. As long conjectured, the one (gigantism) probably is the result of a process which has started before the epiphyses have become ossified—which they never do in the rat—whereas the other (acromegaly) is an expression of the same influence which has started after epiphyseal growth has ceased.

If we are indebted to the rat for the illuminating discoveries just mentioned, we are no less indebted to this same animal for more exact information than we have heretofore possessed in regard to the reverse state of pituitary insufficiency. Most of the early observations on experimental hypophysectomy were made on the cat and dog; and though they have taught us much, control observations have not been wholly reliable or satisfactory, owing to the slower development and life cycle of these animals, and to their great variability in kind. It is quite otherwise

with the rat; and Professor P. E. Smith of Leland Stanford University has devised an operative procedure whereby hypophyseal or parhypophyseal lesions on this animal may be accurately made with results far more dependable than any heretofore attained. Not only are the symptomatic effects of the operations more promptly and strikingly shown than in other animals, but the possibilities of replacement therapy to atone for the glandular deprivation have been for the first time convincingly demonstrated. In comparison, all antecedent observations on the effects of experimental hypophysectomy laboriously made on the dog are become superseded, and remain of little more than historical interest.

In a recent series of papers written with the collaboration of my late assistant, Dr. L. M. Davidoff, we have

entered into some consideration of the effects of disordered pituitary activity on the other endocrine organs, apart from the sex glands, the function of which is so obviously dependent on the hypophysis. In one of these papers¹ the autopsy findings in four cases of acromegaly were described, and emphasis was laid not only on the extraordinary splanchnomegaly which the disease often provokes, but upon the alterations in the other ductless glands, most notably shown as hyperplasia of the thyroid, the parathyroids, and the adrenal cortex; in states of pituitary deficiency, on the contrary, these particular glands are found to be atrophic.

These widespread alterations in the ductless gland series, which so strikingly characterize pituitary disorders as to set them quite apart from the disorders primarily affecting any other ductless gland, are equally apparent in the ex-

FIG. 1.—Roentgenogram (one-third natural size) of experimentally produced gigantism in the rat. (Kindness of T. J. Putnam.)

perimental counterparts of the clinical states. As the outcome of some correspondence with Dr. Smith on this subject, he has kindly given me photographs of certain of his hypophysectomized animals with subjoined protocols, and has generously permitted me to use the figures for the purpose of this address. They tell, far better than can any description, not only what are the symptomatic consequences in the rat of some of these deprivation states, but what may be accomplished, in the laboratory at least, by replacement therapy.

The first of these photographs (Fig. 2) shows two litter-mate brothers born on May 21st, 1925; the animal on the right was hypophysectomized on June 16th, and had grown scarcely at all subsequent to the operation. The photograph was taken four months later when the animals were sacrificed. The thyroid and adrenal glands were highly atrophic.

The next two photographs (Figs. 3 and 4) show two litter-mate brothers born on October 22nd, 1925. The animal on the right, then slightly the larger of the pair, was hypophysectomized on November 27th. Three months later (February 24th, 1926) the control weighed 333 grams, and the hypophysectomized animal 108 grams (though 4 months of age this animal had never mated). At this time, just before the photograph (Fig. 3) was taken, the left testis had been removed from each of the animals, and the

organs are shown. The dwarfed and sexually infantile animal was then given each day a homoplastic hypophyseal transplant, and on April 20th he mated with a female in oestrus and a litter resulted. Daily pituitary transplants were continued until the hypophysectomized animal had almost caught up in weight (268 grams) with its control brother (385 grams). On May 9th, when the photograph (Fig. 4) was taken, the pair was sacrificed and the remaining testis of each is shown in the figure.

The next photograph (Fig. 5) shows two litter-mate sisters born on December 25th, 1923, the animal to the right having been subjected on February 5th, 1924, to an injury of the hypothalamic region without hypophyseal extirpation. On February 27th, 1925, this animal weighed 840 grams to 299 grams for the control. The animal was sacrificed on this date, and an extensive atrophy of the sex apparatus was disclosed, the other ductless glands being of normal size.

measures, surgical or otherwise. These several syndromes have come to have a varied and somewhat confusing nomenclature, which must for a moment detain us.

