Papers relating to the pituitary body, hypothalamus and parasympathetic nervous system / [Harvey Cushing].

Papers Relating to the

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Harvey Cushing

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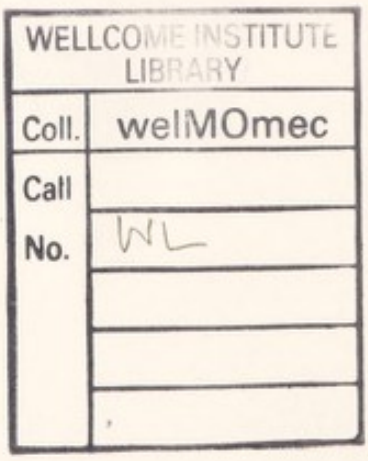
1932



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PREFACE

IN THIS volume from their scattered places of publication, four papers on correlated topics have been brought together for the convenience of those whom the general theme may interest. Though they contain statements some of which I would be glad to modify and others to retract altogether, the papers stand essentially as published. A few changes in the text have been made here and there where, on rereading, the phraseology left the intended meaning particularly obscure. The separate papers contain unavoidable repetition of statement and of citation which could scarcely be eliminated without recasting them entirely. For this blemish the reader's indulgence is sought. Such added notes as have been made will appear in squared brackets.

In the first of the papers—the Lister Lecture—the attempt was made to give a general survey of a subject to which many have contributed other than those to whose publications reference happens to have been made. In this lecture passing allusion was made to a number of topics that deserved amplification. While in the three subsequent communications herein brought together, some of these matters have been separately discussed, there is still great need of a thorough re-appraisal of the symptomatology shown by patients with tumors of the third ventricle; and this now for the first time is likely to be profitable since tumors in this region are at the present day frequently operated upon.

As a supplement to the group of six brief communications forming the basis of the Welch Lecture, bracketed "addenda" are given in which some new evidence has been presented. There will also be found an "addendum" to the third paper on Pituitary Basophilism which serves to strengthen the argument therein presented favoring the pituitary origin of the polyglandular syndrome which was described. At the same time it is suggested that basophilism may have some relation to certain aetiologically obscure disorders like essential hypertension, polycythaemia, and osteomalacia.

Dealing as they do with somewhat novel topics—or at least with old topics from a renovated standpoint—it is quite probable that many of the interpretations are based on false premises and that even those which appear to be more securely grounded will not stand the test of time. This will make little difference provided the papers help to draw attention to the long neglected interpeduncular region of the brain, unquestionably of fundamental importance to each of us, whatever may be his special field of medical work.

For permission to reprint these articles, I am indebted to Sir Squire Sprigge, the Editor of the *Lancet*, to the Board of Editors of the *Proceedings of the National Academy of Sciences*, to the Editors and Publisher of the *Johns Hopkins Hospital Bulletin*, and to Dr. Franklin H. Martin, the Editor of *Surgery, Gynecology, and Obstetrics*. Acknowledgment of a still greater debt is due my secretary Miss Madeline Stanton, for her patience these many years in deciphering my illegibly written and badly spelled manuscript pages, and to Dr. Eric Oldberg for kindly seeing this present collection of papers through the press.

Boston, July, 1, 1932

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INTRODUCTION

JOSEPH LISTER, in whose name this triennial lectureship has been established, was a practitioner of surgery and at the same time a savant—or as near an approach to one as the definition of the term can permit a surgeon to be. It is a rare combination, for the two careers are well-nigh incompatible, one or the other of them, by those capable of either, usually having to be sacrificed. Science demands of the true savant a devotion which admits of no sharing: wholly unconcerned with the application of theory, he consecrates himself to a form of intellectual

Reprinted with illustrations and additions from The Lancet (Lond.) *July 19th and 26th*, 1930, *pp.* 119 *and* 175.

activity which brooks little or no interruption. The surgeon's time, on the other hand, lies open to the behest of afflicted persons who in mounting numbers seek his aid; and if he is at all benevolent they cannot be refused. Seldom, therefore, can the diverging paths be long trodden together; the straddle becomes too great.

Those fully qualified and who have essayed to lead the double life have usually found themselves burdened beyond sufferance. In spite of his unlimited capacity and passion for work, this, in our own time, was the experience, if I mistake not, of that man of superhuman standards, Victor Horsley. John Hunter, who also kept up the divided allegiance throughout a life of unparalleled industry, was constantly harassed by obligations to his patients though they provided the guineas needed for his researches. Others like James Paget, who once said: "There is nothing that a man may not be at the same time that he is scientific," have taken the Vesalian course ultimately, after a brave start, to abandon their scientific pursuits altogether. Lister alone of those whose names come readily to mind had the placid disposition which enabled him to carry the double burden with equanimity. The major problem, to be sure, which he set himself to solve was born of the urge of practical necessity, but this was no less true of many of Pasteur's more important later researches. Each none the less remained a savant for all that.

To invoke these great names within the walls of this College merely serves to emphasize that most surgeons become increasingly involved in the snare of their practical work, the responsibilities of which allow neither leisure nor that freedom of thought necessary for productive research. The time comes when most of them at best merely provide opportunity, stimulus, and possibly ideas and material for younger people to work upon; and yet the high regard in which science is held in these halls is shown by the fact that from Richard Owen to Arthur Keith a true savant has ever been Conservator of the great museum in which the memorials and traditions of Hunter's scientific labours survive.

What personal contributions, therefore, surgeons in their later years are likely to make to the store of scientific knowledge rarely cause any great stir. So what I shall have to say in this Lister Lecture, on a subject which from small beginnings has grown beyond what any one person can readily compass, has mostly to do with the clinical interpretation of the recent discoveries made by others with some few of whom I have chanced to come into close working contact. And should Lister with Hunter and Paget and Horsley happen to look down from the spirit-world upon this gathering, my topic in spite of its modern aspects and terminology will not be wholly foreign to them. Hunter was deeply interested in the factor underlying growth in the abstract, Paget in the pathology of tumors, Horsley in the function of the ductless glands, and Lister, by teaching us how to eliminate wound infection, opened both in clinic and laboratory the innermost recesses of the living body to the surgeon's inspection. Had it not been for Lister, surgery would still be mainly "external" rather than largely "internal" as it has become; and we would have known,

probably, little more about the region of which I shall speak than was known to Galen, to André Vésale, and to Thomas Willis.

PRIMITIVE VIEWS OF THE PITUITA

Nature saw fit to enclose the central nervous system in a bony case lined by a tough, protecting membrane, and within this case she concealed a tiny organ which lies enveloped by an additional bony capsule

FIG. 1.—Vesal's original figure (1538). A, Plexus choreiformis; B, Plexus reticularis ad cerebri basim, rete mirabile.

and membrane like the nugget in the innermost of a series of Chinese boxes. No other single structure in the body is so doubly protected, so centrally placed, so well hidden. Her acts being purposeful, she must have had abundant reason for this, and man's prying curiosity impels him to ask what they were. But we may as well go back to the beginning.

When anatomists first undertook roughly to describe the brain, they were so baffled by the complexities of the region overlying the sella

turcica that the best Galen, the greatest of them, could do was to call it "the seine-like net," and as he thought it an astounding structure those who came long afterward to put him into Latin, used the term *rete mirabile* rather than the plain *plexus retiformis*. So as the "wonderful net" it continued vaguely to be described until, in the arterial plate of his *Six Tables*, Vesalius first essayed (Fig. 1) to give a picture of it—*Rete mirabile, in quo vitalis spiritus ad animalem preparatur.*

Ere long Walter Ryff, of Strasburg, pilfered this diagram and, much to Vesal's annoyance, transferred it ingeniously, line for line and letter for letter, to the drawn surface of the human body (Fig. 2). To offset this plagiary, when the *Fabrica* came to be published two years later, Vesal expunged the *Rete* altogether from his arterial plate and not only gave a separate and a new rendering of it (Fig. 3) but added a drawing to show the mechanism of pituitary distillation (Fig. 4).

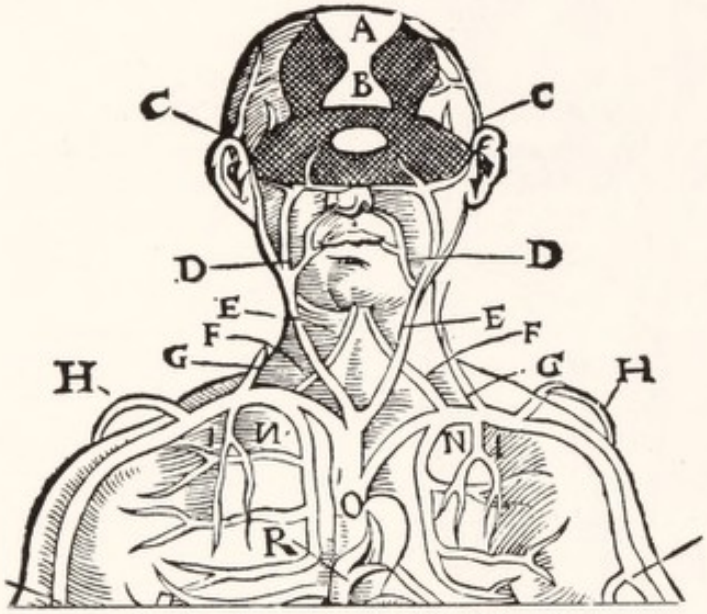


FIG. 2.—Ryff's adaptation (1541) of Vesal's diagram.
A, Blut aderlin in beyden vordern holin des hirns.
B, das wunderbarlich netzlin.

It however was not until well on in the seventeenth century that Willis began to untangle the net by describing the vascular "circle," both arterial and venous, which surrounds it (Fig. 5). Of the functional importance of the region Galen had no doubt, and we need not smile with complacence at the idea of its being a filter or trap whence the slime or *Pituita*—the waste product of the transformation in the cerebral ventricles of vital into animal spirits—found its way into the nose and pharynx.

Willis, to be sure, found this explanation untenable, particularly since Schneider before him had demonstrated that pituita or phlegm was secreted by the nasal mucous membranes themselves. But could he have known, what in more recent times comparative zoölogy and embryology were to teach us, that in ascidian larvae the ventricle and primitive mouth are in permanent communication, that the hypophysial homologue in amphioxus is a ciliated pit with an external secretion of slime, and that a demonstrable duct actually exists in the embryonic stage of all vertebrates, it would have lent strong support to the Galenic doctrine. And likely enough, one or all of these great men may have encountered examples of cerebro-spinal rhinorrhoea still further to mislead them.

We may well look charitably upon this ancient belief that the infundibular funnel and the subjacent gland was a mechanism of external secretion, for we are no less puzzled to-day to know what happens at least to the posterior lobe "pituita," it being now the fashion to believe that it passes in the reverse direction—namely, up the infundibular stalk toward the tuber and ventricle; and in all certainty the recently discovered anterior pituitary hormone of sex has much to do with our vitality and animal spirits though no longer brewed in the ventricular cavities.

In his ample discussion three centuries ago of the functions of the *Rete*, of which he had made a comparative study on all available animal species, Willis stated:

FIG. 3.—Vesal's 1543 diagram expressing his interpretation of Galen's conception of the *Rete*. A and B, entering vessels; C and D, corresponding veins; E, point of discharge for pituita from brain.

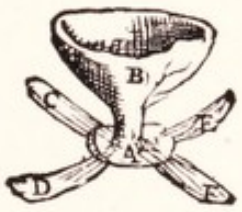


FIG. 4.—Vesal's representation of the infundibular funnel (B) by which the cerebral pituita is distilled into the gland (A) from which four ducts (C, B, E, and F) emerge to neighbouring foramina.

FIG. 5.—The diagram given by Willis (1664) of the *Rete*. (Aa) arteria canalis directus. B, vasorum plexus restiformis. C, glandula pituitaria.

> The ramification of the carotids into a reticulated plexus shows . . . that the blood . . . before it is let into the cerebrum takes some part of the superfluous serum of the pituitary gland and instils another part into the various shoots to be led back toward the heart.

There lies in this statement the kernel of the modern conception of an internal secretion; but the idea was stillborn, and though Harvey by this time had shown what might be learned concerning function by putting things to test of well-devised experiments, the *Rete* and the gland it covered were well out of experimental reach. And not only out of reach, they went practically out of mind after comparative anatomy finally made clear that in higher animals traces might be found of structures that in lower forms had once been of functional importance. So in our ignorance, the pituitary glandule, newly named (1778) the hypophysis cerebri, was conveniently brushed aside and assigned to the limbo of vestigial relics.*

* [This story has recently been much better told and in greater detail by G. Nieuwenhuis ("Einige Anschauungen über die Funktion der Hypophyse," *Janus*, Dec. 1931, XXXV, 345–359)].

HUMOURS AND HORMONES

Advances in scientific knowledge are based on speculative hypotheses, and the grain of truth they may contain is only established or disproved after disappointment and toil immeasurable. Out of Aristotle's theory of matter with its four fundamental substances—air, water, fire, and earth—grew the conception of the four humours—phlegm, blood, yellow bile, and black bile—over which medicine philosophized so long that our very speech has become permeated thereby. Our temperaments to this day are phlegmatic or sanguine, choleric or melancholy, and are likely so to remain, however much we may talk and write in modern hyper- and hypo-hormonic terms.

All this is intertwined with the age-long observations on the blood which the practice of venesection, both in illness and health, abundantly provided for study. In the formation of the clot the blood (*sanguinis*) and black bile were its solidified portion, the serum was yellow bile, and the supernatant "buffy coat" (*crusta sanguinis*) represented the phlegma on whose thickness and character the diagnosis of disease largely rested. In the whole history of medicine no one thing has played a more important rôle than the phenomenon of clotting, which served for two thousand years as the basis of humoral pathology; and the dyscrasias and diatheses of our more immediate predecessors are but the rose by another name.

There came a time, to be sure, when attention was focused (1761) by the *De sedibus* of Morgagni on the solid organs as the seat and cause of disease; but the importance of the body fluids could not long be kept in the background, and soon Théophile de Bordeu, a practitioner of Paris, propounded the view (1776) that each gland and organ provides some specific substance or secretion which, passing into the blood, regulates the physiological integration of the body—an idea that supposedly influenced Bichat in ascribing (1802) a specific vital property to each classifiable tissue.

Not, however, until Claude Bernard's brilliant studies of hepatic glycogen (1853), which supplied the conception of an internal as opposed to an external organic secretion, was there struck what we recognize as a truly modern note in all these speculations. So Brown-Séquard, among others, became imbued with the idea (1856) to which he tenaciously adhered throughout his long life, that each cell secretes on its own account certain products or special ferments which influence all other cells of the body by a mechanism other than the nervous system. From this conception, that something in the nature of an internal secretion is taken up from every tissue by the venous blood, the way was blazed for Bayliss and Starling whose chemical messengers or hormones (1902) have given a new impetus to the experimental studies of the ductless glands, brought back animal extracts into the pharmacopoeia, and provided us with a wholly new kind of humoral pathology.

We have, to be sure, more hormones than Galen had humours, but they serve much the same speculative purpose. It was the pituitary body of old that secreted the phlegm which was cold and humid and when predomi-

nant caused constitutional indolence or apathy. In Galenic terms we could well enough explain the placid temperament of a patient with a chromophobe adenoma as one who is dry and sluggish from retention of pituita in the phlegmatic glandule.

To one Galen in the second century there are uncountable inquisitors of biological phenomena in the twentieth, however Lilliputian their efforts may be in comparison. So it was inevitable that some searcher or re-searcher should again find signs of functional activity in this nigh forgotten gland. It came about, I should say, through Ludwig's invention of the kymographion, by which, on countless miles of smoked paper during experimental procedures, changes in blood pressure, among other things, have since been graphically traced. And when a pressor substance was thus shown by Schäfer to be present (1894) in extracts of the pituitary body, albeit in its posterior portion alone (1898), here was indubitable evidence that the structure was at least not so vestigial as to be functionally extinct.

But this disclosure, important though it was, was not what first drew renewed attention to the neglected organ. Our knowledge of the processes of disease almost invariably starts with the description by someone of a clinical syndrome which others quickly recognize, and only then does the labour of running it down to its seat and cause really begin. So from clinicians such as Addison and Gull, and Graves and Basedow, and Marie, to mention but a few of them, came our first recognition of the group of maladies we have learned to associate with disorders of the ductless glands. And later when Lister had made it possible to extirpate with safety some of these organs that happened to be causing mechanical trouble through tumefaction, the symptomatic effects of glandular deprivation began to be made apparent.

Organs more readily accessible to attack were naturally enough those to be first subjected to this form of inadvertent surgical experimentation, and what part Kocher and Horsley and Halsted, all belonging to this College, I may add, came to play in forwarding our knowledge of goitre and in safeguarding its operative treatment I need scarcely recall. Nature gives up her secrets grudgingly, and in this instance she had virtually to be taken by the throat before the independent rôle played by Sandström's glandules was disclosed; for these inconspicuous bodies served to obscure the actual consequences of thyroid extirpations until Gley finally (1891) showed the reason why. All told, this practical conquest of goitre represents one of the most brilliant achievements of modern medicine. Out of it grew the belief that for each of the ductless glands we might some day expect to recognize a clinical syndrome due to oversecretion and an opposing syndrome due to insufficiency for which treatment by substitution might offer promise of cure.

Thus a conjecture long held by many was crystallized into the conviction that has given birth to the new and special subject of endocrinology which is sweeping aside many long cherished views of disease in a tidal wave as momentous as that which swept over medicine at the end of the

last century upon the discovery of the bacterial origin of the infectious disorders.

II. THE ANTERIOR-PITUITARY SYNDROMES

In Volume VII of Murray's *New English Dictionary on Historical Principles* issued in 1909, the pituitary gland is thus defined: "a small bilobed body of unknown function attached to the infundibulum at the base of the brain; originally supposed to secrete the mucus of the nose." Since learned men were consulted in the preparation of this great lexicon it may be gathered that our knowledge of the activities of the structure in question has been gleaned in the past two decades. But some twenty years before that, what served first to reawaken interest in the region encircled by the Willisian vessels was the ultimate disclosure that the strange malady, which Marie had picturesquely but inadequately named acromegaly, was usually accompanied by an hypophysial tumor. What is more, pathological gigantism was soon recognized as a corresponding condition which differed merely in that it began at an earlier period of life. One can imagine how excited John Hunter would have been at this discovery could it have come in his day and generation. His employment of madder-feeding (1756) in studying the growth of bone may be recalled—a method recently revived (1930) by Handelsman and Gordon in estimating the response of osseous tissues to the pituitary hormone of growth. Indeed, had not Hunter's passion as a collector of specimens momentarily exceeded his thirst for knowledge when he came to prepare the skeleton of the Irish Giant, he could scarcely have overlooked the hypertrophic gland with its enlarged fossa, the presence of which was not detected until Arthur Keith's inquisitive finger was put into it more than a century later.

So it was the tumefied gland that finally betrayed the organic locus of Marie's disorder, and this tumor, in some inexplicable way, was evidently associated with a tendency to hypertrophic changes in the skeleton. But we were far from being as yet on solid ground even in regard to this single and striking factor of growth. Though the difficulties of solving the problem seemed nigh insurmountable, they one by one have been largely overcome by the disclosures with which all are now familiar. It was first learned that extirpation of the gland in young animals checks their growth, a negative indication that acromegaly must be due to glandular overaction rather than to diminished or faulty activity. It meanwhile had become clear from occasional post-mortem studies that the tumor in acromegaly was an adenoma, and the more recent examination of surgical specimens has taught us that it is invariably composed of the acidophil elements of the anterior lobe. And finally came the crowning achievement by Evans and Long, who in 1921 produced experimental gigantism in the rat by repeated parenteral injections of saline emulsions of fresh bovine anterior-lobe tissue.

All this seems simple in the telling. Results get recorded, not the slow and painful process beset with discouragements by which they are attained. One of the chief sources of confusion lay in the disconcerting fact

that, after Roentgen's discovery had laid bare the silhouette of the skull to our direct inspection, many patients with outspoken acromegaly were found to have an unenlarged pituitary fossa; and still more surprising, it was soon found that a tumor-expanded sella without signs of acromegaly was far more common than with them. Out of this it slowly dawned upon clinicians that pituitary tumors of the latter kind had an accompanying symptomatology, once it was pointed out, as characteristic and definitely recognizable as that of acromegaly.

Attention was first drawn to this peculiar combination of symptoms by ophthalmologists and by gynaecologists. Women with unaccountable amenorrhoea not infrequently complained of disturbances of sight, and when their eyes came to be examined indications of pressure against the optic chiasm were often disclosed. Then, as time went on, cases of this sort began routinely to be subjected to roentgenological studies, and the expanded pituitary fossa with which we are now familiar was the usual finding. But these conditions were not limited to women. Men were as likely to be similarly afflicted, and though in the male there is no periodicity of function to be so strikingly interrupted, it was nevertheless clear that entirely comparable disturbances in the attributes of sex were present in them as well.

How the surgeon has come to be drawn into all this is simply explained. The problem at the beginning was purely a mechanical one, similar to that which led to the first operations for goitre. When the enlarged thyroid so compressed the trachea as to produce dyspnoea, surgical intervention was called for, whatsoever the hazard: the pituitary "goitre" similarly affected the optic chiasm by pressure, and unless this was relieved blindness might ensue. And so when ways of operating upon these more common pituitary tumors came to be devised and surgeons with increasing confidence began to attack them and to provide tissues for study, they were found to be adenomas of an altogether different kind from those which accompany acromegaly.

THE ADENOMAS IN GENERAL

Experimentation is by no means confined to the laboratory. The putting of ideas to the test with the elimination of error by trial is also necessarily the practice of the clinic. This is well exemplified in the case of the adenomas of the secretory organs, once regarded merely as curiosities of morbid anatomy but now shown to be functionally active conglomerations of cells which may disastrously upset the physiochemical balance of the body. Through their hypersecretory effects, they lead to recognizable states the contrary of those expressions of glandular inactivity seen in myxoedema, tetany, diabetes mellitus, or Addisonism. One after another they are coming to be recognized. The relation of the thyroid adenomas to hyperthyroidism was first brought to our attention. Then came the knowledge that the adenoma of acromegaly caused its effects by an excess of a normal secretion rather than by some abnormal secretory product as had been surmised. In its turn the association of hypertension

with suprarenal tumors, particularly those composed of chromaffin cells, began to be looked upon as the symptomatic verso of Addison's disease.[1] Then the syndrome of hyperparathyroidism (osteomalacia with muscular hypotonia, multiple bone tumors, and abnormal excretion of calcium) due to a predictable adenoma of one of the parathyroid glandules was in its turn disclosed.[2] And on the heels of this discovery the conjecture that certain clinical states, which bear a symptomatic resemblance to the effects of overdosage with insulin, might be due to an adenomatous hypersecretion of the pancreatic islets has become an established fact. At the time of this writing in my own clinic an exploratory operation on a patient with recurrent attacks of hypoglycaemia has revealed a small removable pancreatic adenoma composed of islet tissue.[3] And to these known hypersecretory syndromes may now be added that caused by a pituitary adenoma of basophil elements the consideration of which must, for the moment, be deferred.

How much more of this lies ahead of us may easily be imagined, and were it merely a question of recognizing, one after another, the clinical syndromes produced by the adenomas of each particular gland, we might expect to advance with unfaltering step. But there are pitfalls in the way, and one of them is the functional interdependence of these glands.

THREE PITUITARY ADENOMAS IN PARTICULAR

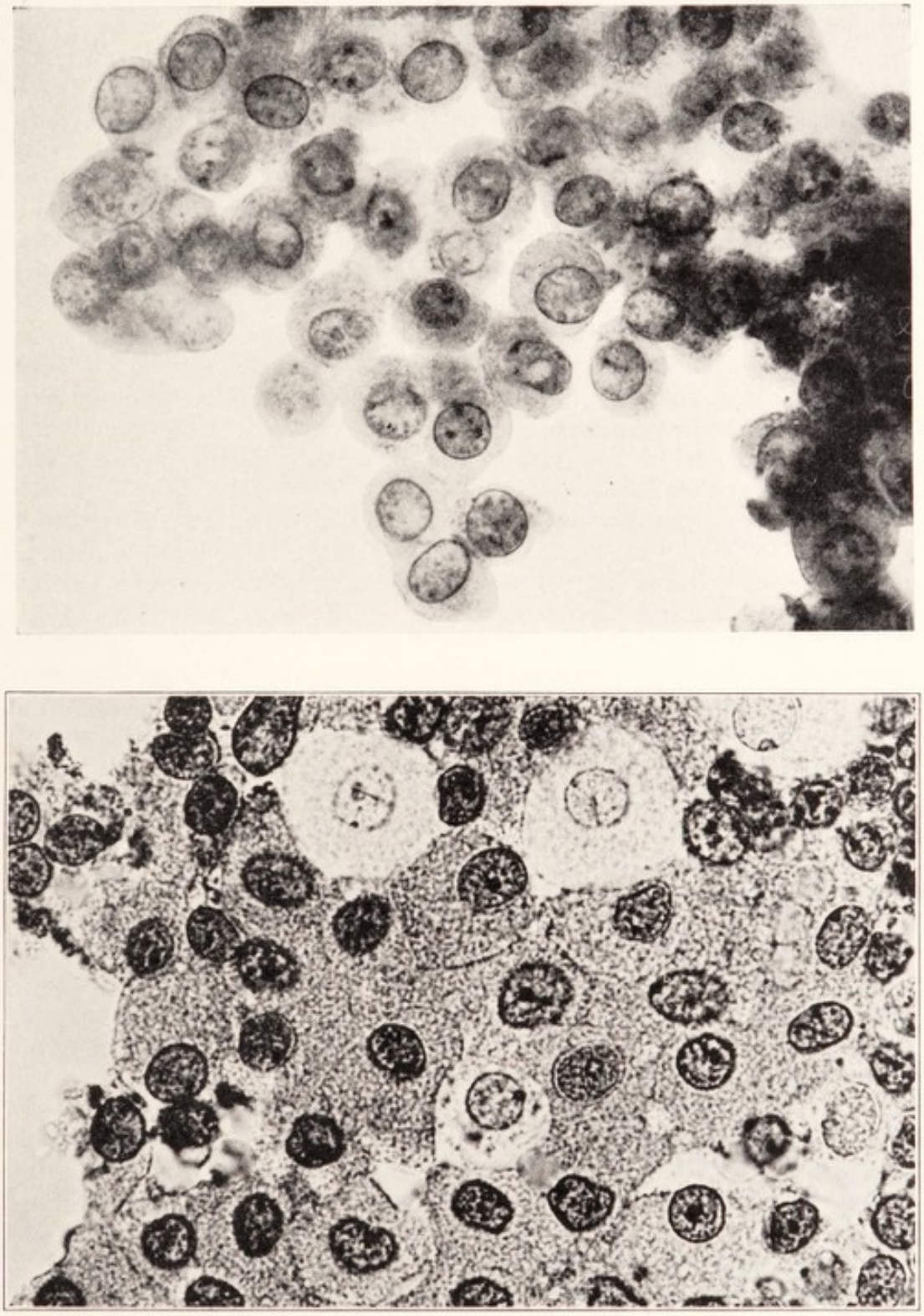
That the histological structure of the anterior hypophysis is complex need scarcely be recalled. There are three types of cells easily distinguishable by their differing affinity for dyes. One type, of whose function we know next to nothing, has a feebly staining (chromophobe) non-granular protoplasm. The other two types, of which far more is known, are characterized by a coarsely granular and chromophilic protoplasm, the granules of the one being acidophil and of the other basophil. These tinctorially distinguishable cells are distributed somewhat indiscriminately throughout the gland, and cytologists have been at a loss to know whether they merely represent differing stages of activity of one and the same cell, or whether they have gained morphological and functional independence. It is safe to assume that they have.

As already mentioned, there are two well-known varieties of pituitary adenoma, chromophil and chromophobe (Figs. 6 and 7), each having its distinctive constitutional manifestations as something wholly apart from the local or pressure effects of the tumor itself—the so-called "neighbourhood symptoms" which chiefly call for surgical intervention. The early

[1] C. H. Mayo has reported a case of paroxysmal hypertension associated with a tumor of this sort which was predicted and removed at operation, *Jour. Amer. Med. Assoc.* 1927, LXXXIX, 1047.

[2] *Cf.* General reviews of the subject by R. M. Wilder (*Endocrinology*, 1929, XIII, 231): also by Donald Hunter (*Proc. Roy. Soc. Med.*, 1929, XIII, 27); *cf.* his Goulstonian Lectures, *The Lancet*, April 26, May 3, and May 10, 1930.

[3] An equally clean-cut case, likewise with disappearance of symptoms after surgical removal of the adenoma, has been reported by Howland, Campbell, Maltby and Robinson, *Jour. Amer. Med. Assoc.*, 1929, XCIII, 674.