NOMENCLATURE.

When terms such as myxoedema, exophthalmic goitre, cretinism, acromegaly, and so on, descriptive of certain clinical states of unknown etiology, become, through use, thoroughly established, it is difficult to uproot them. Even to suggest doing so is perhaps discourteous to those who planted the seed. Descriptive terms, however, may prove to be exceedingly inconvenient from a nosological stand-

FIG. 2.—Litter-mate brothers, showing effect of early hypophysectomy in producing dwarfism with atrophy of the endocrine system. Measurement in decimetres. (P. E. Smith.)

FIG. 5.—Experimental hypothalamic syndrome. Measurement in centimetres. (P. E. Smith.)

Taken in conjunction with the observations by H. M. Evans and his co-workers on experimental rat-gigantism, these illustrations of the counterposed state, to the study of which P. E. Smith has confined himself, show what an immense field has been opened up for future investigations of pituitary function, which can be far more precise, owing to the species chosen for experimentation, than any heretofore undertaken.

This is only the beginning of what we shall some day know about this amazing structure which conducts the endocrine orchestra, and brings therefrom harmony or disharmony, overtones or undertones, according to its physiological mood. But let us see, from the striking results already attained, what light may be thrown upon the several clinical syndromes we have come to recognize, and in what ways the experiments concern our therapeutic

point, and were there any choice permissible it would be preferable to cling to such non-committal eponyms as the syndrome of Gull, or of Graves, or of Marie, as we have done with Addison's disease.

The particular inconvenience in the case, for example, of *acromegaly*, is that the term, which is now associated in the minds of all with a state due to hypophyseal overaction, merely described an enlargement of the acral parts of the body. It accordingly gives no opening for an opposed term to describe the now recognized counterstate of all that "*acromegaly*" once conveyed; for *acromicria*, a smallness of the extremities, would mean nothing at all, and other designations that have been suggested are no more satisfying.

Had the designation *macrosomia*, implying overgrowth in general, suggested, I believe, by Hastings Gilford as appro-

priate for Marie's syndrome, not fallen on sterile soil, *microsomia* would have been a convenient term for the growth deficiencies which are the striking features of the reverse state. Adiposo-genital dystrophy merely calls up a syndrome which may not necessarily be hypophyseal at all, and though such eponyms as Frölich's disease, Lorain's disease, and Simmonds's disease bring to mind certain recognizable clinical types of pituitary deficiency, there are still others unnamed.

However much those who know the appeal of medical history may wish to dwell upon and cherish the names of its eponymous heroes, it would be better for medical terminology to abandon or at least to modify symptomatic

associated tumour, we may properly add a fourth, *apituitarism*, indicating the complete loss of pituitary activity.

Let us now consider, briefly, what are the clinical expressions of these four gradational states, and by what pathological lesions (some of which have definite surgical bearings) they are brought about. We may begin with the effects of complete glandular deprivation.

A. APITUITARISM.

Does such a condition as cachexia hypophyseopriva due to acute destruction of the gland, whether by experimental, pathological, or surgical processes, really exist? This is an

FIG. 3.—Litter-mate brothers, showing comparative size of testes of control and of dwarf three months after hypophysectomy. Measurement in decimetres. (P. E. Smith.)

FIG. 4.—Same animals as in Fig. 3, three months later. To show the growth-stimulating effects of substitution therapy on the hypophysectomized animal and on its remaining testis. Measurement in decimetres. (P. E. Smith.)

designations and eponyms when they no longer convey what a single term should convey. So in the case of the thyroid disorders, though the terms Graves's or Basedow's disease and exophthalmic goitre, for the state counterposed to myxoedema and cretinism, have long served a useful purpose, they are coming to be superseded by hyperthyroidism and hypothyroidism, as being more precisely descriptive, particularly since we have grown to recognize types of thyroid overactivity not associated with exophthalmos.