FIGS. 6 and 7.—Supravital preparations by Dr. Louise Eisenhardt of living cells removed at operation. A chromophobe adenoma (above) to be contrasted with the same type of preparation of a granular chromophil adenoma (below). *Cf.* Figs. 32, 33, pg. 116.

experimental ablations of the anterior hypophysis in adult animals (1909) led to a condition resembling that produced by the chromophobe adenomas in man, and which therefore must represent a deprivation syndrome (hypopituitarism) as opposed to the syndrome of acromegaly (hyperpituitarism). All this was in correspondence with what had been long established regarding the thyroid, and though as a working hypothesis it served a useful purpose for some years, it now proves, in one important respect, to be quite inadequate. A striking feature of the deprivation syndrome whether observed clinically or produced experimentally, was, as we have seen, a sexual dystrophy accompanied by demonstrable regressive changes in the reproductive apparatus. That a corresponding change in the organs of sex was known to accompany the supposedly counterposed states, represented by gigantism and advanced acromegaly, was difficult to reconcile with the assumption that these states were a consequence of secretory overactivity pure and simple. Some unknown but predictable element governing the functions of sex was unquestionably present. This element has been disclosed.

Its discovery was primarily the outcome of Stockard's observation (1917) that in the guinea-pig ovulation could be foretold by a periodic change in the cellular character of scrapings from the vaginal mucous membrane. On testing this out in the rat, H. B. Evans discovered (1921) the existence in these animals of a clock-like four-day ovulatory mechanism; and in the effort to modify this cycle by the injection of various ductless gland preparations, he found that the emulsion of fresh anterior pituitary substance served not only promptly to interrupt oestrus but, when long continued, to cause pathological overgrowth. When, however, the female rats in which the experimental gigantism had been produced came to be sacrificed, their ovaries were found to be greatly enlarged by an excessive luteinization of unruptured follicles within which the ova were imprisoned, thus accounting for the interruption of oestrus. This process, as it happens, is not what leads to the amenorrhoea of acromegalic women, nor was any corresponding follicular luteinization observed by Putnam, Benedict, and Teel (1929) in their dogs with experimental acromegaly; but the observation nevertheless gave a possible explanation for the seeming inconsistency that both hyper- and hypopituitary states served in women to inhibit the ovarian cycle.

Meanwhile, in working on the deprivation syndrome in rats, P. E. Smith showed, to make the long story short, first that the dystrophic genital apparatus could be reactivated by the repeated reimplantation of fresh anterior lobe substance, and also that these effects were more prompt and striking when that portion of the bovine gland particularly rich in basophil elements was used for the purpose. What is more, it was learned that after castration the anterior hypophysis becomes more or less engorged with basophil elements and that pituitary glands so modified are particularly effective in restoring experimentally produced sexual dystrophy; and soon it was discovered that precocious maturity could be induced in infant rats and mice by implantation of hypophysial

tissue or by the injection of glandular extracts containing the sex principle alone.

At the time of Evans's early experiments, in which an emulsion of the fresh anterior lobe was used, the presence of two hormones was not yet suspected, but the successful separation from the gland of the two substances in active form has since been accomplished, the problem of isolating the sex substance having recently been greatly simplified by Zondek and Aschheim's happy discovery (1928) of its presence in the blood and urine during pregnancy.* There is much more about these later-day revelations than space can be given to recount. For present purposes it must suffice to say that the existence of these two chemically separable principles in the anterior lobe obliges us to abandon, or at least to modify, the simple conception of hyper- and hypo-pituitary states as based supposedly on the effects of a growth principle alone.

Clinicians for many years have been puzzled by a peculiar syndrome (improperly called polyglandular, for all pituitary syndromes are essentially polyglandular) characterized by an exaggeration of the secondary characters of sex. That this disorder might possibly be laid at the door of the basophil elements of the anterior pituitary was a natural assumption in view of the disclosures regarding the probable relation of these cells to the sex hormone in question. It is the prepared mind that knows what to look for, and at the autopsy on a victim of this disorder, who had died from an intercurrent infection, Dr. Teel has had the good fortune to find a small but unmistakable basophil adenoma associated with hypertrophic changes in the ovary. It is a discovery which promises to clarify much that has heretofore been nebulous. Basophil adenomas have been previously described, but Teel's, so far as I am aware, is the only recorded instance of a lesion of this type that has been predicted on symptomatic grounds and subsequently verified.†

This independent rôle of the basophil cells provides an explanation for the apparent symptomatic inconsistencies between the hyperpituitary syndrome of acromegaly and the opposed hypopituitary state produced by adenomas of chromophobe type in so far as both are prone to cause comparable dystrophic alterations in the organs of sex, particularly noticeable as amenorrhoea in women. The idea that the discrepancy might be ascribed to the tumor irrespective of its peculiar secretory character was the outcome of a recent study of the results of operations for suprasellar lesions that provoke what is known as a chiasmal syndrome with little or no enlargement of the pituitary fossa. Tumors of various kinds will produce this combination of symptoms, some of them being hypophysial adenomas of chromophobe type in which no secondary constitutional evidences of the lesion such as amenorrhoea are present. In other words, the normal function of the anterior hypophysis remains unaffected

* [This proves not to be so simple, for doubt is now (1932) cast on whether the sex-maturing substances in pregnant urine and pituitary gland are actually the same.]

† [*Cf.* the separate discussion of pituitary basophilism in a later paper, pg. 113.]

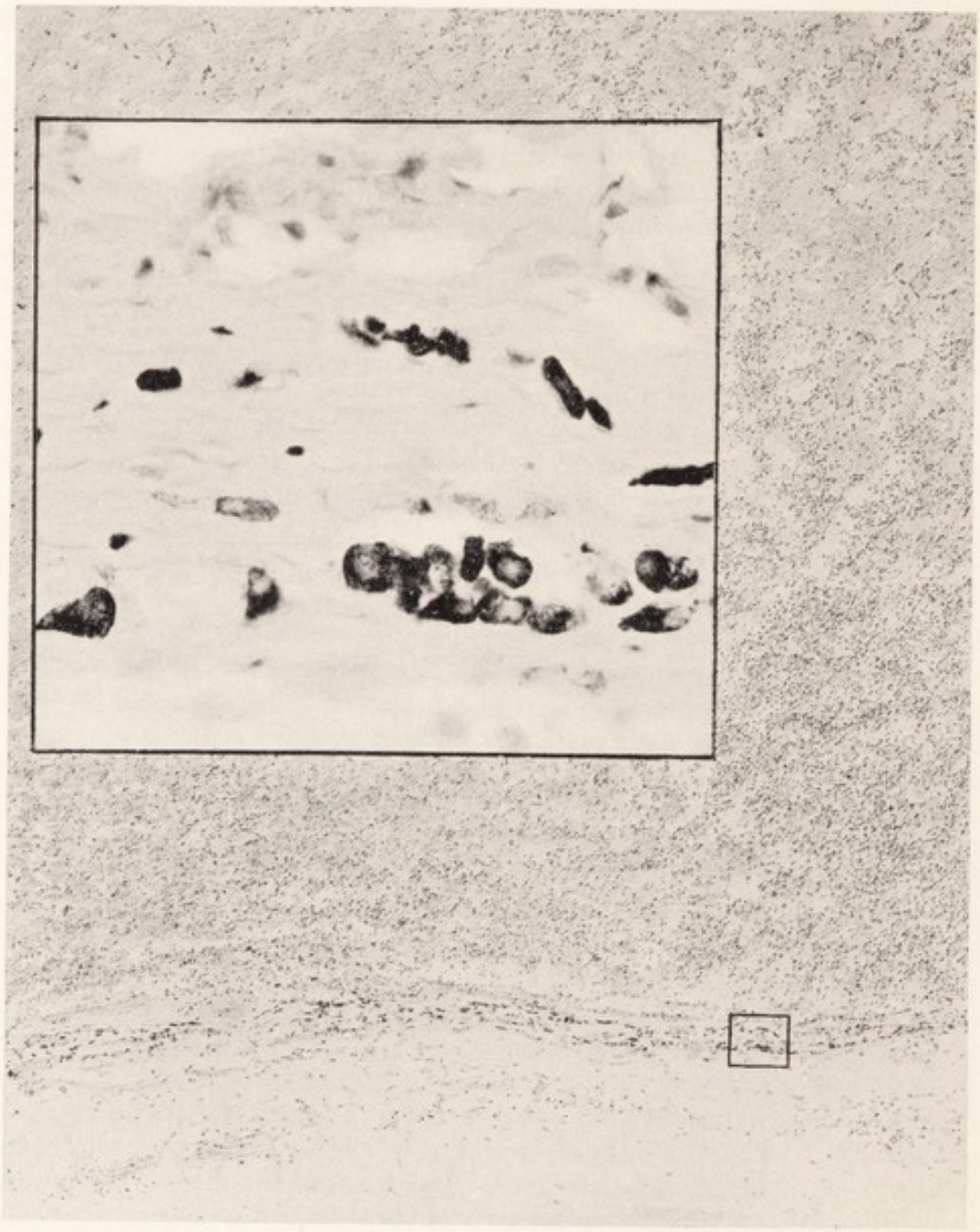


FIG. 8.—Margin of large chromophobe adenoma, ×50, stained with ethyl violet-orange G for granules. Note peripheral rim of compressed granular cells shown in insert, ×600.

under these circumstances, whereas should a growing adenoma of the same type be confined within the sella, amenorrhoea will invariably appear as its first symptom.[4]

Further to illumine this matter, the records of our entire series of verified adenomas have been reviewed by Mr. William R. Henderson, and it

[4] Cushing, H., "The Chiasmal Syndrome of Primary Optic Atrophy and bitemporal Field-defects in Adults with a normal sella turcica." *Arch. Ophthal.*, 1930, III, 505–551 and 704–735.

has been found to be generally true that whether the tumor were chromophil in association with acromegaly or of the chromophobe variety, it was only when the pituitary fossa had become greatly expanded by intrasellar pressure that definite interruption of the functions of sex were certain to occur. Hence it may be assumed that the secretory activity of the basophil cells, which have to do with the reproductive activities, has become inhibited purely by the effect of pressure; and, in further support of this, the fact may be mentioned that in favourable cases, after partial surgical extirpation either of a chromophobe or an acidophil adenoma in women, normal menstruation may be resumed and childbearing occur.

All this, of course, applies no less to men who are afflicted with these processes than to women, and the general principle whereby an hypophysial adenoma of a given cellular type may so squeeze the cells of all other types against the relatively unyielding sellar envelopes as to render them inert, is particularly well shown by the symptomatic consequences of chromophobe adenomas that have happened to occur in childhood. For then both acidophil and basophil cells are thrown out of action sufficiently early to cause cessation of growth and failure of maturation. The highly compressed residue of the gland may sometimes be histologically identified at the periphery of one of these expanding tumors (Fig. 8).

Thus we begin to understand somewhat more clearly the nature of these anterior hypophysial tumors, whose symptomatology depends, to state the matter concisely: (1) on the elaboration of a growth-inciting hormone in the absence of which dwarfism occurs; (2) on the elaboration of a gonadal stimulating hormone without which the normal maturation of the ovarian follicle cannot occur; and (3) on the presumptive elaboration of still another hormone (as yet unproved) that governs the normal function of thyroid, parathyroid, and adrenal cortex.* To be sure, there is much still to learn, for the function of the cells comprising the chromophobe tumors remains unknown, but even so distinct a forward step has recently been taken, which brings the pituitary body again to the fore after a period of doubt raised by those who were led to ascribe most if not all of its presumed functions to an independent hypothalamic source.

III. LOCAL TUMORS AND THEIR EFFECTS

In the foregoing consideration of the pituitary adenomas and their symptomatology, nothing has been said, as will be observed, of that part of the dual structure in whose extracts a functionally active substance had first been detected. Indeed, by the time the sella turcica has become widely distended by a large adenoma, the posterior lobe will have disappeared without recognizable trace. And when added to this one takes into consideration the negligible effect of experimental ablation of the posterior lobe, it would appear that, if there is actually anything vestigial

* [Since both acidophil and basophil elements may produce striking secondary changes in the subsidiary endocrine organs, such as are now known to accompany pituitary basophilism (*cf.* pg. 157) as well as acromegaly, it hardly seems necessary to postulate this third hormone.]

about the pituitary body as a whole, it is this very portion which first excited physiological interest.

Meanwhile, however, an hypophysial tumor of quite another type which often begins seriously to affect the normal activity of the gland in preadolescence, had come to be studied with the unfolding of quite a different clinical story. Nearly a century ago (1838) Rathke had taught us how an epithelial invagination from the primitive pharynx meets the infundibular outpocketing from the base of the cerebral vesicle to form the dual gland. Naturally enough in this complicated formation, with the subsequent obliteration of the craniopharyngeal duct, epithelial "rests" may get sidetracked, and lead later on to anomalous tumefactions. On this basis we account for the variously named parahypophysial tumors of congenital origin which, for want of an inclusive term, may conveniently be called craniopharyngiomas.

Now these congenital tumors, which are surprizingly common, differ greatly in situation, size, and behavior. They may be wholly intrasellar or wholly suprasellar. They may produce symptoms in preadolescence, or symptoms may be delayed until late in life. They vary in size from small, pea-sized cysts to huge, multilocular cystic lesions or to solid, calcareous masses as large as a tennis ball. One thing, however, they share in common, a capacity to damage by compression one or more of the neighboring structures, anterior hypophysis, posterior hypophysis, pituitary stalk, tuber cinereum, chiasm and hypothalamus. Depending, therefore, upon the tumor's precise point of origin as well as upon the age at which its pressure effects begin to manifest themselves, there may be produced the greatest possible variety of local and constitutional symptoms, many of which are largely foreign to the adenomatous lesions which, up to this point, have alone been under consideration. Notable among these new symptoms are polyuria and adiposity in varied combinations with impaired growth and sexual dystrophy.

HYPOTHALAMUS *versus* HYPOPHYSIS

It has been said that if some unusual clinical condition turns up concerning which one seeks information, an account of it is likely to be found in Jonathan Hutchinson's Archives. To this I would like to add, particularly for the benefit of the neurologists, that if Hutchinson fails, try Bryom Bramwell. In his much neglected book on intracranial tumors published in May of 1888, only two years after Marie's description of acromegaly, it is stated:

> Tumours of the pituitary body are in many instances attended with an excessive development of the subcutaneous fat, and in some cases with the presence of sugar in the urine, or with simple polyuria (diabetes insipidus). Whether these symptoms are due to the fact that the pituitary body itself is diseased, or whether as seems more likely, to the secondary results which tumours in this situation produce in the surrounding cerebral tissue, has not yet been decided. Possibly, as Rosenthal has suggested, the diabetes, which is sometimes present, may be the result of secondary changes produced in the grey matter of the floor

of the fourth ventricle. He supposes that the pressure of the tumour first produces irritation of the grey matter lining the third ventricle, and that this irritation travels along the grey matter which connects the third and fourth ventricles and produces secondary changes in the latter.

Medicine was not yet prepared to grasp the significance of this truly prophetic statement; indeed, at the time it was written it was not as yet known with certainty that the malady of Marie had any relation to the pituitary body; and, clinically speaking, the "grey matter lining the third ventricle" was undiscovered country. Thirteen years elapsed before Alfred Fröhlich's description of one of these cases was published as an example of "hypophysial tumor without acromegaly" which shows how confused were the ideas of pituitary function in those days of the widely discussed syndrome of adiposogenital dystrophy. Much still remains obscure, but one can at least now clearly see that the skeletal and sexual infantilism which accompanies such of these tumors as begin to cause symptoms in childhood is due to compression of the anterior hypophysis with consequent inactivation of the acidophil and basophil elements that provide, as we have seen, the hormones of growth and sex. The dwarfism and sexual dystrophy which often accompany these tumors thus become easily explained, and the same is true of the visual disturbances common to all tumors of this region that press against the chiasm; but when we come to the other manifestations of these hypophysial-duct tumors, we find ourselves on less secure ground.

The detailed post-mortem study of one of these lesions found in the body of an adult adipose dwarf led Erdheim (1916) to express the view that adiposogenital dystrophy is nothing more than pituitary dwarfism *plus* adiposity, the latter feature of the syndrome being ascribable to an involvement of the base of the brain—*adipositas cerebralis*. Thus nearly thirty years after Bramwell's statement, attention was again drawn to the possible participation of the hypothalamus in the symptomatology of pituitary lesions. And when this revived conjecture came to be followed a few years later by the disclosure at the hands of Camus and Roussy (1920) and of Bailey and Bremer (1921) not only that an experimental polyuria can be produced by injuries restricted to the tuber cinereum, but that adiposity, sexual dystrophy and, as Roussy believed, even dwarfism as well might sometimes ensue, our accepted views of the relation of these symptoms to the pituitary body itself were badly shaken. One or another, these authors, independently, have gone so far as to express doubts as to whether the pituitary body played any part whatsoever in the hypopituitary effects previously ascribed to it—a challenge which produced a veritable bouleversement of our cherished preconceptions.

Because of these disclosures, most of the earlier experimental hypophysectomies on dogs unquestionably lie open to the just criticism first raised by Aschner (1912) that a coincidental damage of the adjacent tuberal nerve centres probably accounted for the post-operative polyurias and glycosurias, as well as the more tardy adiposity and genital atrophy that not infrequently supervened. Whether the canine gland was ap-

proached from below through the pharynx or from the side by elevating the temporal lobe, these secondary symptoms were apt to ensue. In the rat, however, as in man, the gland is overlain by a dural diaphragm merely perforated for the passage of the stalk, so that either the nervous tissues and pars tuberalis above or the body of the gland below can be separately subjected to experimental lesions. Taking advantage of this fact, P. E. Smith, after devising a parapharyngeal method of exposing the gland in these animals, has shown[5] that a subdiaphragmatic hypophysectomy leads only to those inhibitions of growth and of sexual activity with which we are now familiar: when, on the other hand, the tuber is injured by a supradiaphragmatic attack, an adiposity which at times is truly astounding, may be produced with little if any secondary effect on the functions of growth and sex. Though Smith has made no mention as yet of polyuria in his highly important series of papers, this want has just been supplied by Richter,[6] who, by an accurately placed stab-wound through the base of the rat's skull just anterior to the hypophysis, has produced a persistent polyuria in a series of animals (a ten-fold increase in one instance) in the absence of any ensuing adiposity. By these experiments a strictly hypothalamic syndrome as opposed to a strictly pituitary one has seemingly therefore been produced, there being no apparent overlap in the symptoms.

In consequence of all this, the attention of neuro-anatomists, pathologists, physiologists and psychiatrists who share an interest in the nervous system has come of late years to be riveted on that much neglected portion of the palaeo-cerebrum which lies, roughly speaking, within the bounds of the Willisian circle. In the walls of the third ventricle, with its dependent infundibulum and tuber, various clusters of nerve-cells have been described with complicated tracts running between them. It has come to be appreciated, meanwhile, that these centres are particularly vulnerable to the effects of encephalitis after which diabetes insipidus, obesity, somnolence and so on are frequently observed. What is more, experimental hypothalamic injuries, other than those confined to the tuber, which so markedly disturb the water-balance and fat deposition, have disclosed in the anatomically insignificant 'tween-brain hitherto unsuspected activities, vegetative and emotional, of utmost functional consequence, the separate consideration of which must for the moment be postponed.

IV. THE POSTERIOR HYPOPHYSIS

It will be seen from what has gone before that, during the past decade, attention on the one hand, with great profit, has come to be focused on the anterior-pituitary lobe which proves to be the "moderator" of the endocrine series, and that, no less profitably, attention has been drawn in

[5] Smith, P.E., "Hypophysectomy and a Replacement Therapy in the Rat," *Amer. Jour. Anat.*, 1930, XLV, 205. [A modified and uniformly successful method of hypophysectomy has recently been described by my assistant, Dr. K. W. Thompson (*Endocrinology*, 1932, XVI, 257–263.)]

[6] Richter, C., "Experimental Diabetes Insipidus," *Brain*, 1930, III, 76.

the other direction to the fundamentally significant region at the base of the brain known as the diencephalon. The posterior lobe, meanwhile, has lain unattended in the shadow between these two fires, though there are abundant reasons, other than the known activity of its extracts, for lifting it from its obscurity. Certain of these reasons, both developmental and histological, may be mentioned.

That portion of Rathke's pouch, which comes in contact with and ultimately envelops the down-growth of nervous tissue comprising tuber and pars nervosa, acquires epithelial characteristics quite different from those of the highly vascularized pars anterior. Indeed, this contact is essential for the normal development of the gland, as has been shown by the non-appearance of the infundibular protrusion in the tadpole when the epithelial component of the future gland has been cleanly removed, and by its normal development if a mere epithelial fragment is left behind; and what is more, as recently shown by Blount,[7] the epithelial rudiment of the gland when transplanted in amphibian embryos fails to develop unless some of the nervous tissue is taken with it.

Histological evidences of posterior-lobe activity are based on the presence of a demonstrable secretory product and on the presence of non-myelinated nerve-fibres. In the fully formed adult gland under certain experimental or pathological conditions, one may see viable cells from the pars intermedia streaming into the posterior lobe in great numbers. Even under normal circumstances, as first described by Herring (1908), the pars intermedia cells appear to invade the pars nervosa becoming transformed into hyaline bodies which stream upward toward the ventricle between what appear to be loosely textured, long-drawn-out tails of ependymal glia. It has been shown, moreover, that if the hypophysial stalk is mechanically obstructed, the secretory product becomes dammed back in the lobe which becomes turgid with hyaline. There is strong evidence, therefore, to indicate that these Herring-bodies represent the secretory principle (hormone) which acts either directly on the nervous centres of the tuber, as some assume, or actually passes between the ependymal cells into the infundibular cavity as others have believed. As a matter of fact, under either assumption the hormone might well enough affect the nerve centres, one of the more important of which lies directly under the ependyma; and evidence will be presented to show that posterior-lobe extracts are far more potent when injected into the cerebral ventricles than by any other means of administration.

When studied by ordinary methods of fixation and staining, the posterior lobe has a nondescript appearance. The hyaline is usually dissolved out of its channels, and some chemical property in the lobe apparently counteracts the usual effect of the special stains for which glia and nerve-fibres elsewhere show marked affinity. When successfully stained, however, non-myelinated nerve-fibres in abundance, are found to converge at the infundibulum, whence in a compact bundle they pass down the pituitary stalk to enter the posterior lobe. This was first briefly

[7] *Proc. Nat. Acad. Sci.* Washington, 1930, XVI, 222.

pointed out by Ramón y Cajal who found (1894)[8] in two-day-old mice that from a cell-mass behind the chiasm a bundle of axis cylinders descended along the infundibulum. More recently these fibres have been traced by Greving[9] and Pines,[10] from both the supra-optic and paraventricular nuclei, though more particularly from the former. The fibres not only ramify widely throughout the pars nervosa, weaving themselves, as Greving states, in "basket-like" fashion around what appear to be secretory islands, but they also, according to Pines, can be traced in among the epithelial cells of the pars intermedia. With this the recent observations by Croll[11] and unpublished studies from my own laboratory[12] are in full agreement (Figs. 9 to 12).

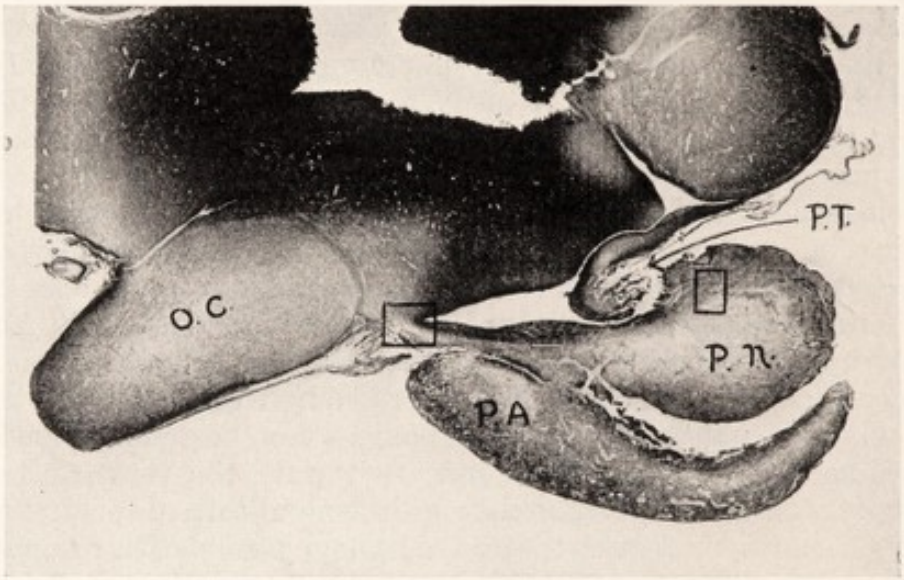


FIG. 9.—Illustrating the Tr. Supraoptico-hypophyseus (Greving). Sagittal section of canine diencephalon just to the left of midline. O.C.: optic chiasm; P.A., pars anterior; P.N., pars nervosa; P.T. pars tuberalis. (×8.) Squared areas finders for Figs. 10 to 12.

This abundant nerve supply from interbrain to gland was unknown both to Camus and Roussy and to Bailey and Bremer whose revolutionary papers appeared between 1920 and 1922. There nevertheless lay before them the inescapable fact that extracts of the posterior lobe could check the more immediate and striking of the symptoms which their tuberal injuries provoked. But even P. E. Smith in a more recent brief description[13] (1930) of the symptomatic effects of dividing the tuber in

[8] *Ann. de la Soc. Espan. de historia natural*, 1894, 2 ser. III, 214 with figure.

[9] Greving, R., *Klin. Wchnschr.*, 1925, IV, 2181; *also: Deutsches Ztschr. f. Nervenh.*, 1926, LXXXIX, 179–195.

[10] Pines, I.-L., *Ztschr. f. d. ges. Neurol. u. Psychiat.*, 1925, C, 123–138.

[11] Croll, M. M., *J. Physiol.*, 1928, LXVI, 316–322.

[12] In our experience they are best shown by De Castro's method, but the tissue must be removed and fixed at the earliest possible moment after death.

[13] Smith, P. E., "Hypophysectomy and replacement therapy in the rat," *Am. J. Anat.*, 1930, XLV, 205–273.

rats fails apparently to take into consideration what may happen to pars intermedia et tuberalis when deprived of its neural connections. And there is still another consequence of tuberal injuries which must be borne in mind; for they are almost certain to interfere with the blood supply to the gland, a varying amount of central necrosis in the pars anterior being the usual sequel of stalk separation.[14] What is more, experimental evidence is accumulating which speaks in favour of the view that the epithelial investment of the infundibular lobe, whether as pars intermedia or pars tuberalis, has essentially the same function.

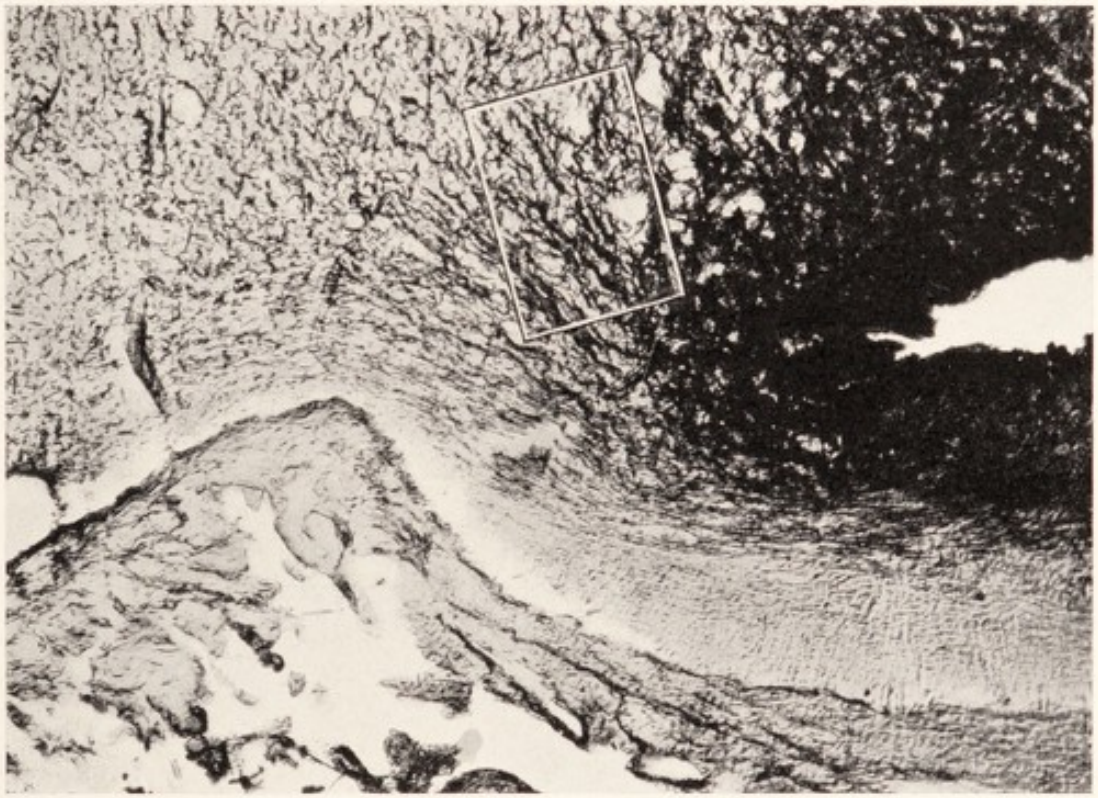


FIG. 10.—Squared area from Fig. 9 to show concentration of fibres entering antero-lateral wall of tuber at turn of ventricle. (×175.)