For similar reasons some years ago the terms *hyperpituitarism*, *hypopituitarism*, and *dyspituitarism* were suggested as correspondingly proper substitutions for acromegaly, for its counterposed state, and for overlapping types of the two; and though these words are quite a mouthful, and, what is more, have a mongrel derivation, hyper- and hypo-hypophyism were phonetically quite impossible. To these three terms, which, of course, apply merely to varying grades of glandular activity and have nothing to do with the presence or absence of an

important question for the surgeon. If the hypophysis can be removed in its entirety without serious ill effects, the problem of treatment of the adenomas, which represent by far the commonest form of tumour affecting the gland, becomes greatly simplified. If, on the other hand, serious consequences are likely to occur, or may occasionally occur, the operation of total or subtotal hypophysectomy must be deferred until some method of substitution therapy has been found sufficiently effective to offset them.

It is obviously a matter to settle in the laboratory, not in the clinic. But the laboratory so far has given conflicting results. My own impression has been that total extirpation often provokes a peculiar train of symptoms passing from cachexia to coma and ultimate death—a sequence, to be sure, more likely to appear acutely in adult than in younger animals; but even in the older animals the same operative procedure, short of a total removal, leads to no comparable ill effects. On the other hand, Dandy and Reichert, who have recently reopened the question, claim that the operations on which the preceding

conclusions were based must have been faulty, to judge from their own negative results on this particular score for dogs of any age. And certainly the young rats used in Dr. Smith's experiments appear to have shown nothing at all suggestive at least of the acute cachexia which had been described.

FIG. 6.—Showing cystic lesions produced by infarcts largely replacing anterior lobe of a pituitary dwarf. Remainder of gland normal. (Simmonds.)

In view of these contradictory experiences, has the surgeon heretofore been unduly fearful of the consequences of total hypophysectomy? Have the disabilities that would ensue possibly been exaggerated, and might he not venture to remove completely an adenomatous gland regardless of the patient's age? A partial answer, which will continue to stay his hand, comes from clinico-pathological observations, which go to show that destruction of the gland by morbid processes of one sort or another, particularly in adults, may lead to a fatal cachexia. In my Cameron Lectures I cited the case of a middle-aged woman apparently in normal health who, suddenly overcome by a severe headache, gradually passed into a deep stupor associated with a surprisingly low body temperature, with a fatal issue on the third day. Nothing abnormal was found at autopsy, apart from a destructive haemorrhage into what must have been an adenomatous hypophysis, that had given no antecedent symptoms.

Largely, I believe, for want of a detailed routine examination of the hypophysis as the possible source of unaccountable deaths, only a few cases of this kind have been reported. But even though the evidence for the syndrome of acutely fatal cachexia hypophyseopriva may be unconvincing, there can be no doubt in the minds of any of the existence of the slower form of cachexia, due to a relative rather than absolute anterior lobe deficiency.

B. HYPOPITUITARISM.

The clinical manifestations of hypopituitarism are most varied. They depend on whether it has originated in childhood or adult life; whether it is or is not associated with tumour; and whether or not there are accompanying disturbances referable to the hypothalamic region. Let us primarily consider for a moment the least complicated of all recognizable hypopituitary syndromes, in which tumour does not enter into the picture.

1. Anterior Lobe Deficiency due to Ischaemic Necrosis (Simmonds's Disease).

To the late Professor M. Simmonds, the Hamburg pathologist, we are chiefly indebted for pointing out the frequency with which the pituitary body, in the course of septic infections, may be affected by embolic processes. They may occur at any time of life, but the consequent symptoms naturally will differ greatly according to the age of onset. In his first communication² he reported thirteen cases in which varying degrees of destruction, particularly of the anterior lobe, had been produced by infarcts, septic or otherwise, not infrequently a consequence of puerperal sepsis. In one instance the patient's premature senility, somnolence, and death were ascribed to the almost complete cicatricial destruction of the gland which the *post-mortem* examination disclosed; and in a subsequent article (1918)³ three other equally striking examples of a corresponding condition were recorded. All three were adult women who before death had shown the characteristic evidences of pituitary old age, and at autopsy, in addition to the destructive lesion involving the hypophysis, there were found atrophic changes involving other glands and viscera (splanchnomericia), exactly the reverse

of the glandular hyperplasias and the splanchnomegaly that characterize clinical hyperpituitarism.