[14] Dandy and Geotsch, at the writer's suggestion some years ago (*Amer. Jour Anat.*, 1911, II, 137), described merely the chief source of the arterial supply to the canine gland. There has been great need of further and more detailed studies of the entire circulatory apparatus; and this want, I am permitted to state, has been filled by Popa and Fielding whose important paper from the Institute of Anatomy at University College entitled "A Portal Circulation from the Pituitary to the Hypothalamic Region," appeared in the *Journal of Anatomy*. [Oct. 1930, LXV, 88–91.] [M. A. Basir (The vascular supply of the pituitary body in the dog. *J. Anat.*, April 1932, LXVI, 387–398) recently pointed out that the systemic vessels to the hypothalamic nuclei are enclosed in a perivascular space whereas the hypophysio-portal supply to the nuclei of the tuber appear to be without such a space and form a well marked capillary plexus under the ependyma, particularly in the region of the nucleus paraventricularis where, in the dog, the ependyma is modified by long tubular gland-like structures.]

In one or all of these three factors—nerve-supply, blood-supply and epithelial cuff of tuber—lies the probable explanation of much that has been contradictory in regard to the effects of experimental hypophysectomy as opposed to injuries of the tuber, more particularly in the dog, but probably in the rat as well. This intermediary neuro-epithelial structure the posterior lobe therefore, cannot be lightly pushed aside in our temporary excitement over the diencephalon and its newly disclosed functional importance. Whether the several known responses to the injection of its extract are due to a single chemical substance or to more than one, is less important than the knowledge that striking physio-

FIG. 11.—Squared area from Fig. 10 to show character and abundance of fibres. (×600.)

logical effects ensue—*haemodynamic*, *antidiuretic*, and *oxytocic*—to which *pigmentary*, *galactagogue*, *antipyretic* and *sudorific* effects may possibly be added. Let us, in the order of their discovery, take up these known responses and see what can be learned in behalf of this symptomatically neglected portion of the gland.

THE BLOOD-PRESSURE-RAISING EFFECTS

Whereas in all studies of adrenal function the haemodynamic properties of its extracts overtop all else, the comparable effects produced by an extract of the posterior hypophysis have been entirely lost sight of. Had not physiologists so conclusively shown that the rise in blood pressure which accompanies emotional states is associated with an increase of adrenalin

in the blood, one might rather have expected to find that the pressor reponse had come from the posterior-pituitary hormone. For, at least, the neural mechanism which controls it, is near at hand whereas the pathway of fibre tracts from hypothalamus to adrenal medulla is devious and long. What part the posterior lobe may conceivably play in paroxysmal hypertension might well be worth looking into, most other likely sources of information to explain these states having been exhausted. [*cf.* pg. 113, et. seq.] A surgical clinic, however, has less to do with irritative or emotional processes than with destructive ones produced by tumors; and these, apart from the functionally active adenomas I have mentioned, can only be expected to evoke symptoms due to loss of activity.

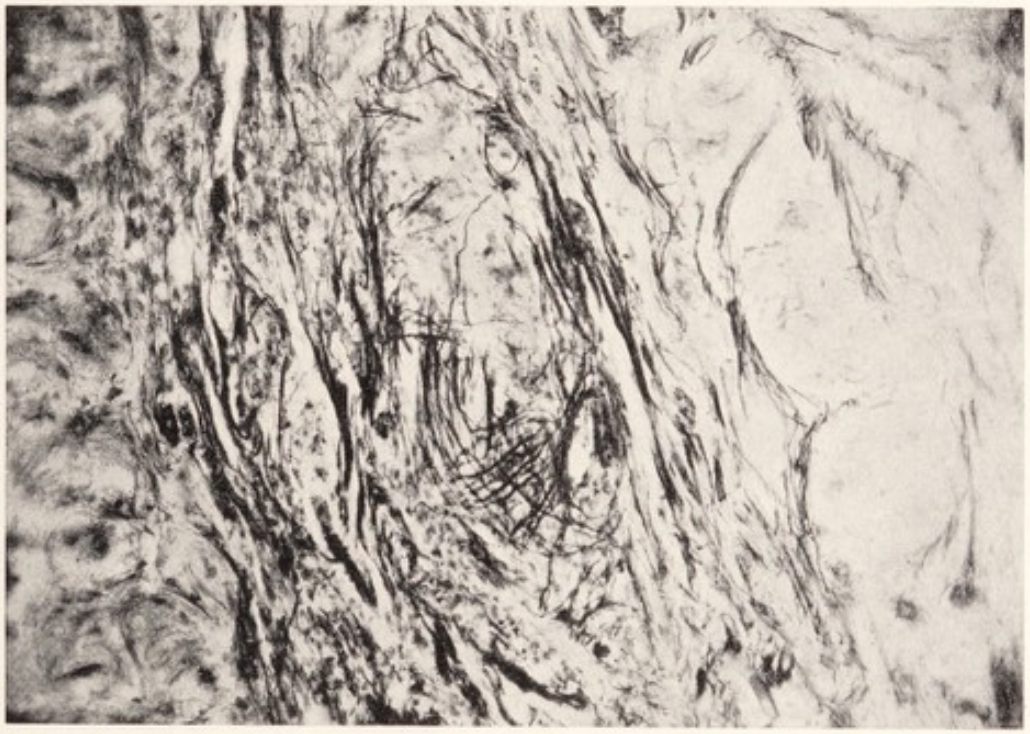


FIG. 12.—Squared area in posterior lobe from Fig. 9 showing basket of fibres about a "secretory island" and fibres (to left) coursing in pars intermedia. (×200.)

Most patients with craniopharyngiomas which have served to compress the pituitary stalk, as these tumors commonly do, have an unaccountably low blood-pressure. Even in adults, a systolic pressure in the 90's is common, and registrations of 85/60 in a patient of 21, of 60/50 in a patient of 23, and of 80/60 in a patient 30 years of age occur in the hospital series. Still more to the point is the fact that patients with large chromophobe adenomas, which remain confined within the sella and compress the posterior lobe but leave the hypothalamus unaffected, usually have a relatively low systolic blood pressure (below 100 in 11 per cent and below 110 in 46 per cent of the cases).

Beyond this we have nothing much to go on. What is more, confession must be made that two out of our series of 243 patients with verified

chromophobe adenomas had coincidental vascular hypertension.[15] In want of a satisfactory explanation of these exceptions to the general rule, it must be admitted that from a clinical point of view the posterior lobe has no such definite influence on blood-pressure as the laboratory experiences with its extract would have led us to expect.

THE ANTIDIURETIC EFFECTS

How it is that the polyurias produced by various tuberal lesions can be counteracted by the injection of posterior-lobe extract remains unexplained by those who ascribe to the hypothalamus an independent rôle in the production of the phenomenon. Doubtless in all the experiments of years past, too much attention had been paid to the symptoms of thirst and polyuria and too little to symptoms the opposite of these, oliguria having been observed not infrequently as a sequel of our early (1908–10) canine hypophysectomies. It may be stated, however, that the large intrasellar adenomas which are almost certain to obliterate the posterior lobe, are not accompanied by polyuria, unless in the process of removing one of them the ventricular wall adjacent to the chiasm should happen to be injured. This would speak strongly in favour of the independent hypothalamic origin of diabetes insipidus were it not for the abundant nerve-fibres that sweep around both sides of the chiasm and descend, as we have seen, in the walls of the tuber and infundibulum to their destination in the posterior lobe.

Owing to a continued interest in the problem of how the active principle of this part of the gland gets into operation, some further experiments have been made by Dr. Maddock in the surgical laboratory at Harvard by the application of silver "clips" at various levels on the hypophysial stalk. That such an occlusion of the stalk leads to a damming back of the hyalinoid substance elaborated in the posterior lobe, first reported with Emil Goetsch (1910), was again alluded to in my Cameron Lectures (1925); but what is more pertinent to our present theme is that polyuria may be produced in this way without extravasation of blood or such widespread damage as the experimental punctures are likely to occasion. In one of Dr. Maddock's animals, an enduring polyuria, which at times averaged above five litres per diem, ensued and, in the absence of any tendency to adiposity or other recognizable symptoms, persisted until the animal was sacrificed nearly two years later.

Thus, in contrast to the temporary polyurias usually produced by

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[15] It should be pointed out that these hypopituitary states are usually accompanied by a greatly lowered basal metabolic rate to which the vascular hypotension might well enough be ascribed. Opposed to this assumption is the fact that the two patients with definite hypertension also had a low basal metabolic rate. [A better understanding of pituitary basophilism (*cf.* pg. 113 *et seq.*) and its relation to hypertension makes it not improbable that the adenomas in these cases were of "mixed" basophil rather than of purely chromophobe type. At the same time, it should not be overlooked that the hypotension of chromophobe adenomas and the hypertension of basophilism are possible secondary adrenal effects due to cortical atrophy on the one hand and hyperplasia on the other.]

canine hypothalamic punctures, this clip experiment led to a more permanent disorder fully comparable to clinical diabetes insipidus. In seeking an explanation for this, I incline to the view that in the puncture experiments some of the conducting paths rather than the actual nerve centres have been damaged,[16] whereas the clip not only served to interrupt the nerve impulses to the posterior lobe but at the same time mechanically obstructed its secretion, a combination of circumstances that obtains in those tumors of the region with which diabetes insipidus is so often associated.

All this admittedly leaves unexplained why a more marked temporary polyuria does not follow the simple removal of the canine posterior lobe unless we accept Trendelenburg's recently expressed views regarding the vicarious action of the residual pars tuberalis. Indeed, it is yet a matter of uncertainty as to whether polyuria after all is a paralytic or an irritative phenomenon, for though it is commonly assumed to be the former, the familiar emotional polyurias would suggest the latter. But the experimental evidence so far contains much that is contradictory, and not until it will be possible to evolve some method of first stimulating and then of destroying the definite cluster of nerve-cells (presumably the nucleus supra-opticus) which govern the response can we begin to feel that we have touched bottom in this watery topic.

THE OXYTOCIC RESPONSE

The discovery by Dale (1906) of the specific action of posterior lobe extracts on smooth muscle, more particularly noticeable on the musculature of the pregnant uterus, has led, as is well known, to their employment in cases of delayed parturition. It was the experience of all, in the earlier experimental hypophysectomies, that when they were undertaken on a pregnant animal, abortion was inevitable, presumably from the setting free of secretion; though it is not impossible, as Aschner believes, that the effect was due to a coincidental damage of the tuber. This could be easily determined by observing the effect of an isolated tuberal injury in the pregnant rat, but so far as I know such a test has not been made. It has been shown, however, by P. E. Smith that after total hypophysectomy in the rat, which leaves the tuber untouched, the muscle-fibres of the uterus atrophy and lose their wave-like contractility; and the fact that the fibers can be restored to their normal state by hypophysial implantations serves to exclude the hypothalamus from any apparent participation in this effect at least.

The peculiarity will not escape attention that the reproductive cycle, after the act of mating, is inaugurated by discharge of the pars anterior sex hormone which initiates the sequence of events that lead to ovulation, whereas, on the other hand, the posterior-lobe secretion facilitates the termination of the cycle by expelling the foetus, both processes in all

[16] In Richter's prolonged puncture-polyurias in the rat (*loc. cit.*) it may be assumed that the supra-optic nucleus was the site of the lesion.

probability being related to some primary neuro-glandular impulses.[17]

The extract also acts, though less strikingly, on the smooth muscle of other organs than the uterus—on that of the intestine, for example. It increases intestinal peristalsis and particularly when injected intravenously may have a prompt cathartic effect. On the other hand, patients with tumors which have destroyed the pars nervosa or thrown it out of function by compression are, in many instances, notably victimized by chronic constipation.

PIGMENTARY EFFECTS

Although the standardized rat threatens to usurp the place once occupied by the frog as the principal contributor to physiological knowledge, the frog and its larvae still have ample contributions to make. Not only has embryology taught us that the rudimentary hypophysis is the first of the future endocrine organs to be differentiated, but in the tadpole its exposed position lays it open to surgical removal. When so removed, as first shown (1916) independently and brilliantly by both Allen and by Smith, the growth of the tadpole is checked, metamorphosis does not occur and the pigmentary system is so affected that the embryo acquires a silvery or albinous appearance owing to the contraction of the cutaneous melanophores. Reimplantation of the hypophysis or the parental injection of fresh pituitary emulsion serve to counteract all these effects; but of especial interest is the fact, of late strongly reemphasized by Allen,[18] that transplants of the pars intermedia from adult frogs into these albinoid tadpoles, while without effect on growth or metamorphosis, serve within a few hours permanently to expand the melanophores, with darkening of the skin. Here, then, is evidence of still another peculiar property of posterior-lobe extracts which must be taken into consideration—their influence on dermal pigments.

It is curious that the principal pigmentary disorder which is clinically recognized is that associated with Addison's disease, the adrenal glands, as may again be recalled, being in a certain sense (the analogy cannot be pushed too far) a fused neural and epithelial structure somewhat akin to the pituitary body. Pituitary disorders, though less conspicuously so, are likewise accompanied by appreciable pigmentary disturbances, and, in passing, attention may be drawn to the reputed exemption of the negro to endocrine disorders of any kind. The complexion of an acromegalic, as is well known, noticeably darkens in colour, whereas the reverse is true of hypopituitary states in which the skin shows, in addition to its other distinctive peculiarities, a characteristic pallor. Presumably, from the inability of the body to elaborate melanin, the skin of these patients no longer pigments readily on exposure to the sun, and when it does so, the exposed parts are apt to be freckled rather than uniformly darkened.

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[17] Fontes (*Compt. rend. Soc. de Biol.*, 1929, CII, 227) claims to have shown the presence of oxytocic properties in the blood at the time of labour.

[18] Allen, B. M., "Source of the Pigmentary Hormone in the Anterior Hypophysis," *Proc. Soc. Exper. Biol.*, 1930, XXVII, 504.

Whether this peculiarity of hypopituitary states would be overcome by the administration of posterior-lobe extracts has, so far as I know, never been tested.

GALACTAGOGUE ACTION

Posterior-lobe extracts were claimed by Ott and Scott (1910) to have the property of augmenting the quantity of milk in the lactating goat, and they have since gained repute as a means of increasing the diurnal yield of cows. Whether this property has any bearing on the extraordinary prolongation of the period of lactation which sometimes afflicts acromegalic women after childbearing seems most unlikely. Examples of continued lactation for as much as seven years has been recorded, and in one of my patients it has persisted for over five. It is reasonably certain that a hormone from some source incites the mammary changes that accompany lactation, but it is more probable that it is liberated from some pelvic organ modified by the chain of events accompanying pregnancy than that it should hark back to the pituitary body (far less its posterior lobe) which set these events going.

The possibility that posterior-lobe extract may exercise an hitherto unobserved *antipyretic effect* and also a *sudorific effect* has been suggested by the lowering of body temperature and by the profuse sweating that follows the injection of pituitrin directly into the ventricle. There will be occasion to return to this possibility later on [*cf.* pg. 41].

V. LOCALIZATION OF FUNCTION IN THE INTERBRAIN

It can be gathered from what has gone before that indications of posterior lobe participation in our several hypophysial tumor-syndromes are, to say the least, inconspicuous, and what slight evidence of such participation there may be has been lost sight of, owing to the recent diversion of our attention to the adjacent walls of the third ventricle. To this region we may now return, for there are other things than the polyuria and adiposity already briefly considered, such as sugar metabolism, the thermo-regulatory mechanism, and the phenomenon of sleep, with which in the past the pituitary body had supposedly had something to do, and which it may yet prove to have.

When one speaks of localization of function in a given part of the brain, it means nothing more than that the nerve centres, which are the primary receiving or discharging stations for impulses from or to other structures, are more or less clustered, and it was with the localized accumulations of cells in the cerebral cortex that experimental neurophysiologists largely concerned themselves from the time of Fritsch and Hitzig and of Ferrier, until with Sherrington's decerebration experiments the study of the deeper and older parts of the brain really began.

What happened, for example, when the precentral gyrus was stimulated, when the calcarine cortex was damaged, when the vestibular nuclei were injured, was easily observed and comparatively easy to understand, but when glycosuria was produced by a puncture of the fourth ventricle,

rigidity by decerebration or, as now, polyuria or adiposity by an injury of the hypothalamic tracts or centres, something far more fundamental and complex has occurred. In all instances, however, it may be taken as a principle that some governing function of a given part of the brain on tissues or organs that lie outside of it has been affected, whether by irritation or paralysis.

Now in the case of the diencephalon, we are dealing with an ancient portion of the brain which remains essentially unaltered in all creatures that have a brain at all. More than that, it proves to have direct neural connections with the first of the organs of internal secretion to become recognizably differentiated and on which, as we have seen, the very perpetuation of the species depends. That structures in such close anatomical juxtaposition should be functionally independent would seem most improbable, even were their demonstrable relationship unknown.

DIABETES INSIPIDUS

Something has already been said of the presumed mechanism of the hypophysial polyurias in the brief discussion of the antidiuretic properties of posterior-lobe extract. Now that the position of the major hypothalamic nuclei are coming to be better understood both in experimental animals and man through such orderly studies as those of Malone (1910–1914) and of Rioch (1930), we may expect that someone soon will definitely determine the locus of the nuclear degenerations in those simpler cases of diabetes insipidus that are unaccompanied by tumors and which are supposedly post-encephalitic in origin. Though studies have already been made in this direction[19] and evidence strongly favours the nucleus supra-opticus, we cannot be certain about it, nor do the reports of experimental polyuria produced by hypothalamic punctures in the dog give us satisfactory histological information on this score. Certainly in none of these experiments could either of the bilaterally placed paraventricular nuclei have been completely destroyed; and the tuberal nuclei, so far as can be determined, do not represent the source of the main fibre tracts that pass down the stalk to the posterior lobe.

Reports have been made by Levy[20] (1924) of retrograde alterations in the cells of the tuberal nuclei, and by Kary[21] (1924) of changes in the nucleus supra-opticus after experimental injury of the canine posterior lobe, but what will prove more illuminating than the identification of such nuclear changes doubtless lies ahead of us in the pursuit of the secondary tract degenerations. The studies by Dr. Maddock of the tissues from his dog with experimental diabetes insipidus, which show an absence of nerve-fibres distal to the point of application of the clip, are, so far as I know, the first in which these degenerations have been investigated.

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[19] *Cf.* Eaves, E. C., and Croll, M. M., "The Pituitary and Hypothalamic Region in Chronic Epidemic Encephalitis," *Brain*, 1930, LIII, 56. These authors state that severely damaging nuclear lesions are less likely to cause diabetes and obesity than those less severe.

[20] Levy, F. H., *Zentralbl. f. d. ges. Neurol. u. Psych.*, 1924, XXXVII, 398.

[21] Kary, C., *Virchows Arch. f. path. Anat.*, 1924, CCLII, 734.

What is known as the "chiasmal syndrome" leads surgeons nowadays to the frequent exposure of this region; and as will be subsequently pointed out, neurosurgical evidence strongly favours the nucleus supra-opticus as the controlling centre for water metabolism. All this is in correspondence with the view that an experimental injury of the hypothalamic part of the mechanism in question gives the most pronounced and enduring reaction. But there is no gainsaying that posterior lobe extirpations in the absence of tuberal injury will also produce the same diuretic response, albeit a less striking one; and this P. E. Smith tells me he has observed in his hypophysectomies on the rat. Unfortunately no operation is likely to be devised which will serve to remove the epithelial investment of posterior lobe and tuber and leave the nervous structures intact, but it would probably lead to an intractable polyuria with the same certainty as would an injury of the hypothalamic nuclei. It has been shown in Tendelenburg's laboratory (1928) that after extirpation of the posterior lobe the pars tuberalis and tuber cinerum contain an abundance of the antidiuretic and oxytocic substances normally to be found there only in trifling amounts, and that only when the tuber is subsequently destroyed does a persistent polyuria occur.*

So far, then, as diabetes insipidus is concerned, the evidence at hand seems reasonably convincing that the disorder can be produced by nuclear degeneration from disease, by surgical injuries of the supra-optic region in operations about the chiasm, by the interruption of the nerve tracts in course whether from tuberal tumors, or punctures, by the experimental placement of a compressing clip on the infundibulum, and probably also (could this be accomplished) by complete removal of the epithelial investment which apparently elaborates the posterior lobe secretion—all of which indicates a diencephalo-hypophysial mechanism which can be broken at any one of three principal points—nucleus, fibre tract, and pars intermedia et tuberalis. We nevertheless, in regard to this most carefully studied of all diencephalo-hypophysial reactions, are left in some doubt as to whether the phenomenon is stimulatory or paralytic.

THE QUESTION OF ADIPOSITY†

An exaggeration of the elemental sensation of thirst is doubtless antecedent to these pathological polyurias just considered, and the imperative and irresistible call to quench it most certainly lies in this particular region of the brain under discussion. A no less primitive and equally impelling sensation is that of hunger, of which less has been said and written

* It is regrettable that the symptomatic effects of the canine hypophysectomies by improved methods, as reported by Dandy and Reichert (*Bull. Johns Hopkins Hosp.*, 1925, XXXVII, 1) were not given in greater detail, particularly since the "stump of the infundibulum and the region immediately contiguous" was cauterized in a considerable percentage of cases to ensure destruction of all epithelial elements. Of thirteen adult animals so treated, seven showed postoperative glycosuria and only five polyuria, whereas adiposity is not mentioned.

† [The relation of pituitary basophilism to acutely acquired adiposity was not appreciated when this section was written.]

in connection with the neuropituitary mechanisms. Patients with hypopituitarism, though they often become adipose, are notably small eaters, while acromegalics, on the contrary, often have a ravenous appetite scarcely appeased by five generous meals a day. This also was observed by Putnam, Teel and Benedict in their dogs with experimentally induced overgrowth.[22] In both states the sensation probably has something to do with the level of metabolism which is consistently low in hypopituitary and high in hyperpituitary states, but whence it originates (unless in the inter-brain) is less clear.

Polyuria and its antecedent polydipsia are striking symptoms, often so abrupt in onset they can hardly escape notice. The acquirement of obesity, on the other hand, is an insidious process less likely to be observed and of which hunger is not a measure in the sense that thirst is of diabetes insipidus. It consequently presents an even more difficult problem than does that relating to the water balance, though there is little question but that the two will be found to have a similar explanation.

In all that has been written about fat metabolism in relation to the hypophysis and hypothalamus, emphasis has been laid almost exclusively on adiposity and little said of emaciation. If the adiposity is an irritative phenomenon, as many assume polyuria to be, should we not expect to see a significant loss of weight as a paralytic phenomenon? The condition of adiposo-genital dystrophy has so long engaged the attention of clinicians, the fact that there are lean as well as fat types of dyspituitarism associated with hypophysial as well as with hypothalamic tumors has not received the attention it deserves (*cf.* Fig. 18).

The tendency to adiposity, which first came to be recognized (1909) in hypophysectomized dogs and which we attributed to their increased tolerance for carbohydrates, has since been ascribed, as already stated, to accidental lesions of the diencephalon produced in the course of these early and awkwardly made operations. That such injuries frequently occurred there can be no doubt, and now that Smith has shown what extreme degrees of obesity may be produced by tuberal injuries in the rat without the possibility of injury to the gland itself, the question would seem to be decided. However, in one of Dr. Maddock's tuberal clip-experiments on dogs, after only a transient polyuria, the animal in the course of the succeeding months has become extremely adipose. So it seems to me not inconceivable that interference with the function of pars nervosa et tuberalis by blockage with retention of secretion through cicatricial formation may have had some part in causing the adiposity observed in our early experimental animals.

There remains, therefore, something to be said for the participation of the hypophysis in the mechanism of fat metabolism, and Smith himself admits that extirpation of the rat's gland in the absence of tuberal injury leads in time to a certain degree of adiposity, even though it is less striking

[22] Putnam, T. J., Benedict, E. B., and Teel, H. M., "Studies in acromegaly, VIII. Experimental canine acromegaly produced by injection of anterior lobe pituitary extract," *Arch. Surg.*, 1929, XVIII, 1708–1736.

and prompt in appearance than after tuberal injuries. He nevertheless observed in his early attempts to destroy the rat's hypophysis by the intrasellar injection of a solution of chromic acid that in addition to the usual sequels of experimental ablation of the gland a marked adiposity occurred (and one may assume polyuria also though no mention is made of this) which may conceivably be accounted for by the diffusion of the corrosive along the stalk with destruction of the pars tuberalis without actual damage to hypothalamus. And in this connection may be recalled the early observations on hypophysectomized tadpoles, a large and persistent fat organ being one of the four striking changes characterizing the "pituitaryless" state. In contrast to its disappearance in the normal tadpole, this fat organ persisted in the experimental animals even on starvation. Injections of posterior lobe extract, however, led to its early absorption, which suggests that a similar treatment might have counteracted the adiposity of Smith's chromic-acid rats.

Though precise figures are not available, it has always been my impression that laboratory animals lost weight when given protracted treatment with posterior-lobe extract; the substance may, therefore, be antiadiposal as well as antidiuretic. It was shown by Coope and Chamberlain (1925) that the injection of pituitrin leads to an accumulation of fat in the liver in the course of eight to nine hours, and subsequent writers have found that the injections cause a disappearance or diminution of blood-fat, together with a decrease in the total fat of the peripheral tissues. Further studies in this direction have been carried out in Biedl's clinic by William Raab (1926–28) who has found that minute doses of posterior lobe extract (pituitrin) when injected into the cerebral ventricles cause a much more rapid disappearance of neutral fat from the blood than when large doses are administered subcutaneously. The fat, meanwhile, is accumulated in the liver where it apparently is transformed. Since this pituitrin-effect is abolished by mechanical destruction of the tuber cinereum, by transection of the cervical cord or by section of the splanchnics as well as by drugs which supposedly paralyze the centres for heat regulation (aspirin, phenacetin, etc.), it was assumed that the extract stimulates the nervous centres of the tuber whence impulses pass, presumably by the descending hypothalamic bundles, to the cord and abdominal sympathetics and thence to the liver. Since it would appear that the normal operation of this neuroglandular apparatus is essential for the storage of such fat as is not immediately utilized by the body, it is assumed by Raab that any disturbance with the mechanism from hypophysis to liver will lead to an accumulation of fat—in other words, to obesity.

Although in the clinic marked adiposity is more often seen in patients with craniopharyngiomas, which lie in a position to compress the tuberal centres, than in patients with strictly intrasellar lesions that have not extruded themselves through the diaphragma, an appreciable adiposity nevertheless occurs in these latter cases also. So it is that most patients with chromophobe adenomas in whom there is no possibility of tuberal

injury (they at least rarely if ever show polyuria) are definitely adipose. With this point in view a review of the clinical histories of our cases reveals that in about 60 per cent of the females a sudden increase of weight (occasionally extreme but averaging about 20 pounds) had occurred early in the course of the malady more or less coincident with the amenorrhoea and long before the evidences of chiasmal pressure served to call attention to the underlying hypophysial tumor. That the adiposity was not related to the amenorrhoea is shown by the fact that in approximately the same proportion of males a corresponding unaccountable early increase in weight had been recorded.

CARBOHYDRATE METABOLISM[23]

That the pituitary body was in some way related to carbohydrate metabolism was first suggested by the frequent association of acromegaly with diabetes mellitus; and when it subsequently became known that both experimental and clinical states of hypopituitarism showed a surprizingly high tolerance for sugars,[24] this was looked upon as another argument in favour of these states being the converse of acromegaly. Since that time, with the discovery of insulin and the development of ready methods of estimating blood-sugar, an intensive reinvestigation by many interested persons of the entire subject of carbohydrate metabolism has been made, and the pancreatic islets might well enough be looked upon as having the entire matter of sugar disposal under their independent secretory control.

Nevertheless, from the time (1858) of Bernard's sugar piqûre to the present day, we have been confronted by the certainty that some neurogenic mechanism lies behind the normal utilization of this form of food. Efforts have been made more precisely to locate the so-called sugar centre in the fourth ventricle, and Brugsch, Dresel and Levy have recently (1921) provided evidence that it lies in the dorsal vagus nucleus whence parasympathetic fibres are supposed to pass to the pancreas and sympathetic fibres to the adrenal. However this may be, and doubt has already been cast on their interpretation, the fourth ventricle can be little more than a relay station for impulses producing glycogenolysis that come from higher up. In a long-drawn-out experimental study of the presumed rôle of the posterior hypophysis in carbohydrate metabolism with Weed and Jacobson as my co-workers[25] we came to believe (1913) that glycogenolysis was produced by the liberation of a pituitary hormone set free by impulses reaching the gland through the cervical autonomic system. These observations have never been repeated and our findings may be capable of other interpretations now that attention has been drawn to the importance of the hypothalamic region whence possibly our

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[23] [That glycosuria and hyperglycaemia frequently accompanies pituitary basophilism was unknown at this time. *cf.* pg. 157.]

[24] *Cf.* Goetsch, Cushing, and Jacobson, *Bull. Johns Hopkins Hosp.*, 1911, XXII, 165.

[25] The Autonomic Control of the Pituitary Gland, *Johns Hopkins Hosp. Bull.*, 1913, XXIV, 40.

glycogenolytic responses originated rather than in the hypophysis itself. One thing, however, we did learn was that the experimental animal must be given the opportunity to store what we called "available glycogen" if the glycosuric response were to be obtained. Possibly on some such basis may lie the explanation of the fact that transient postoperative glycosurias are rarely observed on patients in the clinic after operations involving hypophysis or third ventricle, for they are usually conducted after at least a twelve-hour fast.

That the glycosurias which occur in approximately one out of every four patients with acromegaly [and with pituitary basophilism as well] are not an effect of the tumor in itself, regardless of its type, is further shown by the extreme rarity of glycosuria with pituitary tumors of other sorts than chromophil adenomas: and though the admission must be made that two patients with chromophobe adenomas (out of a series of 200 or more surgically verified lesions of this type) have had coincidental diabetes, glycosuria in the other cases has never been observed even as a transient episode immediately following operation.

The diabetes mellitus of acromegaly, moreover, proves to be notably resistant to treatment by insulin* and it has been repeatedly shown that posterior-lobe extract (pituitrin) will diminish or wholly counteract the blood-sugar-reducing effect of this product.[26] Since it is well known that posterior-lobe extract produces, at least in animals, a transitory hyperglycaemia and glycosuria, one might assume that in acromegaly the neural portion of the gland is activated by the disorder. What is more, the occasional spontaneous recovery from the diabetes mellitus of acromegaly, in spite of the continued progress of the underlying disease, may point toward the gradual elimination of posterior-lobe activity by pressure-destruction from the enlarging tumor; and the occasional disappearance of an existent glycosuria after radical extirpation of a chromophil adenoma suggests the possible resumption of activity in a previously compressed lobe.

With all this, and much of it is purely speculative, there is no gainsaying that the relation of the region in question to sugar diabetes is less evident than to that of water diabetes and to fat metabolism. Though temporary glycosuria may be provoked by experimental hypophysectomies or by hypothalamic injuries to animals, the effect is never prolonged; nor in my experience do operations for lesions of the hypophysis or third ventricle in man lead even to transient glycosuria.

A THERMO-REGULATORY CENTRE

The existence of such a centre has long been postulated and such facts as are at hand tend to place it in close relation to the primitive mechanisms

* [This is also true of the diabetes accompanying pituitary basophilism. *Cf.* case 11, pg. 145.]

[26] This insulin-inhibiting effect of posterior-lobe extract has been shown by Burn (*Quart. Jour. Pharmacol.*, 1929, 1, 509) to lie in vasopressin and not in oxytocin. Houssay and Magenta find that hypophysectomized dogs go into convulsions after smaller doses of insulin than do normal animals.

under discussion. Indeed, Raab[27] (1926) marshals evidence in favour of its being identical with the mechanism which regulates the normal absorption and oxidation of fat within the liver which he takes to be one of the essential factors in heat production. The necessity of a diet rich in fat to sustain warmth in arctic regions and the "fat gland" of hibernating animals on which the animal draws for sustenance during its winter period, come immediately to mind.

An interference with thermo-regulatory control may lead to an abnormal fall or rise in body temperature. A well-known example of the former is the marked fall in body temperature after high transection of the spinal cord by wounds; another, the extreme elevation of temperature that occasionally follows intracranial operations. Both conditions are prone to be fatal and in both, in my experience, the victims are likely to feel comfortable and have no consciousness of the altered body temperature.

In the early experimental canine hypophysectomies, which often led to what was called cachexia hypophyseopriva, the gradual fall in temperature to the time of death in the course of five to ten days was often extreme, almost reaching that of the environment. Injections of fresh emulsified gland served as we thought to check the fall or even to reëlevate the temperature, but efforts to reëstablish warmth by external applications of heat seemed merely to hasten death. It is a matter of general knowledge that patients with tumors which compress or destroy the posterior lobe, such as the common adenomas of chromophobe type, suffer from cold and have a consistently subnormal body temperature often averaging as low as 97°F. This might possibly have some connection with their lowered metabolism; and the low body temperature and low metabolism of hibernating animals is proverbial.

Smith has called particular attention to the inability of his hypophysectomized rats to maintain a normal body temperature. One would naturally suppose that in these hypopituitary states a prompt rise in temperature would follow the injection of posterior-lobe extract, but as a matter of fact it has, at least at the outset, just the opposite effect. Even if given intravenously, the extract causes, among other effects, a slight fall in temperature, but if injected into the ventricles the effect may be so pronounced as to be nothing short of startling. In one instance the rectal temperature fell to five degrees below normal and this was followed in three or four hours by a wave of pyrexia after which the patient experienced a marked sense of well-being. How to account for this unexpected antipyretic action of the drug is problematical.

Even more striking are the counterposed states of pyrexia. What is known as postoperative hyperthermia has long been a *bête noir* of neurosurgeons. It is most likely to occur, particularly in children, after sudden, complete emptying of the ventricles and is one of the most dreaded consequences of radical extirpations of tumors which leave the floor of the

[27] Raab, W., "Wämeregulation und Fettstoffwechsel," *Zeit. f. d. ges. Exper. Med.* 1926, LIII, 317.

dilated fourth ventricle widely exposed and which, at the same time, thoroughly empty the greatly distended and hydrocephalic cerebral ventricles. The body temperature may rise in the course of a few hours to 106° or even 108°F., the extremities meanwhile being so cold and clammy as to mislead the attendants and incline them to apply external heat.

Similar disturbances are known to follow operations for tumors of the third ventricle. I have recently removed a large suprasellar meningioma from a patient with a chiasmal syndrome, who, in the absence of any other postoperative symptoms referable to the third ventricle, for the subsequent ten days had a prolonged unremitting elevation of temperature, unassociated with leucocytosis or any evidence of infection. It was an unaccountable thermic wave almost like the temporary wave of polyuria that may follow one of these operations, slowly to return to normal. Many other examples of this same kind might be given. The fact that these neurogenic hyperthermias are notably influenced by antipyretic drugs which are supposed to act directly on centres in the base of the brain is also of significance.

On experimental grounds, a high and abrupt thermic reaction has been occasionally seen after hypothalamic injuries of various kinds, and such studies as have been made in this direction by my associates have led some of them to believe that a puncture in the region of the corpora mamillaria is more likely than any other to produce them. The whole subject, in short, is one which needs further detailed study, and the recent perfection of an apparatus which will permit of a continuous record of body temperature will make further investigations more precise than was formerly possible.

From what information we have, whether in clinic or laboratory, it would appear that experimental or surgical lesions, whether in third or fourth ventricle, may lead to hyperthermia, and this suggests a pathway from the posterior diencephalon through the descending bundles to the cord, vegetative nervous system and viscera. In this connection we may recall that Cannon's sympathectomized animals were no longer able to regulate their body temperature but became hypothermic in a cold room and hyperthermic in heated ones, owing possibly to the fact that regulatory impulses from the hypothalamus had been cut off.

PATHOLOGICAL SLEEP

On what grounds the carotid arteries, whose intracranial branches enter the *Rete mirabile,* came to be called "the sleepy arteries" is lost in antiquity. Galen knew that their occlusion caused carus or stupor so there was something more in the idea than pure conjecture, but just what the mechanism of sleep and its alternate phase of waking might be was undetermined. Among theories innumerable, that there may actually be a diencephalic centre for the process has been claimed, and the recent demonstration by Hess[28] (1929) of a definite hypothalamic area in the cat,

[28] Hess, W. R., "The Mechanism of Sleep," *Amer. Jour. Physiol.*, 1929, xc, 386.

stimulation of which will promptly induce a condition indistinguishable from sleep, points suggestively in this direction.

Then, too, we have had before us, these past fifteen years, the all too common examples of lethargy associated with encephalitis, a malady whose effects are prone to strike at this particular part of the brain as shown by other symptoms unmistakably hypothalamic in origin. Accordingly, the not uncommon clinical states of periodic somnolence called narcolepsy, which are characterized, in the absence of any other symptoms, by periods of sudden irresistible drowsiness and weakness, are commonly regarded as post-encephalitic disturbances akin to Parkinsonism. And it is not without interest that patients, in whom these states of narcolepsy occur, oftentimes coincidentally become abnormally adipose. Pathological somnolence is also prone to accompany such of the craniopharyngiomas as cause deformations of the third ventricle, but it is a still more common feature of what has been called the hypersomnic form of brain tumor[29]—namely, the gliomatous lesions that involve walls of the third ventricle.

Thus it would appear that pathological sleep, and conversely of course abnormal wakefulness, in all probability are states induced by a disordered function of the hypothalamus, but we cannot at the same time lose sight of the fact that somnolence is also a characterizing feature of many pituitary disorders in which the diencephalon can by no possibility have sustained direct damage. This is particularly true again of the chromophobe adenomas that are often associated with a notable drowsiness which sixteen hours of sleep out of the twenty-four will sometimes scarcely satisfy; and the fact that polyuria is rarely seen in these cases would further emphasize the fact that the adjacent tuber has escaped injury.

There is another thing about sleep that deserves consideration—namely, its rhythmical periodicity. Cyclicism, which may be diurnal, lunar, or seasonal, is a peculiarity of many physiological processes. The unaccountable periodicity of oestrus and of menstruation, of rutting, and of hibernation are examples. That these cyclic occurrences are primitive and fundamental to the species is beyond question. The sloth awakens merely to take food and procreate. Hibernating or estivating creatures pass whole seasons unfavourable for sustenance with their metabolic processes so far slowed down they can survive meanwhile on their own tissues. That these processes are somehow under the control of this ancestral diencephalo-hypophysial apparatus seems most probable.

Some years ago (1915) the attempt was made in collaboration with Emil Goetsch[30] definitely to pin hibernation on the pituitary body, but our opportunities for putting it to a conclusive test were inadequate. Unquestionably the secretory apparatus that controls tissue metabolism must be essentially inactive during hibernation just as it is relatively so in hypopituitary states. And since the hypophysis plays an even more

[29] A series of striking cases of this sort has been reported from the writer's clinic by J. F. Fulton and P. Bailey, *Jour. Nerv. and Ment. Dis.*, 1929, LXIX, 1, *et seq.*, with complete bibliography of the subject.

[30] *Jour. Exper. Med.*, 1915, XXII, 25.

definite governing rôle in these processes than we then ventured to believe, it would seem highly probable that winter sleep is made possible by the seasonal switching off of a mechanism which leads to sleep, oliguria, poikilothermia, slowed pulse and respiration, and the consumption of stored tissue fat at its lowest possible rate. And it may also be noted that on awakening from the hibernating state, almost certainly from resumption of the activity of the anterior hypophysis and its influence on the activities of sex, the mating or rutting season usually sets in.

On the grounds of clinical experience, one must concede that after operation for hypophysial tumors, however radical they may be, postoperative hypersomnia is rarely seen. Only after operations in which the floor of the third ventricle has been subject to contusion, and infrequently then, do we see evidence of pathological sleep of such depth as to excite comment. In a recent case after the removal of an unusually large olfactory groove meningioma which so far overlapped the chiasm and sella turcica as to cause marked deformity of the third ventricle, the patient during the course of the operation under local anaesthesia went into a profound, motionless sleep from which she did not gradually awake until nearly two weeks later. On the other hand, tumors may be successfully removed from the cavity of the third ventricle with no postoperative indications either of abnormal drowsiness or wakefulness in spite of the inevitable contusion of the ventricular walls.

VI. DIENCEPHALO-SYMPATHETIC MECHANISMS

From what has preceded, the tendency to overload the third ventricle with functional responsibilities already begins to be apparent. What is more, there is an irresistible temptation anatomically to allocate these several functions to specific centres.[31] Whether this is wholly justifiable may be doubted, though we need not forget the rôle phrenology once played in adjusting us to the idea of localization of function in the cerebral cortex. In addition to its highly important relation to the vegetative nervous system, the hypothalamus has come to be looked upon as a place where "emotional reactions are integrated." The uninhibited reactions shown by Goltz's famous decerebrated dog, well known to all students of neurology thirty years ago, have been newly investigated by Cannon[32] and his pupils, who describe in decorticated animals a quasi-emotional (pseudaffective) state, designated "sham rage," the hypothalamic source of which Bard[33] subsequently succeeded in delimiting. Since this state is accompanied by the same increase in blood-sugar, elevation of blood pressure, sweating, and outpouring of adrenalin, which characterize true rage, the region must lie in direct connection with the sympathetic nervous

[31] *Cf.* Greving, R., *Die zentralen Anteile des vegitativen Nervensystems*, Handbuch d. mik. Anat. d. Menschen, Bd. IV, (Berlin, 1928), Fig. 120, p. 1043.

[32] *Cf.* Cannon, W. B., "Neural Organization for Emotional Expressions," in *Feelings and Emotions*, Clark University Publications, Worcester, Mass., 1928, Chap. 22, p. 257.

[33] *Am. J. Physiol.*, 1928, LXXXIV, 490.

system. And recently Beattie and his co-workers[34] in their study of experimental cardiac arrythmias have furnished anatomical proof of this connection by tracing the degenerations that follow experimental subthalamic injuries of the posterior part of the third ventricle. More of this might be told, but enough has been said to indicate what a promising field of experimentation has been opened up by these successive disclosures that serve closely to relate the diencephalon to metabolic processes, to the primary emotions, and, lastly, to the vegetative nervous system.

With this mention of what may be regarded as a higher sympathetic centre in the posterior hypothalamus whence non-medullated fibres descend in the spinal cord to be distributed to the viscera, it would appear that we are now getting far removed from any possible participation of the hypophysis in this mechanism—yet we may not be so sure of this. It was shown by W. E. Dandy in my laboratory in Baltimore many years ago[35] that sympathetic fibres spreading from the carotid plexus could be stained by intravital methods and traced along the vessels of the stalk to the anterior hypophysis. It was on this basis that the subsequent study, to which allusion has already been made, was undertaken with Weed and Jacobson, in the attempt to determine whether the autonomic fibres in question could be experimentally shown to have an effect on the pituitary body. We had observed that in dogs a puncture of the third ventricle in the region of the hypophysis was almost as certain to produce glycosuria as a Bernard piqûre. Having then no dependable method of testing blood-sugar, we relied solely upon demonstrable glycosuria and soon found that in the same animal a succession of lesions (a fourth ventricle puncture, transection of the spinal cord at the fourth thoracic segment, stimulation of the superior cervical ganglion, and stimulation of the exposed hypophysis) could provoke an outpouring of sugar provided sufficient time was allowed between sessions for a reaccumulation of "available glycogen."

These experiments doubtless are capable of reinterpretation in the light of new knowledge, but the point I wish here to emphasize in again mentioning them is that Bernard's piqûre may possibly cause glycosuria by injuring the descending hypothalamic bundles which lie superficially placed in the midline of the roof of the fourth ventricle. This, however, is not the only effect that lesions of this important tract may produce. Median cerebellar tumors that arise from the roof of the fourth ventricle are of common occurrence, and of late years, particularly since the advent of electrosurgical devices, they have come in large numbers to be radically attacked and removed. In this process the entire floor of the widely dilated ventricle is laid bare to view with the likelihood of its being subjected to trauma.

For reasons heretofore mentioned, a postoperative glycosuria is rarely observed after these surgical exposures of the fourth ventricle, though a postoperative hyperthermia, as already stated, is a not uncommon sequel.

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[34] *Proc. Roy. Soc. B.*, 1930, CVI, 253.

[35] *Am. J. Anat.*, 1913, XV, 333.

And while on this particular subject there is still another matter to which attention may properly be called. Three fatalities from acute perforations (one gastric and multiple, one duodenal and double, and a third oesophageal) have followed radical extirpations of cerebellar tumors, in two of them the fourth ventricle having been widely opened. The only possible explanation of these disconcerting accidents—and similar observations have been reported in medical literature—is that something injurious has happened to the nervous mechanism which in some way protects the gastric mucosa from autodigestion. It is well known that most patients with peptic ulcer have an antecedent history of worry or apprehension associated with mental strain or fatigue, episodes of this kind being the usual preliminaries to recurrence of symptoms after their temporary recession; and I have been struck by the frequency with which patients with intracranial and particularly with third ventricle tumors have previously or subsequently had symptoms suggestive of gastric or duodenal ulcer.*

All this concerning a diencephalo-sympathetic mechanism, which harks back to the early postulation by Karplus and Kreidl of a higher centre for the sympathetic system, would appear to be remote from any conceivable bearing on the pituitary body. However, the fact emphasized by Raab, in his studies of fat metabolism that posterior lobe extract is particularly effective when injected into the ventricle, has led us to administer the commercial extract "pituitrin" in this way in a number of patients with pronounced hypopituitary states. They had all been previously operated upon for pituitary adenomas, and the injection was easily made through one of the burr openings for the craniotomy. We anticipated that there would be a rise in basal metabolic rate, in body temperature, and in blood pressure, possibly also a temporary hyperglycaemia; but quite the reverse happened.

The reaction has not been marked in all instances but when it does occur, before the extract could be expected to reach the blood stream, the patient flushes, breaks out into a drenching sweat, the blood pressure sinks, and the temperature falls. In one patient the rectal temperature dropped so low it could not be registered for several hours with a clinical thermometer. Two days later the injection was repeated with the record taken on a kymographic thermo-couple; the pre-injection rectal temperature of 98.8° dropped in the course of two hours to 93.8°, where it remained stationary for nearly two hours, and then slowly returned to normal. The basal metabolic rate meanwhile fell from its pre-injection level of −27 to −50 when the temperature was at its lowest, and had only risen to −37 at the end of four hours. When given subcutaneously in this patient the extract had no appreciable effect except as an antidiuretic. When given intravenously, as a control, it caused immediate pallor with no sweating and acted as a prompt purge; but the antipyretic response and effect on the metabolic rate was negligible.

However these effects are to be interpreted, they at least indicate that

* [For an elaboration of this topic *cf.* pg. 175 *et seq.*]

we cannot safely ignore the possibility of some posterior-lobe participation in the activities of the interbrain. Whether there are other drugs that would act by way of the ventricle in this same vigorous way with the same promptitude is not known, but certainly the extract when so administered must act on the hypothalamic centres by direct absorption rather than by finding its way first into the blood-stream, else, when injected intravenously, it would be expected to produce the same reactions with equal or greater promptitude.*

But even should the "hypothalamists" grant that the posterior lobe may well enough be under the influence of the diencephalon now that the two have been shown to have histologically demonstrable neural connections, they would still exempt the anterior hypophysis from any such control. As already pointed out, even the gonadal aspects of the adiposogenital syndrome have been ascribed by them to hypothalamic injuries, and Smith, too, has included (1927) genital atrophy among the characterizing features of the tuberal syndrome in the rat, leaving for the anterior hypophysis only the control of growth and the influence on thyroid and adrenal cortex. In all probability this gonadal effect is merely another instance of interference with hypophysial blood-supply, or of interrupted nerve-supply. Otherwise one could not possibly explain why precisely the same gonadal effect, produced by experimental ablations of the anterior lobe, can be completely counteracted so long as replacement therapy is continued.[36] Moreover, the attribution to the tuber of an independent influence on the reproductive functions would appear to disregard the proven relation of the anterior lobe to these processes through a special hormone.

In short, it is highly improbable that these two corresponding effects should be produced, the one by an hypothalamic lesion, the other by removing the source of chemical messages, in the absence of any functional interaction. Though both are instances of deprivation effects, one paralytic, the other secretory, some light may be shed on the subject by recent observations, dealing with the activation rather than the inhibition of this particular neurogenital mechanism. To this purpose the rabbit lends itself particularly well, for, unlike rats and mice, it is a peculiarity of this animal normally to ovulate only after mating. The actual discharge of the ovum occurs after a lapse of ten to twelve hours, this, as shown by Corner, being approximately the length of time it takes for ovulation to be artificially induced by the injection of the anterior-pituitary hormone of sex. To supplement this, Fee and Parks[37] have found that if the animal is decerebrated and the pituitary body removed within an hour after mating the cycle will be interrupted, whereas if the decerebration is delayed for more than an hour, the normal process of ovulation will go on to completion. It would appear therefore that the

* [Further details regarding these matters will be found on pg. 59 *et seq.*]

[36] Smith, P. E., "Hypophysectomy and a Replacement Therapy," *Amer. Jour. Anat.*, 1930, XLV, 205.

[37] "Studies on Ovulation," *Jour. Physiol.*, 1929, LXVII, 383.

copulatory act must set going some emotional and excitatory impulses which serve with promptitude to release the sex hormone from the anterior hypophysis. Impulses, arising in this way, could scarcely be discharged other than from that primitive structure, the interbrain, common to all mating species, and they must either pass directly to the gland or, what is more likely, reach it in a more roundabout way through the cervical sympathetic. Zondek speaks of the pituitary sex hormone as the motor that sets the reproductive cycle going, but the emotional self-starter is probably in the diencephalon.

VII. CLINICAL CORRELATIONS

We have so far, largely from an anatomical and physiological point of view, considered more or less separately the anterior pituitary, which is typically a gland of internal secretion, the infundibular lobe with its epithelial investment which has a secretory mechanism dissimilar from any other in the body, and finally the diencephalon, an all-important station for the transmission or inauguration of vegetative and emotional messages. And while separately discussing these three loci, stress has been laid at the same time on their unmistakable interdependence.

Though in modern times attention has been redirected to this region of the "wonderful *Rete*" by its tumors, our principal source of knowledge has been, as usual, the experimental laboratory where there are now so many interested workers, ably abetted be it said by the dog, the rat, the ox, and the pollywog, scarcely a day passes without some new disclosures. These may be in harmony or in discord with established views, and to correlate with clinical experience what knowledge the laboratory provides is often difficult, even baffling. This may be for want of that peculiar acumen or instinct that tells what at the bedside is worth recording, but it is partly due to the adaptability of the body to its pathological processes which may so effectually hide their symptomatic effects as to render them scarcely possible to detect. Endocrinology lends itself to two glaring faults, one the popularization of the subject, and the other a tendency of clinical observers to draw upon their fancy in a symptomatology which does not lend itself to precision.

The first thing with which one is forcibly struck in clinic and pathological laboratory is the frequency with which lesions, that supposedly would throw the diencephalo-hypophysial mechanism wholly out of function, may give, at least in the present state of our perception, no appreciable symptoms whatsoever. It is well known, for example, that in hydrocephalus the walls of the third ventricle may become ballooned out to paper thinness, and should they actually be the locus of the important activities ascribed to them one would expect serious consequences from the nuclear degenerations brought about by their wide expansion. There is a clinical tradition that hydrocephalic children are apt to be placid, good natured and well nourished; but apart from this the slow functional elimination of the hypothalamus either causes surprizingly few symptoms, or it may be that we haven't known what to look for.

At the time of this writing, there is a young woman in the clinic who was supposed to have a pituitary tumor. She had optic atrophy, presumably primary; bitemporal field defects; a widely expanded and largely absorbed sella turcica. At operation the chiasm was found crowded forward by a bulging ventricular wall of transparent thinness. It was widely opened for drainage in the manner indicated (Fig. 13); air was introduced

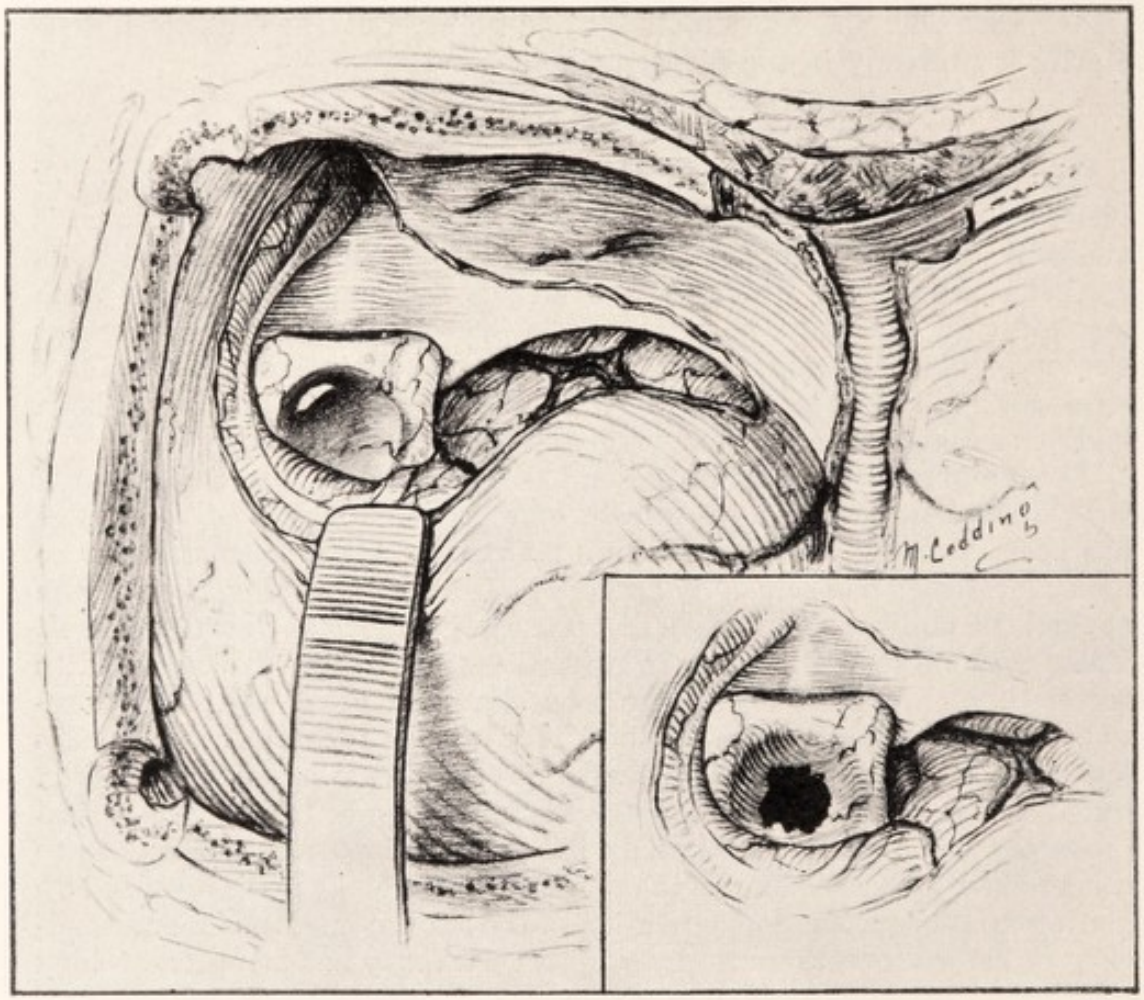
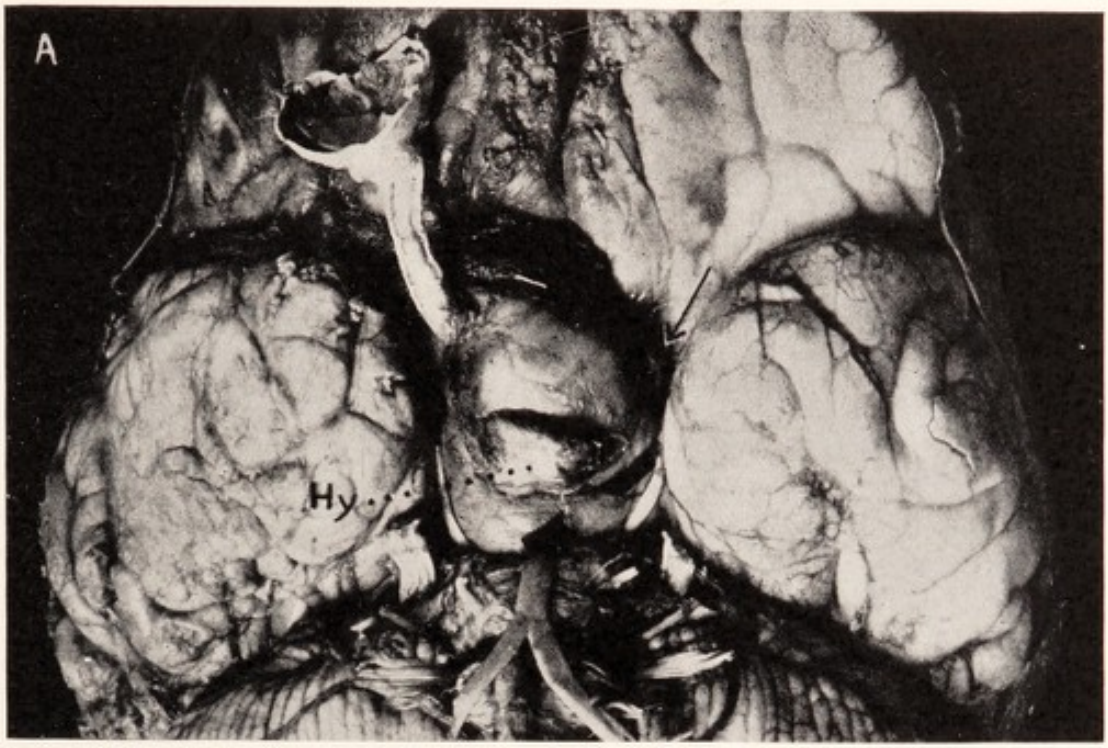
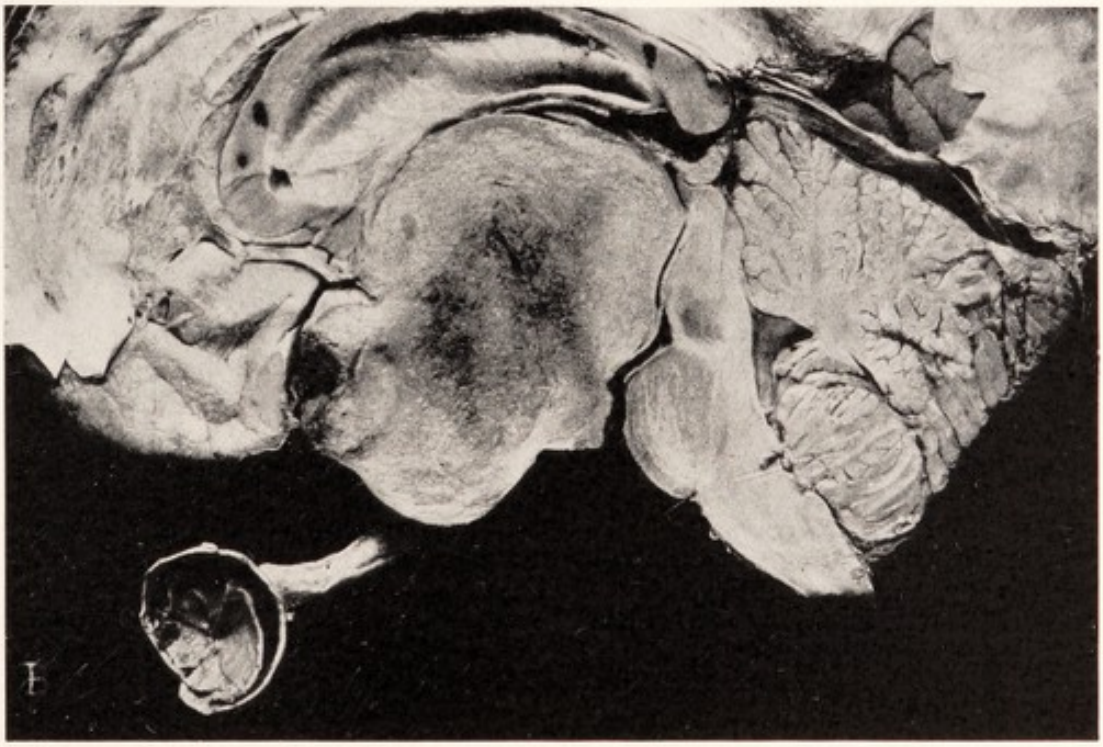


FIG. 13.—Sketch (natural size) to show the typical bulging suprachiasmal wall of the third ventricle as exposed at operation on a patient with generalized hydrocephalus. No preëxistent polyuria or adiposity accompanies these conditions nor does either ensue after the thorough opening of the ventricle for drainage in the manner indicated in the sub-sketch.

and subsequent ventriculograms showed a widely dilated ventricular system with no roentgenological evidence of tumor. Following this procedure, there was not the slightest postoperative polyuria; and one may well ask why not, if the nucleus supra-opticus, certain to have been damaged by this manoeuvre, even if not by the hydrocephalus, actually presides over water metabolism.