Should a comparable infarct of the anterior lobe occur in childhood and be confined to the pars anterior, and should recovery occur, the effects naturally would be still more striking. For the victims of such a lesion would cease to grow, and would remain in a condition of nanism precisely comparable to that brought about by the experimental ablation of this portion of the gland in young animals. Simmonds had the good fortune to make a *post-mortem* examination of one of these cases, which he has reported in a third article in his series.⁴

The patient was a dwarf, 110 cm. in height, a member of a Lilliputian troupe, who died in his twenty-first year from a septic meningitis following otitis media.

The *post-mortem* examination showed, in addition to the usual visceral hypoplasias, an extremely small pituitary body, weighing only 0.2 gram. Histological examination of the gland showed (Fig. 6) a normal posterior lobe and an anterior lobe largely replaced by a number of small cysts.

This, so far as I am aware, was the first reported example of a case of hypophyseal dwarfism in which the symptoms had not been produced by a tumour, leaving it difficult to tell whether the disturbance in growth had been due to a loss of function of the entire gland or to one of its subdivisions. These embolic lesions in all probability are not extremely rare, and doubtless careful *post-mortem* examinations in the future will disclose more of them. Naturally enough, the symptoms will vary from case to case in their severity, and I may briefly report a representative example of a mild grade of this form of nanism, due almost certainly to uncomplicated anterior lobe deficiency, and, in view of the history, probably produced by a septic infarct.

The patient, 28 years of age, is a particularly lively, vivacious, and intelligent young woman, the victim of pituitary dwarfism of the Simmonds type. After a normal childhood she had a severe illness when 8 years of age, which was diagnosed as "black diphtheria," after which she practically ceased growing. Her parents are persons of average size, and she has a sister two years older of normal height. The patient herself (Fig. 7) measures 54½ in. in height, the average height of a child of 11 years, and her weight is also about that of 11 years—namely, 75 lb.

Since the illness mentioned above, she has enjoyed perfect health, has never had any polyuria or polydipsia, and has never had the slightest tendency toward adiposity. She never menstruated, there is no sign of mammary development, and only a few sparse hairs in the axillae and on the pubis. As in so many of these cases, her face looks actually older than her years, and she has the horizontal wrinkles on her forehead and the cutaneous appearance of a middle-aged person.

The x rays show a small sella of normal configuration. The cranial bones, however, are exceedingly thin, and though her teeth are all erupted they have been soft, and have needed constant attention. The epiphyseal lines of the long bones are still present, and there is no question but that, given an active anterior lobe substance, she might even now be made to bloom suddenly into normal and adult womanhood. Her present state, of course, is the exact reverse of gigantism.

Among the many other forms of nanism, all of which are probably either primarily or secondarily of hypophyseal

FIG. 7.—Patient, 28 years of age, with Simmonds's syndrome, following a general infection with probable anterior lobe infarcts at 8 years of age.

origin, there is another striking type, first described by Jonathan Hutchinson, and for which the term "progeria," signifying "premature old age," was introduced by Hastings Gilford. Hutchinson's patient, when 15½ years of age, had the aspect of a decrepit old man, was 3 ft. 7 in. in height, and weighed 38 lb.; two years later he died of apparent senility. A marked example of this condition in a female was observed in my clinic some years ago.* At 8 years of age she was a wizened old woman in miniature (Figs. 8 and 9), weighing 31 lb., and 3 ft. 1½ in. in height. The combination of infantilism and senilism characterizing the syndrome, once seen, is unforgettable.

These forms of hypophyseal nanism uncomplicated by tumour are obviously the clinical counterpart of the dwarfed animals produced by removal of the epithelial

The first impression of the case was that it was one of pituitary tumour associated with myxoedema.