Even more striking is the fact that large tumors may come to fill the third ventricle, and so to distort its walls as to leave no recognizable trace





FIGS. 14 and 15.—[$\frac{3}{4}$ natural size.] Glioma of optic chiasm in a child who showed primary optic atrophy with blindness in right eye and a temporal hemianopsia in the left; also hydrocephalus with distended sella but no third ventricle symptoms. Fatality after surgical exposure of lesion. (A) Basilar surface showing right optic nerve emerging directly from tumor with stump of left optic nerve indicated by arrow; also flattened hypophysis (Hy.) with thinned-out tuber (below which a strip of black paper has been inserted). (B) Median section.

of them, without the slightest symptomatic indication of any interference with the neurohypophysial mechanisms which have been so laboriously analyzed. An example may be cited (Figs. 14 and 15) of a ventricle-obliterating chiasmal tumor of this type in a child who presented no localizing symptoms other than optic atrophy and temporal field defects which led to an exploratory operation with early fatality. An illustration may also be given (Fig. 16) of a moderately large cystic craniopharyngioma in

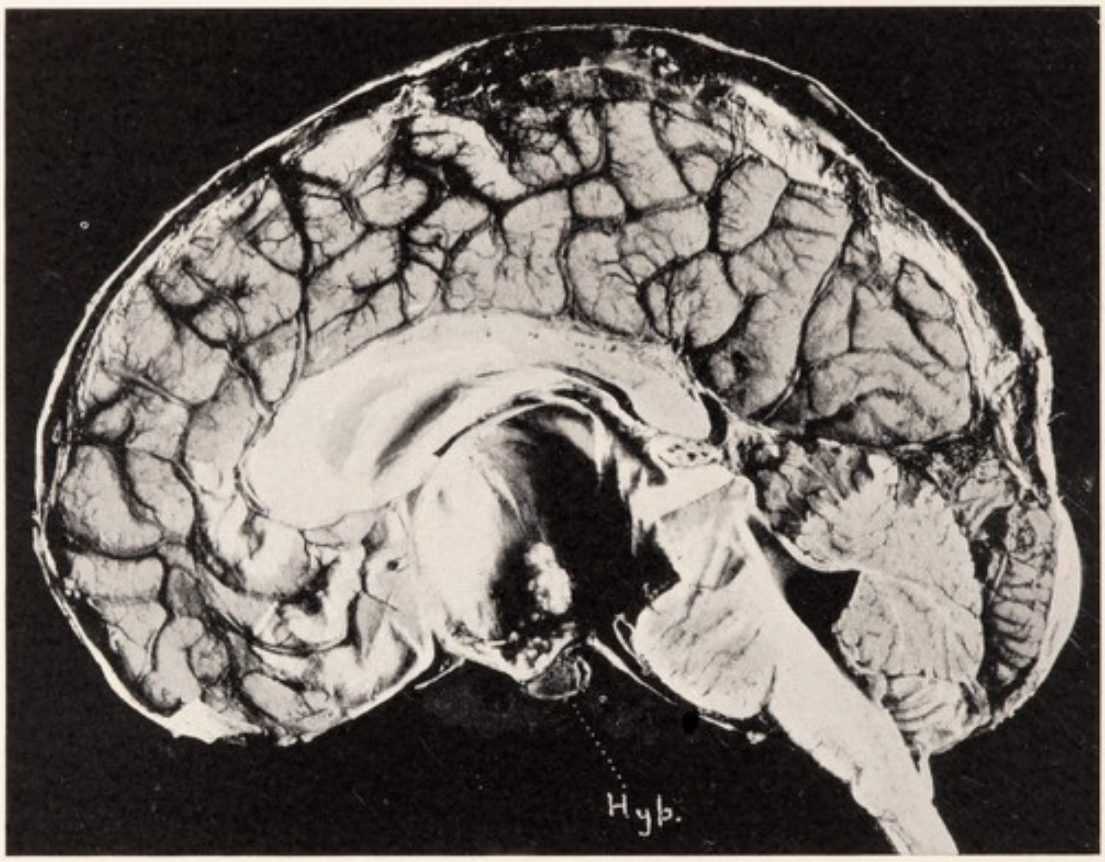


FIG. 16.—A landmark-obliterating tumor (cystic craniopharyngioma) displacing the third ventricle without recognizable hypophysial or diencephalic symptoms. The patient, a woman 41 years of age, had advancing optic atrophy and bitemporal hemianopsia of a year's duration, and died with hyperthermia after a ventricular puncture. Note the subjacent and normal pituitary body (Hyp.) which occupied a roentgenologically normal sella.

which the ventricular land marks were similarly obliterated without any appreciable symptom other than those referable to the chiasm.

Should one wish to present further evidence that all of this talk about the hypothalamus and its functional importance is mere rubbish, the fact may be adduced that tumors of the third ventricle are far more often betrayed by ventriculography than by the neurological symptoms they provoke; and to make this still more emphatic, the further fact may be dragged in that under favourable circumstances tumors of this region may be successfully removed without provoking any of the symptoms heretofore discussed at such length. In two recent cases, by a transcortical

approach through a hydrocephalic lateral ventricle a roentgenographically demonstrated ependymoma filling the expanded third ventricle has, with much trepidation, I admit, been radically dissected out of its bed, leaving a large, raw cavity with no subsequent trace of personality change, of polyuria, adiposity, somnolence, hyperthermia or vasomotor disturbance, one or all of which might well enough have been expected.

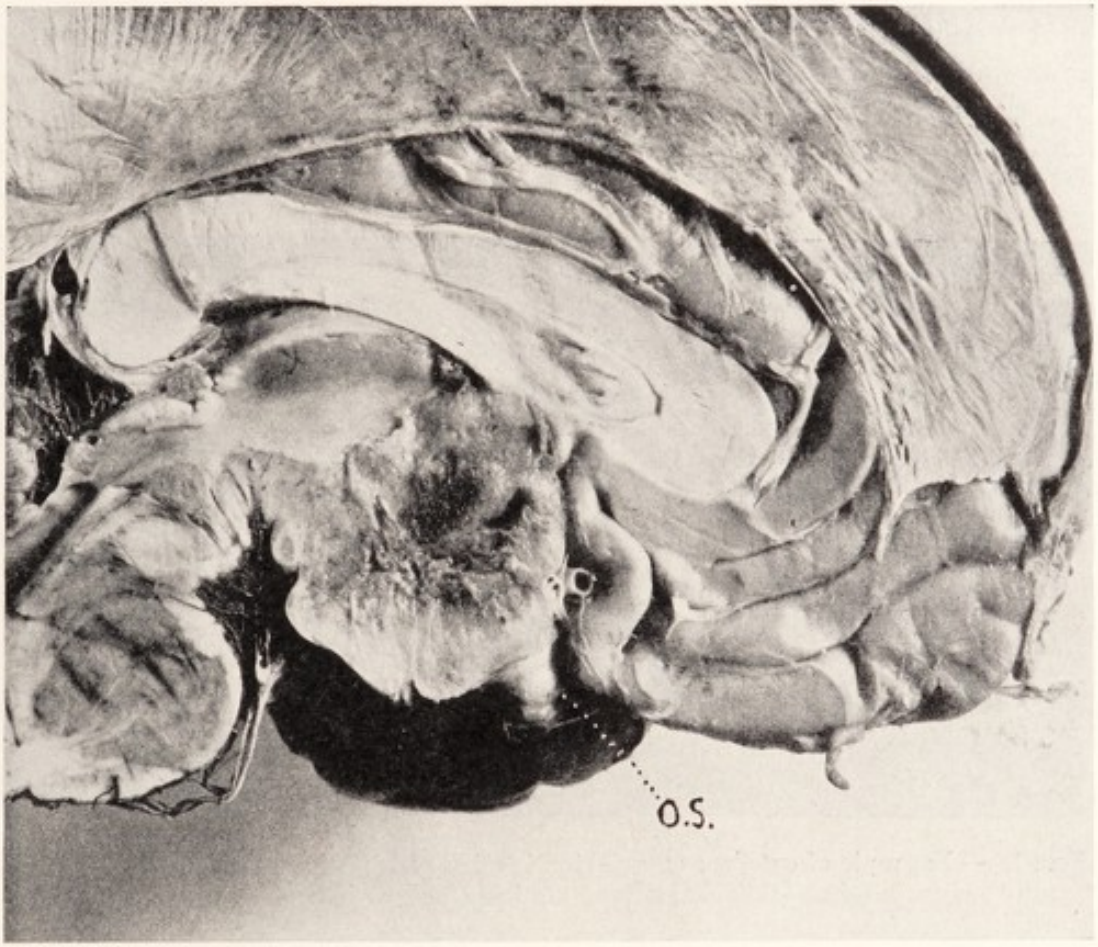


FIG. 17.—To show (nat. size) the backward extension of a primary chiasmal glioma to incorporate practically the entire diencephalon. The patient, 56 years of age, had at the time (1922) no recognizable or recorded hypothalamic symptoms. Death from hyperthermia followed an exploratory exposure of the tumefied chiasm. O.S. = left optic nerve.

But negative observations such as these, however disconcerting, need not be given undue weight. Positive findings when suitably marshalled are more important than any number of circumstantially negative ones; and when cases come to be analyzed in sufficient numbers, there is found to be convincing testimony in abundance. There are two types of tumor of the region which from a symptomatic standpoint are particularly informative. They are the chiasmal gliomas and the congenital tumors of the hypophysial duct to which frequent allusion has already been made in the preceding pages.

THE CHIASMAL GLIOMAS

These tumors, though less common than the craniopharyngiomas, provide an important contrast not only in that they are invasive and destructive but because they primarily involve the region of the supra-optic nucleus, whereas the congenital tumors produce their effects by pressure distortion and are more likely to implicate the hypophysis and the tuberal region.

A report upon these chiasmal gliomas, largely from an ophthalmological standpoint, was made in 1923 in collaboration with Dr. Paul Martin, at which time we had little to say of their tendency to invade the ventricle. In this respect to be sure the tumors differ greatly, for some of them are relatively benign lesions whereas others of a more malignant type soon

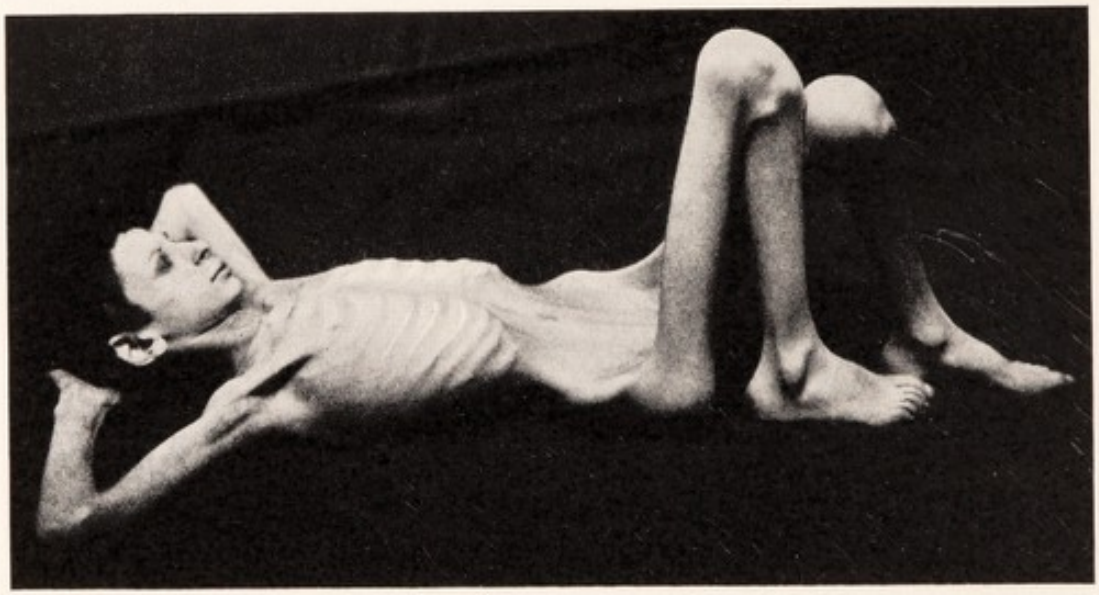


FIG. 18.—Example of extreme emaciation in a lad of 13, originally accompanied by a mild polyuria (*circa* 2000 c.c.) due to a glioma chiefly involving tuberal portion of third ventricle.

involve the anterior wall of the ventricle and in time may wholly obliterate its cavity (Fig. 17).

When one comes to review the clinical histories of the 22 cases in which such a tumor has been histologically verified, it is not surprizing that the older records are found wanting in respect to some of the points on which greater emphasis might be laid to-day, rapid loss of sight having been the urgent symptom to which chief attention was naturally paid. Nevertheless, polyuria was observed in nine instances (six of them being recorded as diabetes insipidus with a daily output of *circa* five litres), and in only four cases was it expressly stated that there was no polyuria. Adiposity was noted (or the photographs of the patients indicate its presence) in eight instances, and in three there was notable obesity. Though one of the obese patients showed excessive polyuria, most of those with pronounced diabetes were, on the contrary, thin and tall; one

of them, a recently observed case, was a spare young man, aged 23, six feet three inches in height, with marked diabetes of over three years' duration. In another instance, a boy 13 years of age likewise with marked diabetes, the emaciation had become extreme (Fig. 18).

Undue sleepiness, occasionally described as somnolence, was mentioned in six instances. The systolic blood pressure was 110 or below in the majority of the cases, the basal metabolic rate was subnormal in the nine patients on whom it could be taken, and the five early postoperative fatalities were all attributable to or at least associated with, terminal hyperpyrexia of high degree.

Occasionally one of these gliomatous tumors may evoke a definite "march" of symptoms which suggests a progressive involvement of the diencephalic centres. Of this the following is an example:

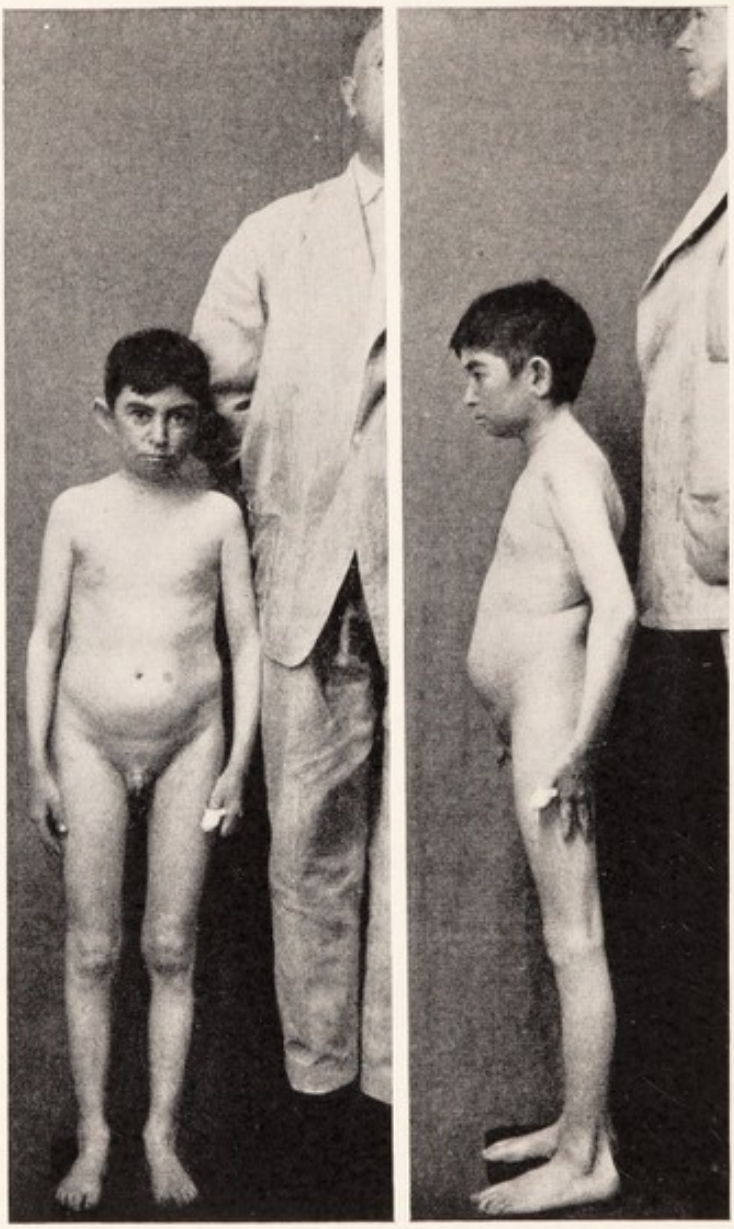
A previously healthy preadolescent school girl resident in New York, an only child, 13 years of age, in *October, 1929*, acquired an oculomotor palsy on the right eye and soon after was found to be blind in that eye. She was taken to a hospital, where on x-ray evidence the diagnosis of a suprasellar tumor was made. Questioning brought out the fact that antecedent symptoms of polydipsia and polyuria had long been present; that during the summer of 1929 she had suddenly grown quite stout (her exact weight had not been taken); and that she had been withdrawn from school that autumn because of abnormal sleepiness (twelve to sixteen hours a day). Vision shortly after became impaired in the other eye, and soon the child showed a marked change in personality. It was difficult to induce her to take nourishment, she became uncontrollable, and soon acquired an unaccountable fever ranging from 101° to 104°F. which persisted for ten weeks prior to her admission to the Brigham Hospital.

On admission (January 25, 1930) the child proved to be more like a wild animal than a human being. She would lie, quiet and apparently somnolent unless approached or touched when, as Dr. Oldberg's record expresses it, "she would become suddenly galvanized into tremendous hyperactivity." She would utter a succession of piercing shrieks, would thrash violently about the bed, meanwhile clawing and scratching at her attendants. Most of the time she was wholly irrational and incontinent and only after prolonged coaxing could she be persuaded to take food or drink. She was found to have: (1) a primary optic atrophy with apparent blindness; (2) a normal sella turcica without suprasellar calcification; (3) a persistent pyrexia without accompanying leucocytosis; (4) a pulse-rate of *circa* 140 with arrhythmia; and (5) an oliguria rather than a polyuria, so far as could be determined. There certainly was no polydipsia.

The child remained in this hopeless state with conditions unaltered for the next three weeks. An exploration offered little but was finally undertaken on February 18, when a soft tumor of malignant type involving the chiasm and spreading widely into the ventricle was disclosed. A considerable mass of this tumor was sucked out and radium seeds implanted. There was subsequent hyperthermia and she died forty-eight hours later with a rectal temperature of 108°.

Here, then, was a case in which disturbance of water and fat metabolism, of thermal regulation, of sleep and possibly of the vasomotor mechanism were finally all obscured by the removal of cortical inhibitions which left the patient in a state quite comparable to the "sham rage"

described by Cannon in decorticated animals. All these symptoms, it will be observed, may well enough be looked upon as purely diencephalic in origin, with no obvious bearing on the pituitary body whatsoever. As a matter of fact, since three out of every four of the recorded chiasmal gli-



FIGS. 19 and 20.—A 30-year-old dwarf with Fröhlich's syndrome due to a surgically verified (1926) retrochiasmal cystic craniopharyngioma in a position to compress pituitary body, infundibulum and tuber and causing mild diabetes insipidus.

omas occur in childhood, since many of them pursue a rapid course, and since the hypophysis does not become directly involved in the process, secondary disturbances of growth and maturation are inconspicuous or wholly absent from the clinical picture.

THE CRANIOPHARYNGIOMAS

In contrast to the foregoing, the symptomatic sequence in the congenital hypophysial-duct tumors is more slowly progressive. Interference with the normal secretory activity of the anterior hypophysis is ordinarily evident from the outset; and owing to the usual point of origin of the lesions they often exert their pressure effects against stalk, infundibulum, tuber and chiasm from behind and below rather than from in front as do the invasive gliomas just considered.

A systematic review of eighty of these cases that have been histologically verified, however disheartening from an operative standpoint, for they represent one of the most baffling of surgical problems, yet provides a fruitful source of study of diencephalo-hypophysial symptomatology. As already mentioned, these tumors vary greatly in position, size, histological character, age of symptomatic onset and ultimate complications. They may be minute, pea-sized cysts, or huge, calcareous masses the size of a tennis ball; they may originate and remain confined within the sella or, what is more common, lie wholly above it, and consequently most of them compress the tuber and hypophysial stalk early in their course.

Two of the constitutional features characterizing the syndrome of Fröhlich—namely, the retardation of growth and adolescence—are sufficiently well explained in the younger patients by the interference, through compression, with the normal secretory activities of the anterior lobe (Figs. 19, 20). An explanation of the adiposity is less clear, and the fact that it often occurs in the absence of polyuria shows that these two symptoms do not necessarily go hand in hand. Indeed, patients with a tumor confined within the sella, often show moderate adiposity when the tuber could hardly have been affected.

The age-distribution of these cases at the time of their hospital admission has been by decades as follows: 15 in the first; 27 in the second; 15 in the third; 10 in the fourth; 7 in the fifth; 4 in the sixth; and 2 in the seventh decade. By far the more striking symptoms occur in the younger groups, in which evidence of anterior-lobe impairment is shown by delayed growth or actual dwarfism and by retarded maturity or persistence of actual infantilism. Most of these younger patients at the same time show a tendency to be overwell nourished, or they may be definitely obese. This, however, is not invariable, for some of them are actually thin or emaciated; and others become definitely progeric in appearance (Fig. 21) suggesting the gradually developing cachexia observed by Smith in his hypophysectomized rats.

Some of these purely anterior-lobe symptoms may be carried over from early life to the third decade, but this is unusual, for the almost inevitable secondary complication of hydrocephalus ordinarily serves to end the story before this. When, on the other hand, symptomatic evidence of the lesion, usually signalized by a disturbance of sight, is postponed to the third decade or later, growth and development may have been normal in all respects. Amenorrhoea, or, in the male, sexual dystrophy, then usually

puts in an appearance, but under certain circumstances depending on the site of the lesion even these indications of anterior-lobe involvement may be wanting. Our most recent case provides, through a sorry experience, an example of this.

A woman 27 years of age (Surgical No. 35994), having previously enjoyed normal health, was married in *January 1925*, and soon became pregnant. At

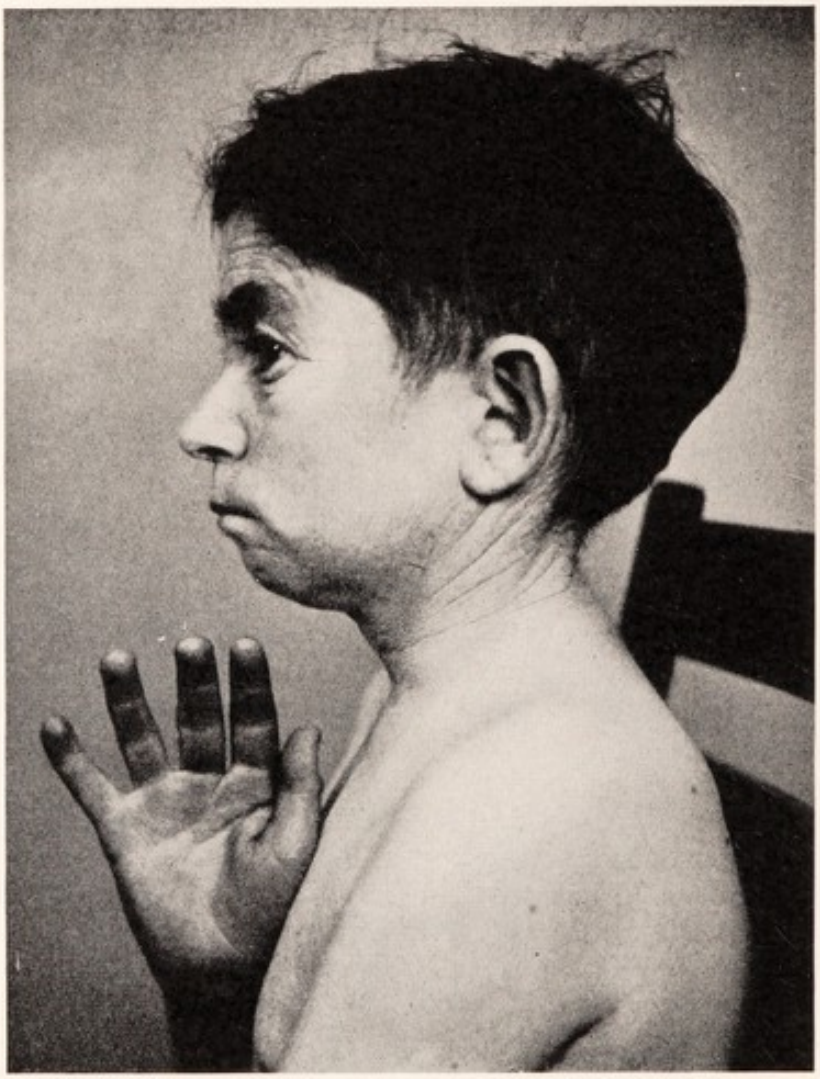


FIG. 21.—To show in greater detail the aged (progeric) appearance of a 30-year-old patient essentially hypophysectomized from infancy by a craniopharyngioma (*cf.* Fig. 19).

the time of parturition expulsion was impossible, and after a prolonged labour recourse was had to a forceps delivery which the child did not survive. For no apparent reason, in the absence of suckling, she continued to lactate for twelve months. Three years later, at her second pregnancy, precisely the same sequence of events occurred. Following this, she became hypersomnolent and showed marked mental changes accompanied by periods of fright that were regarded for some months as a postpartum psychosis until the presence of a frontal tumor was finally suspected.

On admission to the hospital she was found to have a choked disc of six diopters associated with suprasellar calcification and secondary hydrocephalus, possibly accounting in part for her mental symptoms. Perimetry was precluded; also the metabolism estimation. Her temperature was subnormal, registering 96°F. on one occasion. The blood pressure was exceedingly low, 80 systolic over 40 diastolic. Her skin showed a blotchy pigmentation. There was no adiposity or polyuria.