This case was reported in the days before cranial roentgenology had been greatly perfected; and to-day one may only conjecture that the syndrome was produced by a congenital cystic tumour, the walls of which usually become sufficiently calcified to cast a shadow to the x ray. The patient, however, was not a dwarf, nor was he old enough to show sexual dystrophy; and Fröhlich's chief contribution lay in his assembly of similar cases gathered from the literature which showed how often tumours in the pituitary region were associated with adiposity and a peculiar appearance suggesting myxoedema, for which pituitary insufficiency may be easily mistaken.

A similar case, also from Frankl Hochwart's clinic, was

FIG. 8.—Patient, 8 years of age, with the Hutchinson-Gilford syndrome, progeria. Probably an expression of extreme anterior lobe deficiency dating from early life.

FIG. 9.—Same as Fig. 8, to show atrophic character of skin and subcutaneous tissues.

portion of the gland; and they show what would be the consequences of its surgical extirpation at correspondingly early periods of life. Such an exigency, however, would only be likely to arise during the course of an operation for tumour; and a few of the more important neoplasms which are accompanied by hypopituitarism may now be considered.

2. The Deficiency Syndromes due to Compression of Parahypophyseal Tumours (Fröhlich's Disease, etc.).

As previously stated, long before we knew much about pituitary dysfunction and the disturbances of growth produced thereby, cases had been reported by a number of clinicians who had been struck by some peculiar symptom or combination of symptoms in a patient known to have an hypophyseal tumour. One of the early reports of such a syndrome was made by Alfred Fröhlich (1901) from Frankl Hochwart's clinic in Vienna.*

The patient was an intelligent 14-year-old boy who had long suffered from periodical headaches, and who had shown a sudden tendency to become adipose. Coincidentally there was a rapid loss of vision, with total blindness in one eye and temporal hemianopsia in the other, associated with a primary optic atrophy.

ere long reported, in which Erdheim found at autopsy a congenital tumour overlying a supposedly intact hypophysis, a fact which led him to believe that the dystrophies shown by the patient were hypothalamic rather than hypophyseal in origin; and over this disputed point much ink has since been spilled.

The syndrome these tumours provoke is much less clean-cut than that of Simmonds's disease just discussed, because the various portions of the gland (pars anterior, posterior, and tuberalis) as well as the adjacent hypothalamic centres may, in varying degrees, have been functionally interfered with. Consequently we may meet with Rathke's pouch tumours which have first given local symptoms in middle age, no evidences of dyspituitarism whatsoever being recognizable. On the other hand, what is more common, signs of pituitary deficiency may have been evident from early life; and even though children victimized by these lesions are mentally alert, being in this respect quite unlike cretins, they may show extreme degrees of adiposity or emaciation, of polyuria or the reverse, of dwarfism, of sexual infantilism, or of premature physical senility.

There have been, all told, 81 verified examples of these tumours in my series, and, as it happens, one of the patients, a dwarf who exhibits certain evidences of senium praecox suggestive of progeria, is at this writing under observation in the hospital.

FIG. 10.—Pituitary infantilism with diabetes insipidus, due to a cranio-pharyngeal pouch (Rathke) tumour. (Child with father.)

(Surg. No. 25031.) A girl, aged $3\frac{1}{2}$ years, a child of Hungarian parents, was originally admitted on October 21st, 1925, owing to a rapid loss of weight associated with headaches, vomiting, polyuria, and polydipsia, of four months' duration.

She was (Fig. 10) an extremely undersized, undernourished child, weighing only 20 lb. and 34 in. in height. The optic discs showed marked pallor; to gross tests there was a bitemporal loss of vision, and the x ray revealed a slightly widened sella with superimposed calcification (Fig. 11)* which left no doubt as to the diagnosis.

An operation was not thought advisable and she was discharged; but a month later, owing to an increase of symptoms with subnormal temperature, somnolence, and an exaggeration of her polyuria, she was readmitted to the hospital and was operated upon on November 17th, 1925.

By the usual right frontal osteoplastic approach (Figs. 12 and 13) a cranio-pharyngeal pouch cyst was encountered and was withdrawn apparently in its entirety (Fig. 14). The operation was extremely well borne; her headaches completely subsided and the symptoms of diabetes insipidus ceased. Subsequent to her discharge she began to gain in weight, and there was a marked improvement in vision.