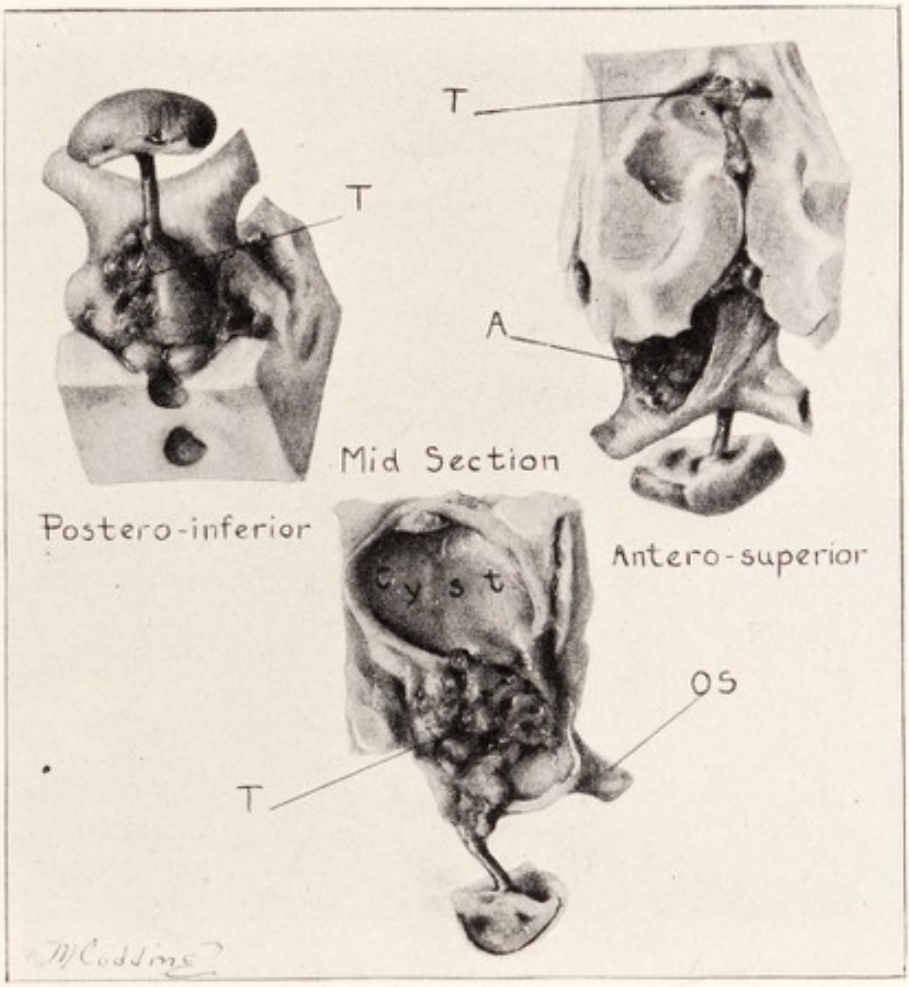


FIG. 22.—Drawings (natural size) before sectioning of the block of tissue enclosing the tumor (T). Note the pendant normal pituitary body and stalk. On mid-section the solid portion of the tumor is seen to be obliterating the tuberal region and a moderate-sized cyst lies above. The retrochiasmal point of surgical attack is indicated in the antero-superior view at (A). Left optic nerve (O.S.).

At the operation a subchiasmal tumor was disclosed and in the hope of thereby relieving the hydrocephalus its calcified portion was dislodged and an overlying cyst emptied. From this operation she never regained consciousness and died twenty-four hours later, apparently from cardiac complications without hyperthermia. A comparatively small cystic tumor, chiefly involving the tubero-infundibular region with intact pituitary body and stalk, was found at autopsy (Fig. 22).

Here, then, is an example of a craniopharyngioma involving the tuberal region which had given no symptoms of any sort till the third decade;—and even then none that could be definitely ascribed either to diencephalon or to hypophysis unless possibly the repeated difficulties of parturition were in some way attributable to lack of posterior-lobe secretion. As an offset to this case, one in which pronounced diencephalo-hypophysial symptoms first put in their appearance at a still later period of life may be cited:

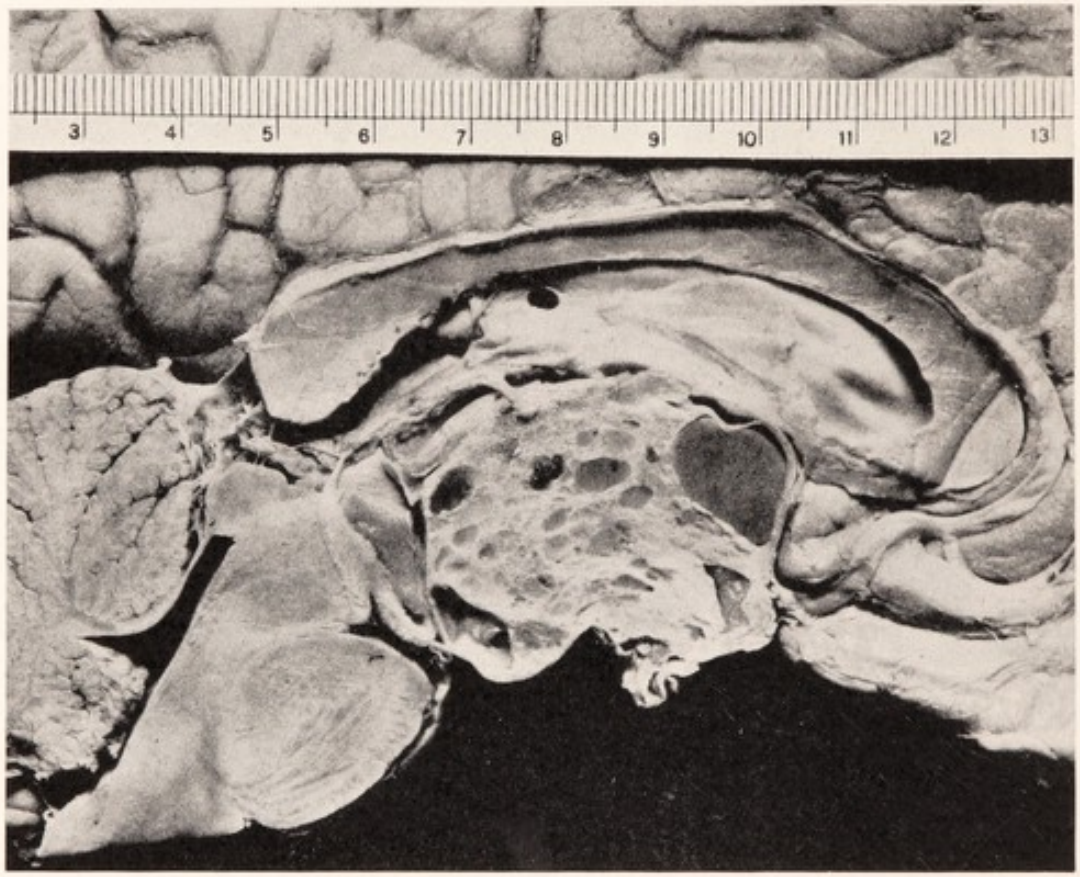


FIG. 23.—Mid-section of the brain of a 47-year-old man showing a sparsely cystic craniopharyngioma which for the brief period of nineteen months had caused primarily a disturbance of sight followed by diabetes insipidus and somnolence. Pendant from the lower portion of the growth is the broken neck of its adherent protrusion into the undistended sella (*cf.* Fig. 24).

The patient, 46 years of age, a classical scholar holding a professorial chair, had always enjoyed excellent health, had been married for fifteen years, and was the father of three children whose ages were 14, 11 and 8 years respectively. His height was 5 ft. 9 in.; his average weight had long been stationary at about 182 lbs.

Some six months or so before his hospital admission (*viz., October 3, 1928*) he began to experience a subjective blurring of vision. Soon after this, in uncertain sequence, he become impotent, extremely drowsy, acquired an abnormal thirst with evident polyuria, and definite personality changes were soon observed.

Examination.—The patient was quite indifferent to his breakdown, bored by the neurological tests and note-taking, and though polite and serene if aroused, if left alone tended to drop off to sleep. He was occasionally incontinent and was once found in bed between the sheets with his boots on, fully dressed. The fundi were regarded as normal in spite of the presence of a large central scotoma in the left eye and a lower temporal field-defect on the right. There was unquestionable diabetes insipidus, his polyuria averaging from four to five litres daily. He was, perhaps, overwell nourished but not more so than might have been expected of a man of his age accustomed to a sedentary life. The basal metabolic rate was −32 per cent. The sella turcica was of normal size and contour. The examination otherwise was quite negative and ventriculograms were interpreted as showing normal conditions.

The patient remained under observation for a month with the nature of his lesion undiagnosed, and as he was evidently deteriorating, a transfrontal exploration was finally made on the assumption that a suprasellar tumor of some sort must be present. A solid craniopharyngioma was disclosed (*November 5, 1928*) largely underlying the chiasm, which was pushed upward. The better to expose the lesion, the chiasm was split anteroposteriorly whereby the anterior wall of the third ventricle and supra-optic nucleus could scarcely have escaped injury.

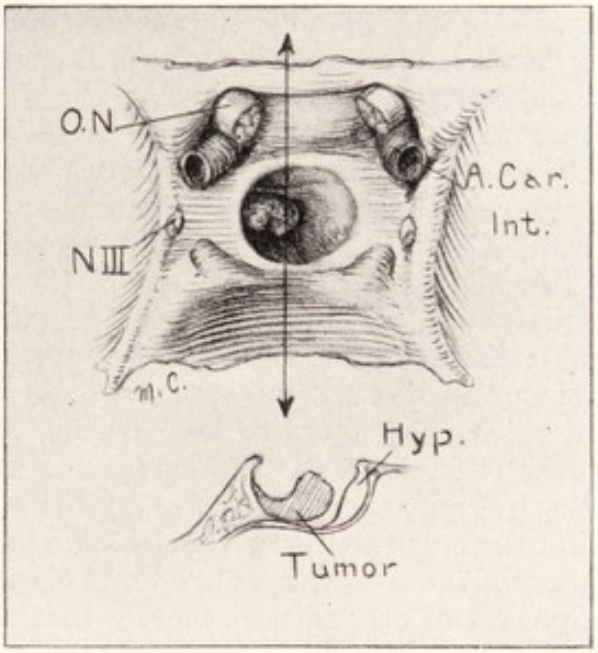


FIG. 24.—Sketch of the suprasellar region showing the pocket into which the tumor (*cf.* Fig. 24) projected. In the sub-sketch on mid-section is shown the broken and adherent portion of the growth. The flattened residual of the gland (Hyp.) lies anteriorly, there being no recognizable trace of pars nervosa, stalk, infundibulum or tuber.

From this operation the patient made an excellent recovery with improved visual acuity in spite of the permanent bitemporal hemianopsia to which he was committed. Instead of there being an increase in the polyuria it definitely and progressively diminished, and at the time of his discharge (*November 26, 1928*), three weeks later, the intake and output had dropped to about 1500 c.c. daily. Meanwhile, instead of gaining weight he had lost, from 191 to 175 lbs.

He subsequently attempted to resume his college duties. This, however, was too much for him and he spent most of his time in sleep during the winter and spring, there being occasional periods of transient polydipsia but no gain in weight. During the following summer he was much better, quite like himself for the first time since the onset of his malady, but by the end of *September* he had again become so somnolent he would sleep twenty hours out of the twenty-four. A month later pressure symptoms set in, with headache, vomiting, rigidities, Cheyne-Stokes respiration, slowed pulse, and on *November 26, 1929*, came the end, scarcely more than eighteen months from the first observed symptom.

The emotional negativism shown by this man is highly characteristic of these particular lesions and stands in marked contrast to the violent psychomotor agitation ("sham rage") in the patient with a glioma previously described. Between the negative and positive emotionalism shown by these extreme types there are countless gradations that have long excited the interest of neurologists and psychiatrists.

The tumor in this particular case (Fig. 23), a non-calcified though largely solid type of craniopharyngioma, not only filled the entire interpeduncular space, but projected into without enlarging the sella turcica (Fig. 24), the pituitary body having become greatly compressed. The notable symptoms were impotence together with diabetes insipidus and moderate adiposity, both of the latter subsiding as the malady progressed, an increasing somnolence being the major terminal symptom. On the other hand tumors fully as large as this may cause scarcely any appreciable symptoms and would remain practically silent were it not for the customary disturbances of vision from compression of the chiasm and the terminal manifestations of hydrocephalus.

It would be superfluous to cite further clinical examples of diencephalohyphophysial symptomatology. These few may well suffice. Here in this well-concealed spot, almost to be covered by a thumb-nail, lies the very mainspring of primitive existence—vegetative, emotional, reproductive—on which, with more or less success, man has come to superimpose a cortex of inhibitions. The symptoms arising from disturbances of this ancestral apparatus are beginning to stand out in their true significance. That the older literature proves to be filled with reports of cases as telling as any of those cited herein, goes to show that we have advanced no whit in powers of observation, merely that modern science has permitted us to give to them revised interpretations.

VIII. FINAL ARGUMENT

There is indeed nothing wholly new under the sun; what appears to be new is no more than something old in a novel aspect. In support of this, and before attempting to assemble the arguments favouring the interdependence of diencephalon and pituitary body, I may be permitted a quotation from the writings on one of your countrymen, a seventeenth-century physician and anatomist:[38]

> Seeing therefore there is such an affinity as before mention'd, between the *Rete Mirabile* and *Glandula Pituitaria*, and taking it for granted, that the office of the *Glandula Pituitaria* is not what it hath generally hitherto been believ'd, to the end we may attain a more exact knowledge of what it really is; it seemeth not altogether immethodical to take that part into consideration in the next place, together with the *Infundibulum*, which last hath not only as near a relation to the Gland as the Gland hath to the *Rete*, but such a close communication with it, that *it seems in a manner almost impossible to treat of one independently of the other.*

[38] Ridley, H., *Anatomy of the Brain*, London, 1695.

Though the italics are mine the original conception that pituitary gland and adjacent tuber cinereum can scarcely be considered separately, is far from being so; and it may not be "altogether immethodical" in closing this address to supplement the statement made by Humphrey Ridley over two centuries ago by newly acquired, though at times somewhat contradictory, testimony, derived at many hands from diverse sources—evolutional, morphological, biological, pathological and clinical.

The pituitary body is a combined neuro-epithelial organ present in all craniates. Its purely epithelial lobe is the first of the endocrine organs to be differentiated in the embryo; its neural portion is an outgrowth of the oldest part of the brain to be laid down. If the rudimentary organ is removed from the amphibian embryo its further growth and metamorphosis are promptly checked; if reimplanted, these effects do not occur, but the rudiment will not long remain functionally active unless neural tissue is included in the transplant. The infundibular lobe is an expansion of that ancient portion of the cerebrum, the diencephalon, which retains its simple structure in all creatures that can boast of a brain at all. Herein lie ancestrally important mechanisms common to all species which have to do not only with their vegetative functions, but with their primitive instincts—in mating, in satisfying hunger and thirst, in restoration from fatigue by sleep, in regulation of body temperature, in self-protection by combat or escape. From the diencephalon non-medullated nerve-fibres pass direct by way of the infundibulum to be distributed in the posterior lobe and its epithelial envelope. Extracts of this lobe contain a peculiarly active substance or substances, the injection of which serves to counteract one, at least, and probably more than one of the symptomatic effects of irritative or paralytic injuries to the suprajacent interbrain. Non-medullated nerve-fibres also connect this ancient station by way of the spinal cord and the sympathetic nervous system not only with the thoracic and abdominal viscera but some of them even turn back to act upon the anterior hypophysis itself. Hence diencephalic messages may be relayed to this somewhat insulated part of the gland on whose hormones depend not only normal body growth and the normal function of certain subsidiary endocrine organs but, indeed, the very perpetuation of the species. For without the presumably emotional discharge from it of the hormone of sex, the chain of events leading to the escape, fertilization, and implantation of the ovum cannot take place.

Though information may be gained by the independent study of its separate parts, physiologically the diencephalo-hypophysial mechanism can only be properly interpreted when looked upon as a whole, and even then only when its influence on the entire organism is taken into account. So, at the end, I may appropriately quote what Thomas Willis said of that "divine artifice," the *Rete mirabile* and its function: "There is nothing in the whole fabric of an animal body more worthy of admiration . . . nothing can be conceived as more skilful, and nothing which argues more forcefully the providence of a divine Author."

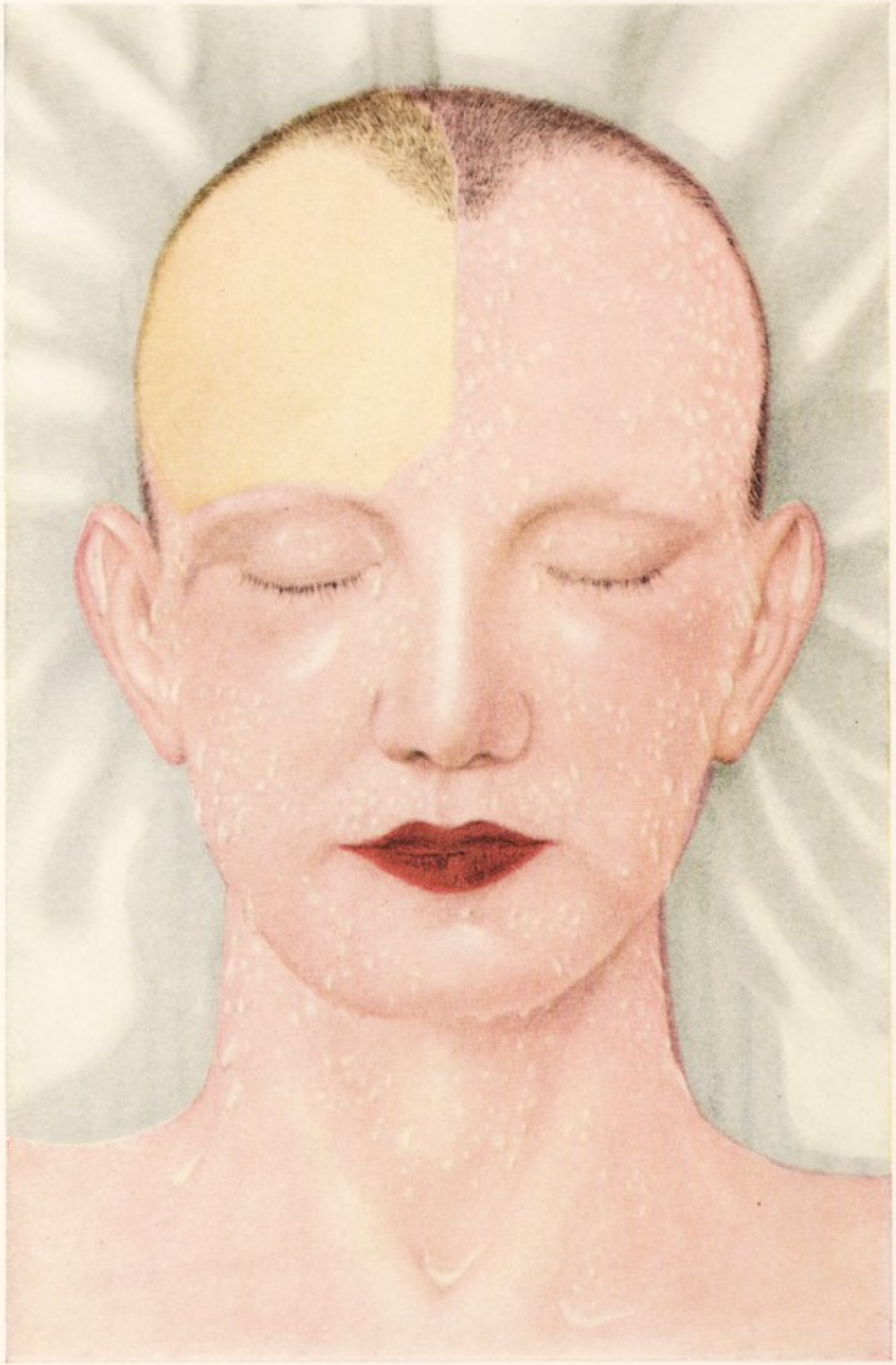


FIG. 25.—Showing the vaso-dilator and sudorific effects (sparing the bone-flap) of 2.5 milligrams of pilocarpine injected into the cerebral ventricles: an intraventricular injection of a cubic centimeter of pituitrin in susceptible persons gives an equally marked response.

II. Posterior-Pituitary Hormone *and the* Parasympathetic Nervous System*

I. THE REACTION TO POSTERIOR PITUITARY EXTRACT (PITUITRIN) WHEN INTRODUCED INTO THE CEREBRAL VENTRICLES†

INTRODUCTION

IN 1908,[1] P. T. Herring first clearly described the peculiar hyaline bodies often seen in sections of the neuro-hypophysis and expressed the belief that they represented the secretory product of the epithelial investment of the posterior lobe known as the pars intermedia. The globules appeared to find their way toward the tuber cinereum and in favourable histological preparations could be seen passing between the bodies of the ependymal cells to enter the infundibular cavity.

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* Reprinted from the *Proceedings of the National Academy of Sciences*, April and May, 1931, xvii, 163–180 and 239–264.

† Although the attention of physiologists and pharmacologists was first called to the pituitary body by the discovery of the haemodynamic and diuretic properties found in extracts of its posterior lobe, the function of this obviously important portion of the gland has remained a physiological mystery. One of my anatomist friends who has made notable contributions to our knowledge of the anterior lobe hormones has challenged me to produce any corresponding clinical or experimental evidence of posterior lobe activity. To this challenge, this and the succeeding papers are a partial answer.

Two years later (1910), Cushing and Goetsch,[2] in support of Herring's observation, supplied experimental evidence in two directions: (1) by showing how occlusion of the pituitary stalk served to dam back the secretory product in the pars nervosa; and (2) by demonstrating, however inconclusively, that the active principle of the lobe was detectable in the cerebrospinal fluid, their deductions having been based on the haemodynamic, peristaltic and diuretic responses to concentrated human ventricular fluids injected for the most part intravenously into rabbits.

From *the histological side* Herring's discovery has received abundant substantiation, though interpretations regarding the source of origin and destination of the hyaline bodies have varied. It is evident that the cells of the pars intermedia et tuberalis, under some nervous stimulus, disgorge their ripened cytoplasm into the pars nervosa and that the extruded product undergoes hyalinoid transformation during its migration upward toward and into the tuberal projection of the diencephalon. Indeed, under certain circumstances large numbers of apparently intact cells, for they still contain recognizable nuclei, may actually thus migrate from its epithelial investment into the substance of the pars nervosa in their passage through which they subsequently become hyalinized.*

This casting off of the cytoplasm in mass or the actual discharge of the entire cell body are by no means unique modes of secretion of glandular cells.† What is more, the process, as we know now, is unquestionably under the direct control of certain nerve centers in the interbrain. The presence of a large number of non-myelinated nerve fibres in the neurohypophysis, apparently first observed by Ramon y Cajal in immature mice (1894), was subsequently confirmed by his pupil, Tello[3] (1912), for the human gland. It, however, was not until the papers of Pines[4] (1925) and of Greving[5] (1926) that the amazingly rich arborization of fibres in the posterior lobe came to be fully appreciated and was brought to the attention of physiologists and clinicians.

The interstitial passage of the hyaline bodies through the neurohypophysis and its stalk toward the tuber has meanwhile been observed by many. Edinger[6] injected the posterior lobe with india-ink and though the mass tended to spread in the direction of the tuber, it did not enter the ventricle. Herring, however, as did Cushing and Goetsch, gave photomicrographs showing hyaline globules actually caught in the process of their extrusion into the ventricle, an observation which has been confirmed, among others, by Hines,[7] by da Costa,[8] by Espino,[9] and by Remy Collin.[10,11,12]

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* A photomicrograph illustrating such a cellular migration was given in the author's monograph on the pituitary body, 1912, pg. 199.

† The three methods of secretory discharge which histologists now recognize are: (1) *merocrine*, in which the secretory granules are periodically extruded without particular change of form in the cell, as in salivary, gastric or anterior pituitary glands; (2) *holocrine*, in which the entire cell body is cast off, as in the sebaceous glands; (3) *apocrine*, in which the ripened cytoplasm is disgorged, as in mammary secretion and in the case of certain cutaneous glands, particularly of the lower animals.

From *the physiological side*, though the conclusions drawn from their early experiments by Cushing and Goetsch met with criticism,[13] the unmistakable presence in the fluid of a substance, which if not the active principle at least possesses similar properties, has since been clearly demonstrated by a number of workers who have taken advantage of the more exact and dependable oxytocic and melanophore-expanding properties of the extract subsequently discovered by Dale and by Hogben. Thus Cow[14] (1915), Dixon[15] (1923), Trendelenburg[16] (1924), Jánossy and Horváth[17] (1925), Miura[18] (1925), Trendelenburg[16] (1926), Blau and Hancher[19] (1926), Mestrezat and van Caulaert[20] (1926), McLean[21] (1928), Hoff and Wermer[22] (1928), and Karplus and Peczenik[23] (1930), have successively shown: (1) that a substance whose pharmacological properties resemble those of posterior lobe extract* is often demonstrable in normal ventricular and cisternal though not in the lumbar fluids;[20] (2) that it may be augmented by the administration of certain organic extracts[15] as well as by certain drugs, particularly those producing diuresis;[22] (3) that it disappears after hypophysectomy or occlusion of the pituitary stalk;[16] (4) that it is increased by emotional stimuli;[22] and finally (5) that it is augmented by direct electrical stimulation of the tuber cinereum.[23]

McLean[21] in the writer's laboratory was led to believe that the active principle is detectable in the jugular vein in larger amounts than in the cerebrospinal fluid. He consequently concluded that it was initially absorbed solely by the vascular route (the abundant "portal circulation" connecting hypophysis and hypothalamus recently described by Popa and Fielding[24] would readily make this possible), and that, being a readily dialyzable substance, it found its way back into the cerebrospinal fluid through the choroid plexuses. On the other hand, the recent brilliant demonstration of Karplus and Peczenik,[23] who showed that the amount of the oxytocic and melanophore-expanding substance in the fluid is increased by electrical stimulation of the tuber, amply justifies their conservative conclusion that the active principle of the posterior lobe is discharged, at least in part, into the ventricular fluid.

It was the original assumption of Goetsch and Cushing that the extrusion of the hyaline bodies between the ependymal cells into the infundibular cavity, whence they were swept along by the cilia of the ependymal cells until dissolved, represented a form of "external secretion" which, in its cerebrospinal fluid medium, was destined ultimately to reach the blood-stream by way of the arachnoid villi. It did not occur to them that the substance, owing to its ready diffusibility, might, by resorption,

* It should be mentioned that Van Dyke, Bailey and Bucy (*J. Pharmacol. & Exper. Therap.*, 1929, XXXVI, 595–610) after a painstaking chemical study have come to the conclusion that the oxytocic and melanophore-expanding effects of cerebrospinal fluids are wholly ascribable to differences in the calcium concentration between the test fluids and the bathing fluids. They have made a strong case but it would be difficult to believe, for example, that an increase in the oxytocic and melanophore-expanding properties of the fluid after electrical stimulation of the tuber could be due to increase of calcium.

act directly upon subependymal nerve centers in the walls of the third ventricle. Indeed, twenty years ago little was known of these hypothalamic nerve centers, and the functional importance of the diencephalon was scarcely suspected.

INTRAVENOUS VERSUS INTRAVENTRICULAR EFFECTS OF PITUITRIN

When injected intramuscularly or intravenously, in addition to its well-known antidiuretic effect, pituitrin causes prompt blanching of the skin and mucous membranes from a vigorous vaso-constrictor action, dryness of the mouth from loss of salivary secretion, and an early evacuation due to stimulation of the lower bowel. That injection of the extract directly into the cerebral ventricles calls forth a wholly different response was briefly reported in a recent address [Lister Lecture] dealing in general with what were called neurohypophysial mechanisms. It was therein stated that the extract thus injected will in certain cases cause an astonishingly prompt response characterized by intense flushing from vasodilatation, by profuse perspiration, by retching and vomiting, by salivation, by a marked fall in body temperature, and by a coincidental lowering of the basal metabolic rate. These responses occur in the absence of any significant pupillary change, pilomotor reaction, or stimulation of the lower bowel.

Though the intensity of the reaction varies considerably from case to case, the following protocol may serve as an illustration of a moderately pronounced effect:

The patient, a vigorous young man with outspoken acromegalic gigantism, was admitted to the hospital on *December 8, 1930*, with the single complaint of failing vision. He was found to have a bitemporal hemianopsia, primary optic atrophy with loss of reading vision and a greatly expanded sella turcica.

On *December 19* the usual right transfrontal osteoplastic exploration was made. A large chromophil adenoma was exposed and radically excavated by a combination of electro surgical methods and suction, restoration of the temporal fields of vision being demonstrable at the conclusion of operation. He made a perfect recovery from this procedure with no polyuria or other evidence of tuberal contusion.

Apart from the prompt restoration in vision, the only postoperative change detected was a considerable drop (20 points) in the basal metabolic rate, together with the customary loss in weight shown by acromegalics after one of these operations. He was a coöperative and intelligent young man and before his discharge willingly submitted to the tests which we proposed to make.

8.30 A.M. January 8, 1931. Preliminary Observations.—Fasting. Basal metabolic rate −13. Weight 85.8 kgm. Erythrocytes 5,160,000. Blood sugar 0.099. Voided 440 c.c. urine. Rectal temperature 99.8°F.* Pulse 80. Room temperature 73°F. Respiration 21. Blood-pressure 130/80. Skin dry. Hands and feet rather cool and moist. Pupillary measurements registered.