Following an attack of scarlet fever, and because of a tendency of headaches to return, she was brought back to the hospital for observation on May 16th, 1927. During the eighteen months' interval, though she has increased 10 lb. in weight, she has

these cysts, even when there is no pre-existent polyuria, diabetes insipidus may be produced by contusing the deformed hypothalamic region. The fact that she has not grown, or grown very slightly, since the operation makes it probable that the anterior lobe has been permanently damaged either from the long compression by the tumour or in the course of its removal. And this brings up again the point from which we cannot get far away—the essential need of substitution therapy if we are to deal effectively with these secondary symptoms, whether they are associated with a tumour or not. In this particular child Dr. Putnam is attempting to see what can be done to stimulate growth by parenteral injections of an active anterior-pituitary extract he has elaborated, fully realizing, in view of Dr. Smith's experiences, that homoplastic transplants, were they obtainable, would be far more effective.

FIG. 14.—Portions of the cranio-pharyngeal pouch cyst removed at the operation.

3. Hypopituitary States Associated with Chromophobe Adenomas.

Of all pituitary syndromes, these are most often encountered, and they occur almost exclusively in adult life. To May 1st, 1927, there have been in my series 188 histologically verified examples—almost three times as many as the chromophile adenomas associated with acromegaly.

Though the disorder is a very common one, as common in all probability as goitre, one would hardly venture to make a diagnosis in the absence of definite local evidences of the growth, and since these patients, with rare exceptions, have already attained their full stature, the constitutional evidences of diminished glandular function are often inconspicuous, being limited to the well known cutaneous changes, with a tendency to adiposity and loss of hair, to sexual dystrophy, and so on. Unquestionably these states in

FIGS. 12 AND 13.—The patient ten days after operation, showing the customary incision in exposing the hypophyseal region by an osteoplastic flap.

grown a scant half-inch. However, her vision is apparently normal, and the x rays show no trace of suprasellar calcification.

That this child should have recovered from the diabetes insipidus is unusual, for in the effort to dislodge one of

their minor grades, when the patient has no particular complaints, entirely escape attention; and, indeed, even when deficiency symptoms, in addition to those of tumour, have become unmistakable, it is not unusual for the patient to be treated as a presumptive case of myxoedema.

* This will be published in our next issue.

It was the experimental reproduction of similar states in adult dogs (without the tumour signs, of course) that gave the first clue to these disorders; and, what was then not so clear, the symptoms in all probability are almost wholly due to deficiency of the anterior lobe from which the adenomatous lesions originate. For even though these tumours may attain a large size and extend into the cranial chamber, they rarely cause hypothalamic symptoms.

To be sure, one sees occasional exceptions to the usual syndrome—namely, an adult patient with primary optic atrophy, bitemporal hemianopsia, and a ballooned sella, coupled with the constitutional evidences of diminished pituitary activity. We have, for example, encountered a typical chromophobe adenoma in a young child; and I have recently operated upon a middle-aged woman with primary optic atrophy and bitemporal hemianopsia associated with a sella turcica quite normal in size, in whom, owing to the absence of any hypopituitary symptoms, a small suprasellar meningioma was suspected. Consequently the chiasmal region was exposed by a transfrontal operation, and I found to my surprise a small enucleable chromophobe adenoma which had arisen from the upper part of the gland, and had pushed its way up under the chiasm without having distended the sella in the least.

But this was a most unusual experience. Ordinarily in these cases there is a greatly distended sella, and the usual operation is conducted from below by what is known as a transphenoidal procedure, in the course of which as much of the exposed growth as is thought expedient is spooned or "sucked" out with the sole purpose of counteracting its local pressure effects. The operations, in other words, are not undertaken with any expectation of altering the coexistent hypopituitary symptoms. For these either remain unaffected if, as is usual, nothing but adenomatous tissue is removed; or they may be exaggerated if any physiologically active though compressed remnants of the gland happen to be removed together with the tumour tissue; or they may, indeed, be lessened in severity should such remaining normal portions of the gland be enabled to resume their normal activity because of the decompression. Though we have seen examples of all these secondary consequences of the operation, its main purpose has been to preserve or to restore vision, and the degree of hypopituitarism has not entered largely into the question.