10.39 A.M.—Injection into lateral ventricle of 1 c.c. of *surgical pituitrin.*

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* In all these observations the continuous record of the rectal temperature has been taken on a Leeds & Northrup Resistance Thermometer Recorder.

10.45.—Sensation of warmth. Definite flushing of skin except over site of bone flap. Sudden profuse sweating.

10.51.—Slight rise in blood-pressure. Profuse perspiration with no appreciable lachrymation, salivation or change in pulse. Complaint of intestinal uneasiness. Borborygmi auscultable. Hands and feet have become warm.

10.58.—Flushing has become very pronounced. Sweat excessive. Pillow and sheets wringing wet (*cf.* frontispiece).

11.00.—Temperature beginning to fall. Erythrocytes 4,550,000. Blood sugar 0.121. No pupillary change.

11.11.—Rectal temperature 99.3°. Flush persists. Slight temporary increase in pulse rate to 100. Brief preliminary drop in systolic blood-pressure to 110 now followed by pressor response to 140.

11.20.—Temperature falling rapidly. Now 98.5°. Flush persists. Perspiration still excessive. Nauseated but no cramps.

11.30.—Rectal temperature 97.7°. Condition otherwise unchanged.

11.38.—Gradual slowing of pulse to 60 and of respiration to 12. Blood-pressure fallen to pre-injection level of 130. Rectal temperature 96.8°.

11.50.—Rectal temperature 96°. Flush fading. Perspiration much diminished.

12.00 noon.—Rectal temperature 95.3°. Flush barely perceptible. Skin drying. Still nauseated.

12.10 P.M.—Rectal temperature 94.8°. Pulse 60.

12.20.—Rectal temperature 94.2°. Vomited 75 c.c. of bile-stained mucoid fluid.

12.30.—Rectal temperature continues at 94.2°, its lowest point, a drop of 5.6° F. in 1 hour 40 minutes. Erythrocytes 4,800,000. Blood sugar 0.114.

12.41.—Basal metabolic rate −31. Rectal temperature has started to rise, 94.4°. Beginning to feel cold though he has been well covered and room temperature at this time is 77°F.

2.30.—Weight 83.9 kgm. Loss of 1.9 kgm.

2.45.—Vomiting again, 150 c.c. of yellow mucoid fluid. Unable to void voluntarily. Bladder feels empty.

3.00 et seq.—Returned to ward. Rectal temperature (taken by thermometer) did not regain pre-injection level until 6 P.M. and continued to rise to a maximum of 101°F. at 2 A.M. Voided 400 c.c. at 6 A.M. Morning rectal temperature 99.8°F. 8.30 A.M. basal metabolic rate −1, a rise of 30 points from low injection level of day before.

To summarize: The injection in this case gave a marked reaction, its more striking features being the vaso-dilatation and sweating (sparing the skin over the bone-flap); the drop of 5.6°F. in body temperature in the course of an hour and a half with coincidental lowering of the basal metabolic rate from −13 to −31. Vomiting was less pronounced and more tardy in appearance than usual but the patient stated that he never vomits easily. The customary salivation and lachrymation were not noted. There was no temporary increase in erythrocytes as has been observed in some other tests though the loss of fluid from sweating would have led one to expect there might be, regardless of a possible contraction of the spleen.

Similar injections with varying amounts of the extract (one cubic centimeter of surgical pituitrin being the customary dose) have been made up to the present time on 38 occasions in 24 subjects. The majority

of the patients who have submitted to the tests were convalescing from operations for pituitary adenoma of one sort or another, the larger number of them with adenomas of chromophobe variety associated with moderate signs of pituitary insufficiency (hypopituitarism). As this clinical state is usually accompanied by more or less pallor and by an extreme dryness of the skin, the flushing and sudorific response have been the more striking. Because the operations on these patients had been conducted for the purpose of restoring vision lost from pressure against the chiasm of a large adenoma, this fact implies that the posterior lobe was in all probability thrown out of function by the expanding intrasellar lesion, which might conceivably have had some bearing on the intensity of the reaction. However, other persons without pituitary adenomas and with normal third ventricles prove to be equally susceptible to the effects of the injection.

As might be expected, due partly to individual idiosyncrasy of the subjects of these tests as well as to the variety of intracranial disorders by which they were victimized, and due partly to possible differences in the activity of the commercial preparation employed, precise standardization of which is difficult, considerable variability in the intensity of the responses has been observed from case to case. In one patient a cubic centimeter of "obstetrical pituitrin" gave no reaction whatsoever. In another, the customary cubic centimeter of "surgical pituitrin" gave only the slightest reaction; but two days later 1.5 c.c. gave a severe reaction with the usual pronounced flush, sweating, vomiting, salivation and lachrymation with fall in temperature of 5.9°F. within two hours. In this particular instance, shivering accompanied the fall in body temperature and, contrary to the usual rule, there was a rise in the metabolic rate. Ordinarily the rate falls, a drop from −27 per cent to −50 per cent having been observed in one patient with a chromophobe adenoma.

No characteristic pupillary reaction has been detected in any case. Observations on blood sugar, on blood fat, on the erythrocyte count have not been as yet sufficiently numerous or sufficiently striking to justify an attempt to interpret them. The expected haemodynamic response has in most cases been surprisingly slight and brief or altogether absent even when the reaction has been otherwise marked; when it has occurred there has usually been a slight slowing of the pulse. There has almost always been a temporary oliguria, but the effect on the excretion of urine has been obscured by the fact that the tests have been made on fasting patients with considerable loss of fluid from vomiting and sweating.

The injection in all cases has been made into the lateral ventricle and the question naturally arises as to the way in which the extract acts when thus introduced. Two possibilities suggest themselves: (1) Resorption into the blood-stream; and (2) the direct stimulation of hypothalamic nuclei by diffusion of the substance through the ependymal lining of the third ventricle. The former is highly improbable not only because of the promptitude of the reaction but for the reason already mentioned,

that pituitrin when injected into the blood-stream or intramuscularly has a vaso-constrictor effect and causes cutaneous pallor, whereas vaso-dilatation with flushing and hyperhidrosis are evoked by its intraventricular injection. Other evidences of a more negative character, which will be reserved for a subsequent paper, speak in favour of the view that the extract must act as a direct stimulant to subependymal hypothalamic nuclei.

In three patients who have previously shown a marked reaction to one cubic centimeter of pituitrin in the ventricle, the commercial products of "pitressin" and "pitocin" have subsequently been given in like (1 c.c.) amounts. A slight reaction to each substance was observed in one instance but nothing comparable to the effect of pituitrin itself. In one patient, indeed, a cubic centimeter of each substance was given coincidentally with no observable effect whatsoever.

SUMMARY

Though extracts of the neurohypophysis are known to possess pharmacological activity, extirpation of this portion of the gland or its destruction by disease leads to no symptoms that are as yet clinically recognizable. Nevertheless histological evidence has been provided which shows: that the lobe is under control of an abundant non-myelinated nerve supply from the tuber; that the hyaline bodies of Herring probably represent the secretory product; that these bodies not only may pass into the recently discovered sinusoids of the tuber but also into the ventricular cavity. A substance having the properties of posterior lobe extract has been found by many in the cerebrospinal fluid; stimulation of the tuber has been shown to increase its amount; and commercial pituitrin injected into the ventricle has a pronounced stimulatory effect, essentially parasympathetic in character, apparently nuclear in origin, and presumably due to diffusion of the substance through the ependymal lining of the ventricle.

CONCLUSION

Though the function of the neurohypophysis has been wholly overshadowed experimentally and clinically by the recent attention drawn on the one hand to the hormones of the anterior lobe and on the other to the centers in the hypothalamus, the striking response to the injection of its active principle into the ventricle not only gives additional evidence in favor of its normal passage into these cavities, but shows that the posterior lobe must play a far more important rôle in neurophysiology than has been heretofore appreciated.

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II. THE SIMILARITY IN THE RESPONSE TO POSTERIOR LOBE EXTRACT (PITUITRIN) AND TO PILOCARPINE WHEN INJECTED INTO THE CEREBRAL VENTRICLES

IN THE preceding communication it was pointed out that the intraventricular injection of "pituitrin" has a profoundly different effect from that which follows its subcutaneous or intravenous administration. Instead of the customary pallor of the skin with evacuation of the bowel, there usually occurs a prompt cutaneous vaso-dilatation with an extreme sudorific effect, often with repeated vomiting and a considerable fall in body temperature.

This peculiar and striking response to pituitrin when put in the ventricles was so suggestive of the known pharmacological reaction to pilocarpine that it seemed advisable to make comparative studies of the effect of the extract and of this drug. Accordingly, in one of the patients who had shown at an earlier session a well-marked reaction to intraventricular pituitrin, a test was first made with a subcutaneous injection of 12 mgm. of pilocarpine. This led to the familiar response characterized by moderate flushing, slight sweating with salivation and lachrymation, some intra-abdominal uneasiness but no vomiting, a temporary increase of 20 points in the pulse rate but no change in blood-pressure or pupils, and an insignificant fall in rectal temperature of 0.8°F. A slight rise of 7 points in the basal metabolic rate was observed but this was considered to lie within the margin of error.

On the following day, less than half of this dose of pilocarpine, namely, 5 mgm., was introduced into the lateral ventricle. Almost immediately there was a rise in pulse rate of 20 points without appreciable alteration in blood-pressure or change in size of the pupils. In a few moments the patient had a sensation of warmth soon followed by a marked generalized flush, a drenching perspiration, and excessive salivation accompanied by prolonged retching and vomiting. In the course of the next two hours the temperature dropped off two degrees, from 98.8° to 96.8° but with no change in the basal metabolic rate.

This reaction was more severe than had been anticipated and in the six other patients, on whom similar tests have subsequently been made, one-half of this amount of pilocarpine, namely, 2.5 mgm., has been introduced; but this smaller dose has elicited the same prompt and striking reactions in all instances but one. The exception was in a patient who had a glioma involving the tuber and in whom the intraventricular injection of 1 c.c. of surgical pituitrin had likewise caused no appreciable effect.

To show how nearly comparable are the reactions to the two substances administered in this way the following protocols may be given side by side.

The patient, John S., was convalescing from an operation for the removal of a large glioma of the left temporo-occipital region unassociated with hydro-

cephalus. At the time the tests were made his wound was healed, there was no tension, and he was wholly free from symptoms. A previous intraventricular injection of 1 c.c. of surgical pituitrin in the ventricle had caused a definite though inconspicuous response leading to a fall of temperature of one degree only and, contrary to the usual rule, a rise in metabolism from +1 to +8. He was then given a test with 2.5 mgm. of pilocarpine which evoked such a marked reaction that on a subsequent occasion, for better comparison of the two effects, a dose of 1.5 c.c. of pituitrin was injected. The protocols of these two tests are subjoined.

REACTION TO PILOCARPINE (*cf.* CHART I)	REACTION TO PITUITRIN (*cf.* CHART II)
Jan. 17, 1931.—Preliminaries, *9 A.M. et seq.* Basal metabolic rate −1; weight 65.4 kgm. *Blood:* erythrocytes 5,010,000; sugar 0.124 mgm.; total lipoids 0.652. Pupils 5 mm. (unaffected throughout). Rectal temp. 99°F.; pulse 65; blood-pressure 124/75.	*Jan. 22, 1931.* Preliminaries, *9 A.M. et seq.* Basal metabolic rate; +3; weight 66.4 kgm. *Blood:* erythrocytes 4,290,000; sugar 0.098 mgm.; total lipoids 0.635. Pupils 4.5 mm. (unchanged throughout). Rectal temp. 98.9°F.; pulse 65; blood-pressure 124/76.
10:30 Ventricular tap; 5 c.c. fluid withdrawn.	*10:28* Ventricular tap; 5 c.c. fluid collected.
10:38 *Injection 2.5 mgm. pilocarpine* with prompt slight enduring rise in blood-pressure to 156/95.	*10:38* *Injection 1.5 c.c. surgical pituitrin* with prompt slight enduring rise in blood-pressure to 150/90.
10:43 Borborygmi; nausea; vomiting; slight flush.	*10:42* Nausea; slight flush; feels warm; skin moist.
10:48 Continued vomiting; marked flush; free sweat.	*10:47* Perspiring freely; salivation; lachrymation; blood for erythrocytes 4,570,000.
11:09 Periodical retching and vomiting continuous. Heavy sweat.	*11:00* Marked flush; heavy sweat; nausea continues.
11:10 Temp. begins to drop (after thirty-two minutes).	*11:04* Temp. begins to drop (after twenty-six minutes).
11:17 Retching; vomitus blood-streaked.	*11:31* Continued rapid fall in temp. to 96.4°; no vomiting.
11:20 *Blood:* erythrocytes 4,950,000; sugar 0.160; total lipoids 0.685.	*11:47* *Blood:* erythrocytes 4,450,000; sugar 0.111; total lipoids 0.657.
11:30 Sweat still profuse; retching less frequent.	*12:10* Flush fading; cessation of sweat; temp. 93.8°.
12:20 Flush fading; skin drying; temp. 96.6°.	*12:29* Reaction about over. Temp. at lowest level, 93°. Shivering though body and extremities warm to touch.

REACTION TO PILOCARPINE
(*cf.* CHART I)

(*Continued*)

12:35 Reaction practically over. Temperature at lowest level, 96.4°.

1:00 Metabolism taken, +6. Weight 63.8 kgm.

1:20 Chart discontinued. Temp. at 97.2°. Blood-pressure remains slightly elevated. Rectal temperature subsequently taken half-hourly by thermometer; preinjection temperature not regained until 3:30.

REACTION TO PITUITRIN
(*cf.* CHART II)

(*Continued*)

1:00 Metabolism +46 (shivering); weight 64.3 kgm.

1:20 Metabolism +23. Temp. 94°. Comfortable; no shivering.

2:20 *Blood:* total lipoids 0.686; metabolism +22; temp. 95°.

3:20 Metabolism +26. Temp. 97°.

4:20 Metabolism +29. Temp. 97.8°. Weight 64.3 kgm. Chart discontinued. Subsequent rectal temperatures taken with thermometer half-hourly. Pre-injection temp. of 99° not regained until 7 P.M.*

The *similarities* in the reactions to the given doses of pilocarpine and pituitrin noted in these protocols are possibly still more apparent from the plotted records which are here appended (Charts I and II). These charts show the prompt slight pressor response which endured throughout the period of reaction; the secondary slight slowing of pulse rate; and the downward chute in rectal temperature which began after the lapse of about half an hour. Both substances produced the same pronounced flush and drenching sweat which lasted approximately one hour and a half. There was no appreciable change in the size of the pupils with either injection.

The chief *differences* in the responses lay: (1) in the more marked vagal effect from pilocarpine with continued retching and vomiting until positive blood was shown by the guaiac test whereas there was only a brief period of nausea with pituitrin; (2) in the far more pronounced and enduring fall in body temperature from pituitrin which persisted long after the cessation of the sweat, the normal rectal temperature not having been regained after the 2.6° drop due to pilocarpine until three hours had elapsed, and after the pituitrin test, with a 5.9° drop to its lowest level of 93°, not until the lapse of six and one-half hours.

One peculiarity in the reactions shown by this patient was the unexpected increase of 43 per cent in the basal metabolic rate which coincided with the lowest temperature caused by the pituitrin injection.

* [It should have been emphasized that there is apt to be a moderate thermic rebound after the period of subnormal temperature. This same patient a year later, when again tested (*cf.* pg. 128), had a thermic rebound from 96° to 104° seven hours after the injection (2.5 mgm.) of intraventricular pilocarpine, and there was a moderate rebound of 4° after intraventricular pituitrin.]

For this astonishing reaction with the body temperature at 93° there is no ready explanation unless it was that the patient was shivering. The finding was so contrary to the usual rule, it was repeated hourly for the next four hours, the rate as recorded in the protocol still remaining high though shivering had ceased; and on the following morning it was found to be still elevated at +13 though the patient was comfortable, composed and without fever.

At an earlier session, as mentioned above, a cubic centimeter of pituitrin had given only a mild reaction, and it may be presumed, had we cared

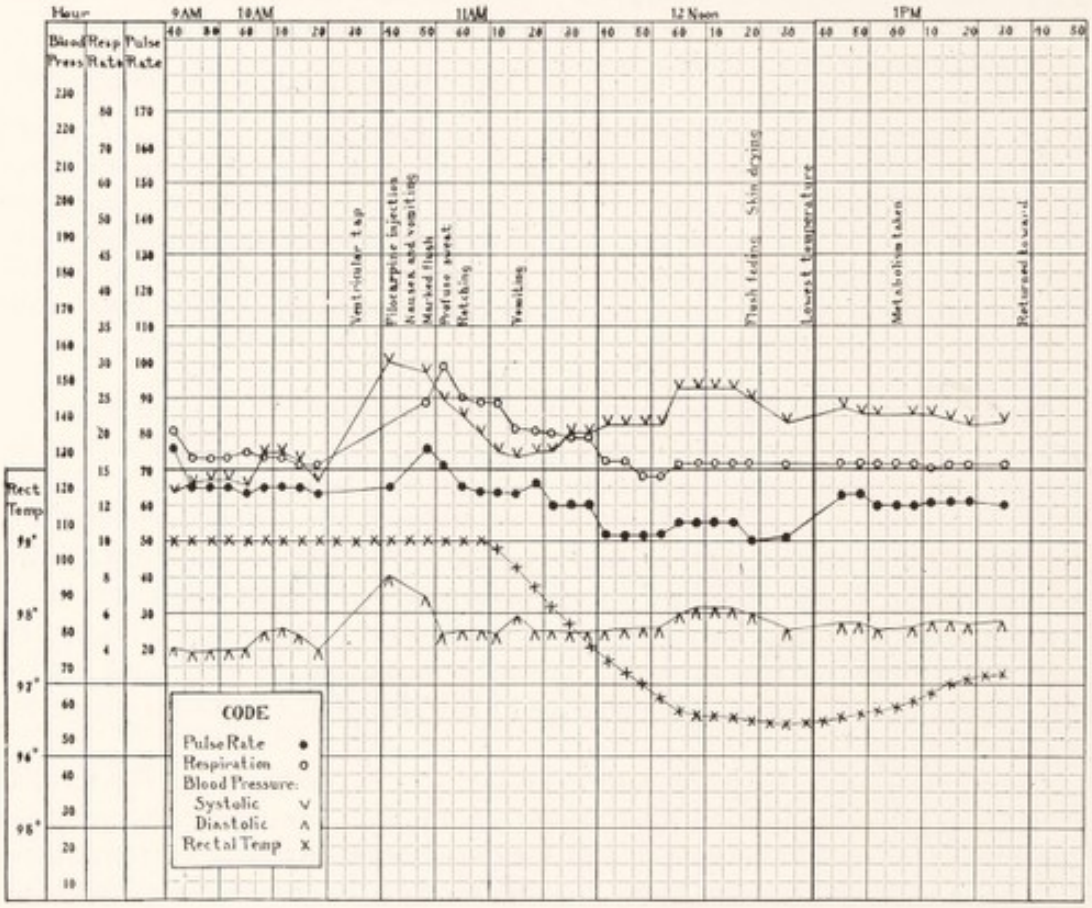

CHART I

Showing the effect on pulse rate, respiration, blood-pressure and rectal temperature of an intraventricular injection of 2.5 milligrams of pilocarpine.

to subject this willing man to further tests, that a dose of pilocarpine larger than 2.5 mgm. would have given as striking an antypyretic response as the 1.5 c.c. dose of pituitrin evoked. In the two patients in the series who had received 5-mgm. intraventricular doses of pilocarpine, one showed a fall of 2° in temperature in one and one-half hours and the other a fall of 4.5°. Personal idiosyncrasy doubtless is but one of many factors in the variability of the reactions; the remarkable thing is that the responses to the two substances, under the inexact circumstances of these observations, not only bear such a close resemblance but are chronologically and quantitatively so similar.

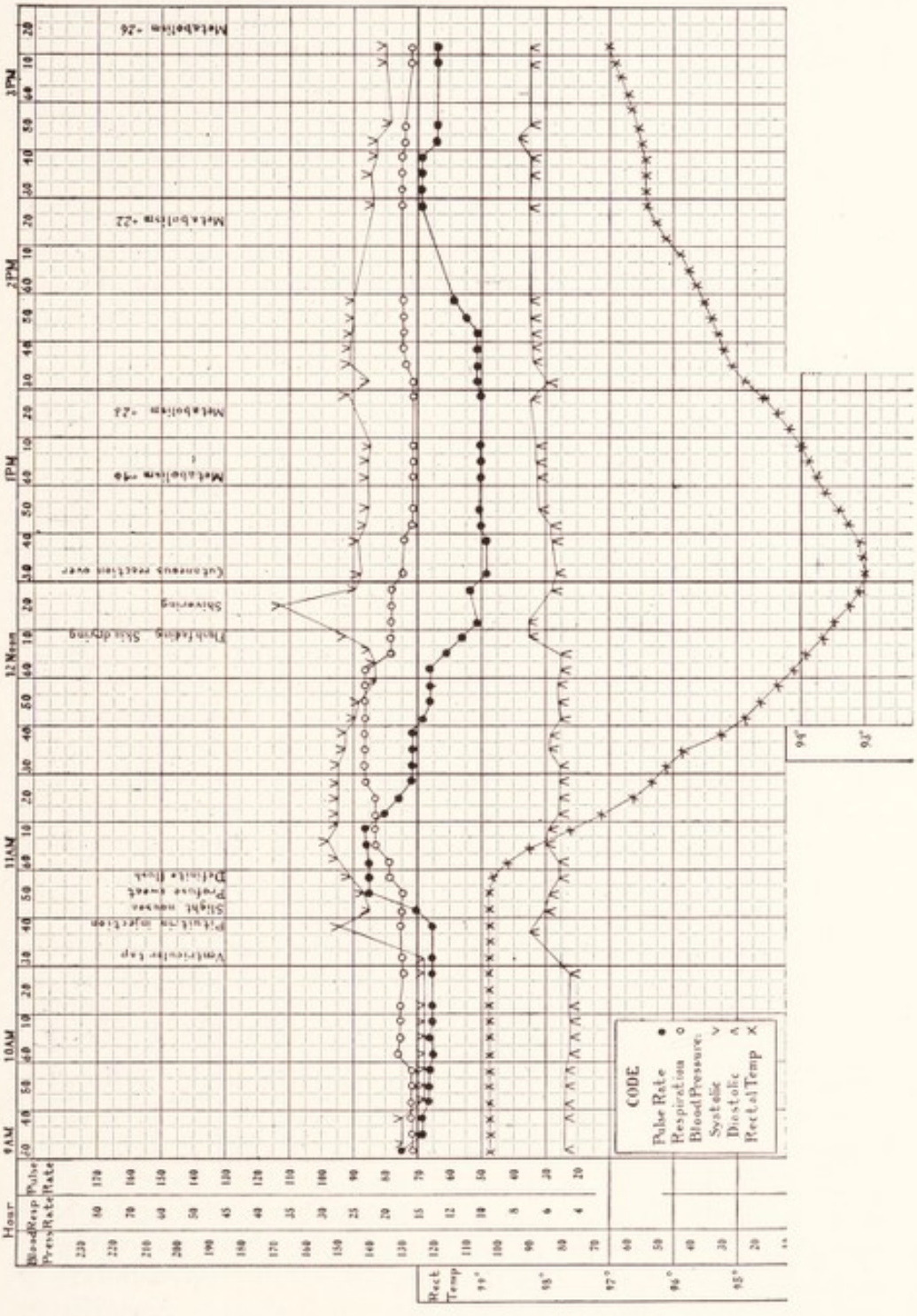

CHART II

Showing (for comparison with Chart I) the effect of 1.5 cubic centimeters of pituitrin injected into the ventricle of the same patient at a subsequent session.

Just how and where pilocarpine and its allied drugs act upon the secretory glands seems to be not fully agreed upon by pharmacologists. They are supposed to have an excitatory effect on the parasympathetic nerve terminations in the various glands and at the myoneural junction of smooth muscle. And since the effect of atropine is antidotal to that of pilocarpine, it has been assumed to have a paralytic effect on the same terminal apparatus whether in salivary, gastric, pancreatic or sudoriferous glands of unstriated muscle. Some authors, indeed, have claimed that the action of muscarine and allied drugs is a direct one on the organs themselves and that the nerves are not in any way involved. However this may be, all authorities agree that the effect of these drugs on the circulation varies in different species, and so far as man is concerned neither has a haemodynamic response been observed nor any effect on the pulse rate in any dose that one would feel justified in administering.

Though the physiological action of pilocarpine is evidently expended somehow in stimulating the autonomic nervous system, the possibility that it might act on a higher center controlling the system rather than peripherally does not seem to have been given due, if any, consideration. This may, indeed, be true of other drugs, the effects of which are similarly apt to be studied on unanaesthetized animals or on pithed animals under artificial respiration.

Though the subject, whose tests have been cited in the protocols above, happened to be convalescent from an operation for a cerebral glioma which had been exposed from the side, the larger number of tests in the series have been made upon patients following frontal osteoplastic operations for pituitary adenomas. In the process of making the customary bone flap for all such procedures four or more preliminary perforations are made through the skull and these small holes make subsequent access to the ventricle by a needle even more simple than the performance of a lumbar puncture. The flap, moreover, is so outlined that its lower leg, for purposes of concealment, passes through the line of the eyebrow which necessitates division of the supra-orbital nerves to the corresponding side of the forehead. Hence the scalp overlying the bone flap, though its blood supply is intact, is denervated and remains anaesthetic until, in the course of some months, the nerves reunite.

It has long been known to clinicians that paralysis of the peripheral nerves renders the corresponding skin field irresponsive to the sudorific effects of pilocarpine. This fact, utilized long ago by Victor Horsley to determine the upper level of a spinal cord lesion, has been more recently employed by Otfrid Foerster as a means of mapping out the dermatomes after the surgical division of the spinal nerve roots. However, owing to overlap of the skin fields supplied by the spinal segments, the boundary of the affected area under these circumstances is less sharply demarcated than in the operations under consideration.

As shown in Miss Codding's colour sketch (opposite pg. 59), the perfectly healed flap remains pale and dry in striking contrast to the rest of the face and body which may be greatly flushed and dripping with sweat. With a

sufficient dose, either of extract or drug, to give a marked reaction the contrasting colour effect in the forehead is brought out by either intraventricular pilocarpine or pituitrin and also by an intramuscular injection of pilocarpine. On the other hand, the intramuscular or intravenous injection of pituitrin, as already pointed out, causes a generalized pallor which affects the skin of both sides of the forehead alike. Since the circulation of the bone flap remains intact, this would appear to indicate that the effects both of pituitrin and pilocarpine introduced by way of the ventricle are not exerted on the sweat glands through the medium of the circulating blood or of sympathetic fibres which accompany arterial blood-vessels, but must be produced by effector impulses which travel from some higher centre along fibres which accompany the peripheral sensory nerves.

Both of these substances, moreover, the drug as well as the extract, give reactions that suggest a parasympathetic rather than a sympathetic (thoraco-lumbar) stimulation; and whether it is justifiable to assume that these supposedly reciprocal systems, if they are actually separable, is each under the control of its own higher hypothalamic centre further studies may possibly show. Unquestionably the action of other drugs, particularly those of the muscarine series, when introduced into the cerebral cavities is a matter that needs ventilation.

CONCLUSIONS

Pilocarpine and pituitrin have a similar action in producing widespread vaso-dilatation, sweating, vomiting and lowering of the body temperature when injected into the cerebral ventricles. The effects suggest a central autonomic stimulation predominantly parasympathetic in character.

III. THE ACTION OF ATROPINE IN COUNTERACTING THE EFFECTS OF PITUITRIN AND OF PILOCARPINE INJECTED INTO THE CEREBRAL VENTRICLES

IN THE two preceding papers it has been shown: (1) that the intraventricular injection of pituitrin leads to a striking response characterized by nausea and vomiting, flushing, sweating, salivation and a marked fall in body temperature usually though not always accompanied by a drop in the basal metabolic rate; and (2) that a reaction of surprizingly similar type promptly follows the intraventricular injection of pilocarpine.

Since we have in atropine an effective antidote to pilocarpine, it was felt that should the reaction of pilocarpine by way of the ventricle be checked by atropine, we might expect the pituitrin reaction to be similarly checked if the two substances, the drug and the extract, in the production of their similar effects, actually operated through the same, and probably central, nervous mechanism.

On one or two occasions when the reaction to pituitrin had been more

marked than expected and the subject was rendered unduly uncomfortable from the recurrent retching and vomiting, it had been observed that an injection of 1 mgm. of atropine and 5 mgm. of morphia effectually checked the reaction. Under this suggestive lead, the matter was first put to test as follows:

A patient, convalescent from a highly successful operation for a chromophobe adenoma, had shown on *October 14, 1930,* a typical, moderately severe response to the intraventricular injection of 1 c.c. of pituitrin with sweating, vomiting and a fall of temperature of two degrees in two hours accompanied by a drop in the basal metabolic rate from −11 to −18. On repeating the test four days later, with the coincidental subcutaneous injection of 1 mgm. of atropine, there was no discernible response.