C. DYSPIUITARISM.

Though this term was originally used to cover all clinical expressions of disordered pituitary function, it would seem preferable to-day, now that these states are becoming clarified, to restrict it to that particular group of cases in which preceding hyperpituitary symptoms have become overshadowed by those of the reverse state. The experimental counterpart of dyspituitarism would be produced, accordingly, by hypophysectomizing a giant rat, which would impose a deficiency syndrome on the established hyperpituitary gigantism. Though such a state as this, so far as I am aware, has never been studied experimentally, there is clinico-pathological evidence that such a transitional syndrome exists.

In a recent paper from my clinic by Drs. Dott and Bailey,⁷ attention was drawn to certain mixed types of adenoma, of which fourteen definite examples have so far been identified out of our total verified series of 271 adenomas of all kinds—not a large proportion, to be sure, but all questionable cases have been excluded. What first called attention to these transitional adenomas, formerly classified as chromophobe, was the fact that it has been sometimes difficult to tell clinically whether the patient's malady has been accompanied by a deficiency syndrome from the outset, or whether it may not in its early stages have been hyperpituitary, to judge from suggestive traces of pre-existing acromegaly or gigantism.

However, since in these mixed or transitional cases the surgical problem does not differ from that discussed above under hypopituitarism, due to chromophobe adenomas, we may pass to the consideration of our final and most important group of cases, to which all this long story is merely preliminary.

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The Mackenzie Davidson Lecture.

ON THE EFFECTS OF RADIATIONS ON PATIENTS AND RADIOLOGISTS, AND ON PROTECTION.*

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Introduction.

IN December, 1895, the late Professor W. K. von Roentgen of Würzburg, by what has often been described as a fortunate accident when working with a Crookes's tube, forestalled Crookes and others who were working on the same lines and within measurable distance of the momentous discovery of x rays. Radiology is therefore barely thirty-two years old, and many of us can compare the face of medicine now with what it was in the days that were earlier. It is to the credit of our profession, often conservative in adopting new ideas and advances, such as those so long advocated by Lister, that the first practical application of x rays was in surgery and medicine.

Youth has the advantage of enthusiasm and a more or less uncharted field of inquiry before it, and the advances in medicine made by radiology in such a comparatively short time have been revolutionary, thus contrasting with

the changes made in the practice of medicine by the discoveries of percussion by Leopold Auenbrugger (1761) of Vienna, and of auscultation by Laennec (1819), which were slow to take effect. In the preface of the English translation of Laennec's *L'Auscultation médiate* (1821), Sir John Forbes hazarded the prophecy, which indeed was fairly correct, that its general adoption was extremely doubtful. The history of the ordinary method of physical signs when compared with the dramatic rise of radiology and its new revelations suggests some thoughts. Radiology, like bacteriology, so frequently appears to clinch the diagnosis in a case which still remains doubtful as the result of ordinary physical examination, that when an x-ray department is available there is a tendency to fly at once to it for a solution, without going systematically through the time- and thought-consuming process of routine examination. This is the easy path and line of least exertion which the student, resident, or busy physician may naturally pursue; but unless and until radiological outfit becomes, like the wireless or the low-priced motor car, within the reach of all medical men, there is a nemesis before the man who leaves the well equipped hospital to practise in some distant and isolated district where he, perforce, has to rely on his own resources, and finds that for him physical signs are a lost art. Since this siren-like call of radiology thus has a potential influence for harm, clinical teachers must set a useful example of exhaustively investigating all other available methods of ordinary examination before invoking the aid of radiology.

There are three personal aspects of radiological work to which reference may be appropriate: (1) the position of radiologists in the medical profession, (2) the physical

* The lecture, which was delivered before the Röntgen Society and the Electro-therapeutic Section of the Royal Society of Medicine on June 30th, has been slightly abridged.