Another patient, likewise convalescent from a similar operation for the same malady, had shown on *October 16, 1930,* a somewhat tardy (thirty minutes) but typical response to 1 c.c. of intraventricular pituitrin with moderate sweating, flushing and vomiting over a period of two hours and a drop in temperature of 1.2°F. Eight days later, 5 mgm. of intraventricular pilocarpine provoked a prompt and vigorous reaction with vomiting, sweating, flushing, lachrymation and salivation, and a drop in rectal temperature of 4.4° in ninety minutes, the basal metabolic rate remaining unchanged. After an interval of three days, on *October 27, 1930,* the intraventricular injection of 1 c.c. of surgical pituitrin, when repeated with the coincidental subcutaneous injection of 1 mgm. of atropine, caused no appreciable reaction apart from a subjective dryness of the mouth, a possible slight temporary contraction of the pupils, a trifling increase in pulse rate and a moderate pressor response.

It remained to be seen whether atropine would have an inhibitory effect on the response to pituitrin as well as to pilocarpine when coincidentally injected into the ventricle. A favourable opportunity to make the test occurred in the following case:

The patient, a woman fifty-six years of age, had been operated upon *November 10, 1930,* for a fairly well encapsulated left parasagittal glioma which was easily removed, apparently intact. From this operation she made an excellent recovery with perfect wound healing and no febrile reaction at any time until the 17th postoperative day when for the first time, following a series of x-ray treatments, she showed a slight wave of pyrexia, reaching 102°F.

Having already come to realize the possibility that the temperature-lowering effect of intraventricular pituitrin might be utilized to combat the neurogenic hyperthermias which sometimes occur after serious operations for tumors,* though there was no reason for suspecting that this patient's mild fever was of this type, it at least gave an opportunity of seeing what would be the effect of the injection as an antipyretic.

Accordingly on *November 28* at *4:25 P.M.*, the rectal temperature being 102.4°F., 1 c.c. of *surgical pituitrin* was introduced *into the ventricle* with the usual, though in this instance only a moderately striking reaction, which was somewhat delayed in onset and occurred without appreciable change in pulse rate or blood pressure. After an interval of 10 minutes there was nausea, lachry-

* These hyperthermias are more commonly observed in children after the radical removal of median cerebellar tumors which lead to the abrupt collapse of the secondary hydrocephalic distention of the ventricles.

mation and salivation; in 15 minutes, the temperature had begun to drop (101.7°); in 35 minutes sweating and flushing were first definitely noted; after 60 minutes there was a copious evacuation of the bowels (temp. 100.8°); in 1 hour 20 minutes there was an initial attack of vomiting followed by other similar attacks during the course of the next two hours by which time the reaction was over, though the rectal temperature continued to fall until *8 P.M.* when it was at its lowest point of 98.4°F., a drop of 4 degrees.

Four days later, *December 2, 1930*, with the rectal temperature at 99.8°, she was given at *9:40 A.M.* an *intraventricular pilocarpine test* (2.5 mgm.) which gave a typical reaction as follows: There was a prompt pressor response from 110/70 to 140/80 which endured throughout the test; at the end of 5 minutes she experienced abdominal uneasiness followed by nausea and retching; after 9 minutes, first appearance of sweating, flushing and salivation, soon becoming excessive; 11 minutes, an explosive, copious bowel movement;* in 16 minutes, owing to the patient's agitation the reaction was checked by a hypodermic injection of morphia 5 mgm. and atropine 0.5 mgm. This injection promptly quieted her and within 5 minutes, though the flush continued, the sweat had ceased, together with the salivation, leaving her with a dry mouth. Periodical vomiting nevertheless recurred during the next hour and a half, the last specimen showing a positive guaiac test for blood. The rectal temperature slowly dropped in the course of two hours from its initial 99.6° to 97.1°, its lowest level.

This patient, therefore, having shown a moderate reaction to an intraventricular injection of 1 c.c. of surgical pituitrin and an unduly exaggerated one to the intraventricular injection of 2.5 mgm. of pilocarpine, permitted us to try the effect of the preliminary intraventricular injection of atropine on these responses. Accordingly, on December 4, 1930, 0.5 mgm. of atropine was introduced in the ventricle, without any appreciable effect other than the sensation of dryness of the mouth and questionable slight increase in the diameter of the pupils. Thirty minutes later, one c.c. of surgical pituitrin was introduced without any subsequent subjective effect or objective reaction whatever on the part of cardiovascular, gastro-intestinal or thermo-regulatory mechanisms.†

On December 8 at 11:25 A.M., again after the usual preliminaries, another 0.5 mgm. of atropine was injected into the ventricle, the same subjective sensation as before of dryness in the mouth being produced, but there was no determinable pupillary change. Thirty minutes later 2.5 mgm. of pilocarpine was introduced, and though the tongue appeared to become somewhat more moist there was, apart from this, no observable effect of the drug whatsoever.

Whereas, after the typical response to pituitrin or pilocarpine given alone, this patient, as has been true of other subjects similarly tested, showed for some hours inappetence due to subdiaphragmatic uneasiness with waves of nausea, on the conclusion of each of the tests which were counteracted by atropine she eagerly ate a hearty lunch.

Atropine, in the opinion of pharmacologists, exercizes a paralytic

* It will be observed that both intraventricular pituitrin and pilocarpine in this case had an unusually definite effect on the sacral autonomic.

† Whether the atropine served to check the usual oliguric effect of the extract unfortunately could not be determined.

effect, like curare, at the peripheral nerve termination of the glands as well as at the myoneural junction of involuntary muscle. In other words, the drug supposedly acts at the same peripheral points at which pilocarpine causes its excitatory effects, the two drugs being peculiarly antidotal. These observations herein reported if correctly interpreted would seem to suggest that both drugs may act centrally as well, and if this is so they must probably operate through some diencephalic centre where parasympathetic impulses may be discharged or inhibited.

CONCLUSION

Atropine whether given subcutaneously or previously introduced in the cerebral ventricles appears completely to counteract the customary effect both of pilocarpine and of pituitrin when administered by way of the ventricles.

IV. THE METHOD OF ACTION OF PITUITRIN INTRODUCED INTO THE VENTRICLE

IT HAS been heretofore shown: (1) That the extract of the neurohypophysis (pituitrin) when injected into the cerebral ventricles usually provokes a striking and characteristic reaction; (2) that pilocarpine likewise introduced causes a highly similar response; and (3) that the preliminary administration of atropine, whether given subcutaneously or put into the ventricle, appears completely to inhibit the intraventricular response not only to the extract but to the drug.

Do these substances so introduced act peripherally after resorption into the blood-stream, or do they act directly upon subependymal and diencephalic nerve centres? In the attempt to answer this question it might be assumed, since the substances have always been injected into the lateral ventricle, that they might easily become resorbed into the blood-stream either through the ependyma or by way of the choroid plexuses which lie exposed in the ventricles.

It has been pointed out that this action by resorption is scarcely probable, at least in the case of pituitrin, because when given intramuscularly or injected into the blood-stream its effect is wholly different from that which follows its introduction into the ventricle. In the case of pilocarpine, on the other hand, no such differences in action are apparent, and it might well enough be assumed, since pilocarpine acts quickly by whatever method it is administered, that it is resorbed in some way into the blood-stream and then acts, as pharmacologists assume that it typically acts, on the myoneural junction in the case of smooth muscle and on the peripheral mechanisms in the case of the secretory glands which are affected by it.

In looking for an answer to this query, as propounded, it has been felt that the several patients in whom the intraventricular injections either of pilocarpine or pituitrin have been without effect might give valuable information. The negative responses which have occasionally been ob-

served are divisible in three principal groups: they occur (1) when an insufficient dose has been administered; (2) when the ventricles have been greatly expanded by hydrocephalus; and (3) when the interbrain has been the seat of tumor. These three groups will be separately considered.

1. INSUFFICIENT DOSAGE

Necessarily, owing to inexperience, the effective dose either of pituitrin or pilocarpine given in the ventricle has been a matter of guesswork. To establish the smallest dose of any drug that will provoke a characteristic response and the largest dose that can be given with safety is a pharmacological problem difficult enough, because of individual idiosyncrasy, even in normal subjects. Nor has this been the purpose of these studies in which the tests have all been made on patients convalescent from operations for a variety of intracranial disorders. The fact that the responses which have been described occur under any circumstances is surprizing enough and we must for the present let it go at that. The main point to be borne in mind is that all of the subjects (apart from those that fall in the groups 2 and 3 to follow) possess, so far as one can judge, normally reacting interbrains unaffected by the disorder for which the operations were done even in the case of the pituitary adenomas which dominate the list.

That a cubic centimeter of "surgical pituitrin" should have been hit upon as a fair average dose was purely fortuitous, and even so there is great variability in the responses, from one so mild it might easily escape notice, to one so severe it is humane to check its course by a hypodermic of morphia and atropine. In one instance a cubic centimeter of the weaker "obstetrical pituitrin" failed to cause any discernible reaction whereas the same dose of "surgical pituitrin" gave a marked response. And in a preceding paper an experience was cited (pg. 68) with a patient, almost certainly with a normal ventricular system, whose response to 1 c.c. of surgical pituitrin was mild whereas the response to 1.5 c.c. was extreme.

2. AN ACCOMPANYING HYDROCEPHALUS

On a few occasions pituitrin has been injected into hydrocephalic ventricles usually, though not always, with a negative effect. This might be explained in various ways: by the degree of dilution of the extract in the abundant fluid; by the possibility that secondary pathological changes of some sort in the choroid plexuses or ependyma prevent resorption; or (and what seems most probable) by the extreme distension of the third ventricle in whose paper-thin walls the nuclei, on whose stimulation the responses are assumed to depend, have either been destroyed or thrown out of function. The following experience is an example:

Mrs. P., forty years of age, had suffered for two years from suboccipital headaches with increasingly unsteady gait and recent blurring of vision. Examination showed unmistakable signs of a cerebellar tumor with secondary hydrocephalus and a choked disc advancing to atrophy. At operation, on *October 10, 1930*, a large median cerebellar astrocytoma was encountered and extirpated intact together with the roof of the widely expanded fourth ventricle.

She made an excellent recovery from the operation and on *October 24* an *intraventricular injection* of 1 c.c. of *surgical pituitrin* was given through the burr hole which had been made over the occipital pole to tap the ventricle during the course of the operation. There was no recognizable reaction of any sort. On the following day, *October 25*, 2 c.c. of surgical pituitrin were similarly introduced again with no determinable symptomatic response apart from a drop in urinary secretion to 400 c.c. for the ensuing twenty-four hours.

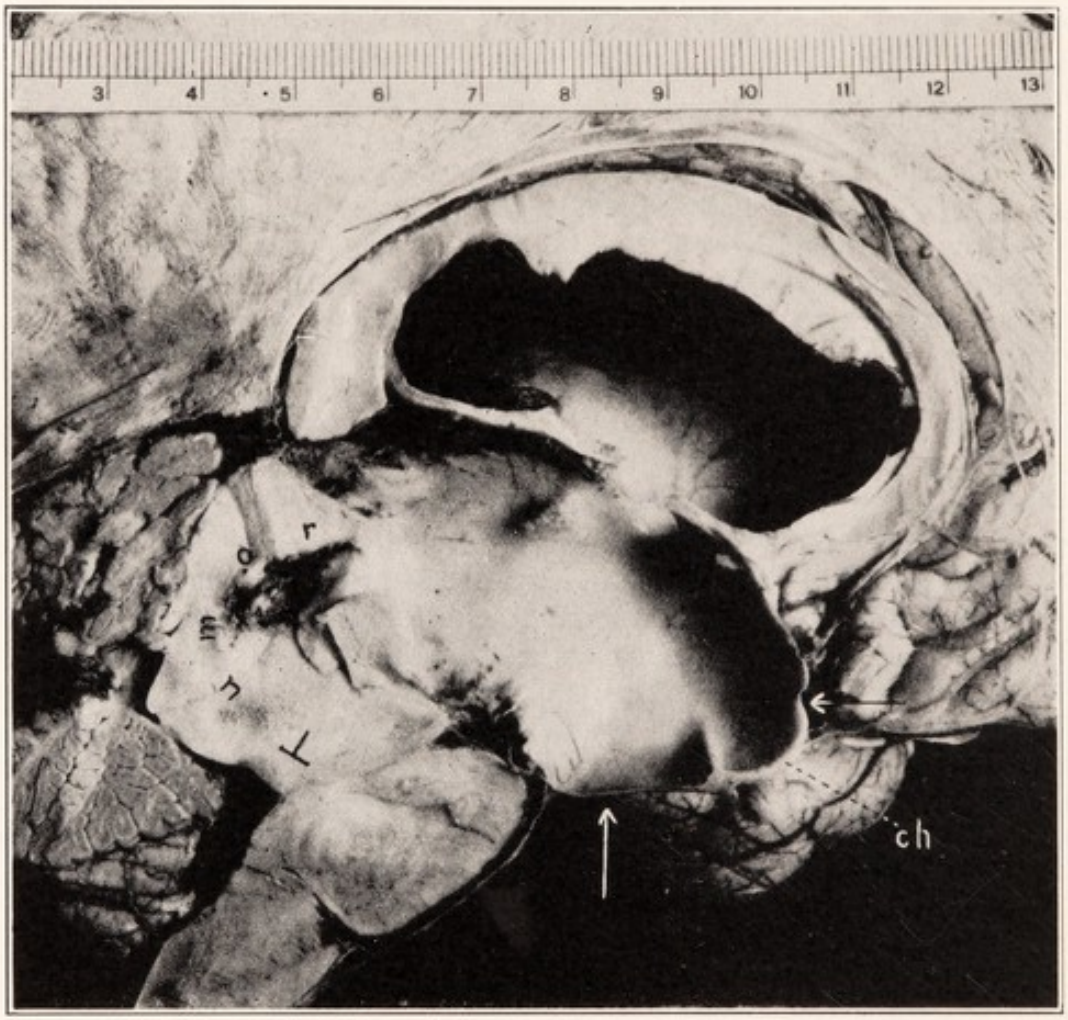

FIG. 26.—Showing (natural size) the extreme degree of expansion of third ventricle in obstructive hydrocephalus due to tumor of the corpora quadrigemina. Note the paper-thin walls of the ventricle above and posterior (arrows) to the chiasm (ch).

It is assumed that in this patient the long-standing extreme dilatation of the ventricles produced by a slowly growing cerebellar tumor, which from the first must have caused some degree of hydrocephalus, had in the course of time left the hypothalamic nuclei unresponsive to the effect of the extract. Whether in such a case, now that the hydrocephalus has been relieved, the damaged hypothalamic nuclei will regain their susceptibility to the direct action of pituitrin is undetermined; but I am inclined to believe that they will.

In another instance a patient with a more acute hydrocephalus secondary to an acoustic tumor showed, after operation, a reaction to 2 c.c. of pituitrin so marked it was checked after forty-five minutes by an injection of atropine, the temperature meanwhile having dropped 2.8°F. Hence in the presence of secondary hydrocephalus a variability in the responses may be expected, depending, one may assume, on the degree of anatomical and functional alteration in the hypothalamic nuclei brought about by the ventricular distension.

Still another instance may be cited. A child with a long-standing hydrocephalus of marked degree secondary to a chronic inflammatory process around the brain stem, had a marked hyperthermia after the prolonged cerebellar operation undertaken to reëstablish the escape of fluid. A cubic centimeter of pituitrin injected into the ventricle twice a day for several days had an apparent definite effect in lowering the temperature but there were no other appreciable symptoms.

The degree to which the walls of the third ventricle may be thinned out by a chronic hydrocephalus is well known. A typical example is shown in the accompanying photograph (Fig. 26). Histological studies of the paper-thin walls of such a ventricle show the presence of scattered and highly degenerated nuclei whose functional impairment would appear to be complete.*

3. WITH HYPOTHALAMIC TUMOR INVOLVEMENT

In this connection, though there are only two cases to report, and they were not as fully checked as one might now wish they had been, we nevertheless may feel on a little more certain ground than in the foregoing discussion regarding hydrocephalus. The essential details of the more informing of the two cases are as follows:

The patient, a married Russian Jewess, forty-nine years of age, was admitted to the Medical Service on *September 8, 1930*, with a history of vomiting and epigastric pain of two weeks' duration. There was a suspicion that she had a carcinoma of the stomach but this was finally ruled out by gastro-intestinal studies. A lumbar puncture disclosed xanthochromic fluid, and curiously enough her brother, whose cerebrospinal fluid had also been found xanthochromic, had died in the hospital several years before with the diagnosis (unverified) of a cerebral tumor.

She was transferred to the Surgical Service on *September 20* at which time examination showed a highly emaciated woman apparently quite unaware of her surroundings and in no seeming pain or distress, but wholly uncoöperative, incontinent, and in a peculiar speechless state of mental negativism. There was constant picking at the bedclothes, a marked clutch reflex, so that it was difficult to disengage her hands from what might be put into them, some exaggeration of the deep reflexes and an apparent stiffness of the neck. A slight, questionable papilloedema was noticed in the right eye alone. There was pupillary inequality, the right usually being a little larger than the left. The neurological

* Similar observations have been reported by Korst from Mogilnitzky's Pathological Laboratory in Moscow (*Ztschr. f. d. ges. Neurol. u. Psychiat.*, 1928, CXVII, 553–561).

examination was otherwise negative. Her cranial roentgenograms showed no abnormality.

A frontal tumor, possibly metastatic, was suspected. Ventriculograms showed an irregular filling defect involving the anterior part of the third ventricle, with evidence also of a mesial filling defect in the anterior horns of both lateral ventricles, particularly the left (*cf.* Fig. 28).

On *September 24*, a right osteoplastic flap was turned down and a subtemporal decompression made with the expectation that ventricular distension would cause a subsequent bulging of the flap which would facilitate an attack on the tumor at a later time. As a matter of fact, the decompression remained collapsed and there was no subsequent elevation of the flap or other evidence of any increase of intracranial tension up to the time of the patient's death in the hospital four weeks later.

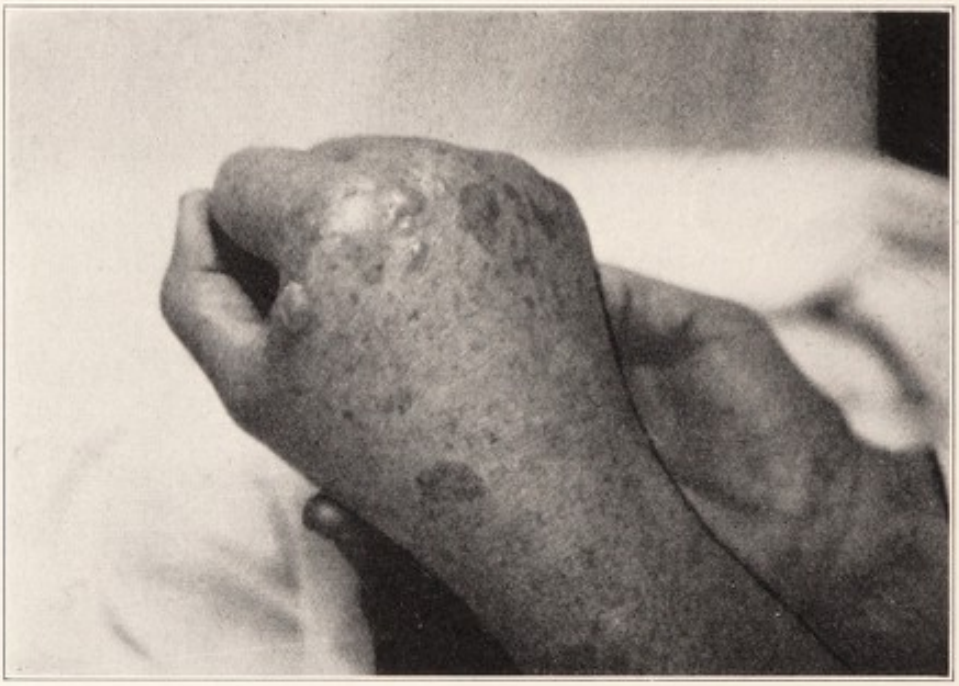

FIG. 27.—Showing the acute oedema with neurotrophic (?) formation of bullae in the clutched hand of the patient with tumor destroying the tuber cinereum.

She had been given in the interim a series of x-ray treatments, and on *October 11* ventriculography was repeated to see whether the ventricles had dilated and whether there had been any advance in the filling defect caused by the lesion, but no change was demonstrable.

One peculiar thing happened on *October 17*, namely, a sudden bilateral oedema of both hands associated with the rapid development of bullae (Fig. 27).

Intraventricular injections of pituitrin and pilocarpine.—Under the belief that the patient's symptoms of "negativism" indicated a destructive lesion of the hypothalamus it was thought justifiable to make a test with intraventricular pituitrin to see whether it would give the customary reaction. Accordingly on *October 19* a cubic centimeter of surgical pituitrin was introduced with no determinable change whatsoever in rectal temperature, pulse, or blood-pressure; there was no vomiting or appreciable alteration in the colour or degree of moisture of the skin.

A few days later an intraventricular injection of five milligrams of pilocarpine gave no reaction except three explosive attacks of vomiting 10 minutes, 20 minutes and 25 minutes after the injection. No other recognizable effects of the drug whatsoever were detected.

During the next three weeks there was a slow, gradual failure with progressive emaciation in spite of the fact that she took nourishment well. Though apparently conscious, she never moved other than to hold clutched the bedclothes or whatever might have gotten into her hand; and she never spoke. She was sup-

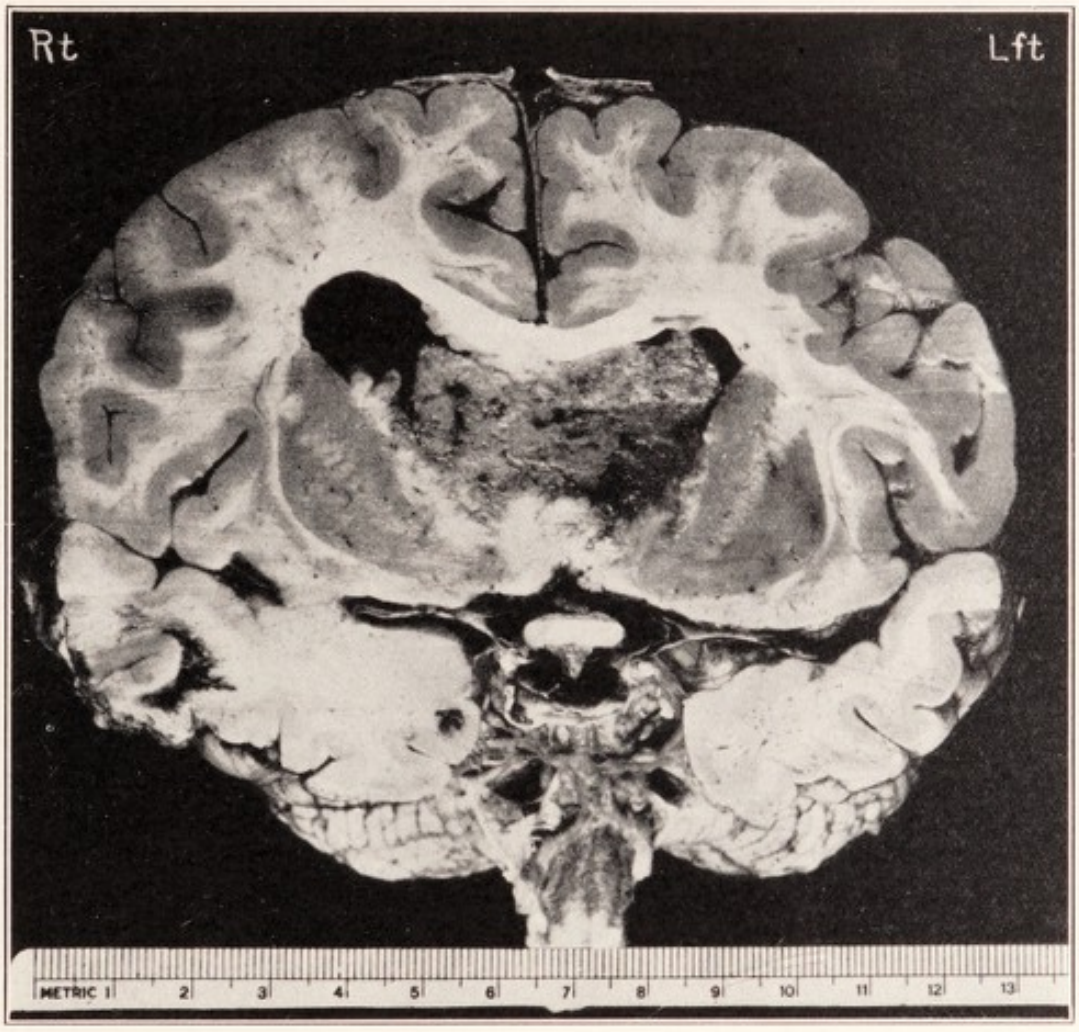

FIG. 28.—Coronal section at level of chiasm, to show the subcallosal glioma projecting into and involving the frontal horns of the ventricles.

posed to be hypersomnolent, but as she usually kept her eyes open it was difficult to say most of the time whether she was sleeping or not. There was no evidence at any time of a polydipsia. Owing to incontinence the urine could not be measured. A sudden rise in temperature to 105° on *November 17* ushered in the end.

The post-mortem examination was limited to the brain. Coronal sections showed a median, subcallosal, anteriorly placed glioma (Figs. 28 and 29). The tumor had completely destroyed the septum and had projected into the ventricles. It occupied and wiped out the anterior part of the third ventricle, leav-

ing the foramina of Monro open and the posterior part of the third ventricle intact. There was only a slight dilatation of the lateral ventricles, within which the choroid plexuses appeared normal. A mesial section of the brain showed that a gravitation metastasis from the tumor into the infundibulum had almost completely destroyed the tuberal region (*cf.* Fig. 30).

This, then, was a case in which pituitrin and pilocarpine introduced into the ventricle failed to have their usual stimulatory effect, presum-

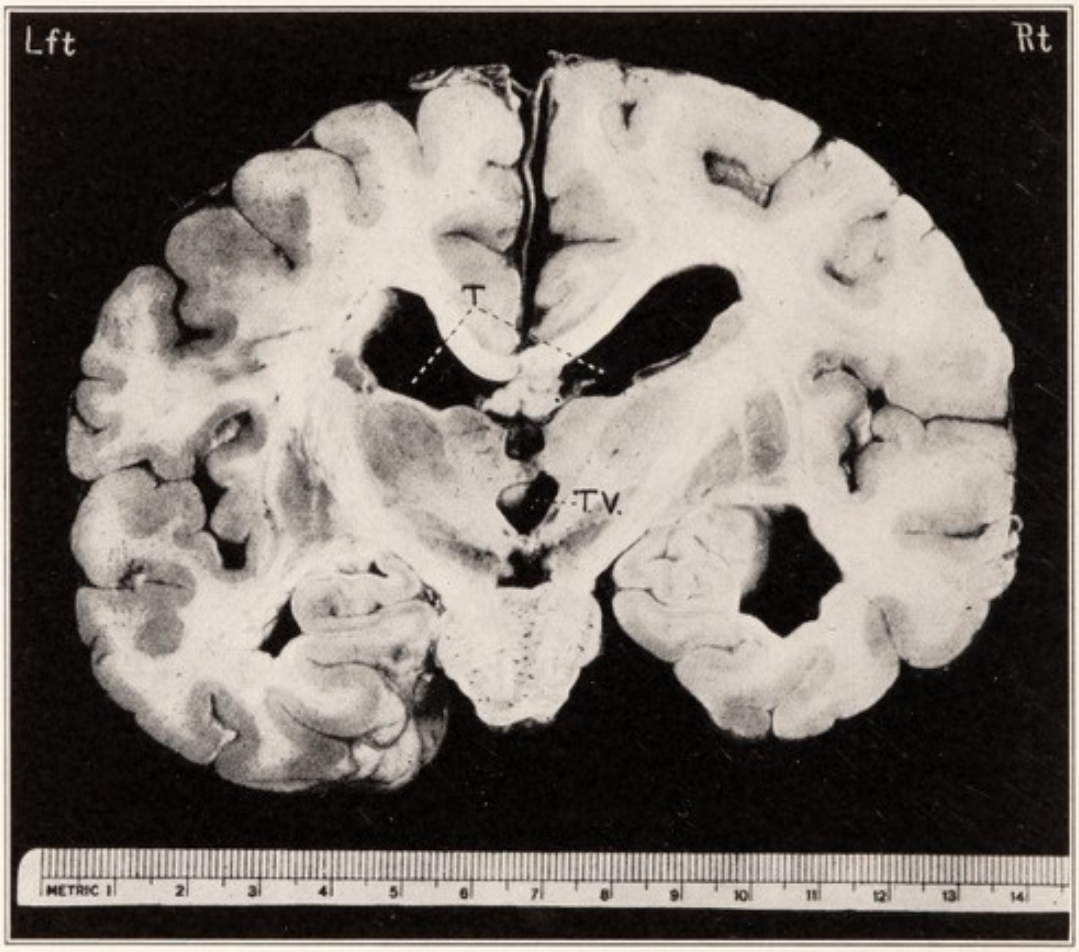

FIG. 29.—Coronal section (*cf.* Fig. 28) to show from behind the slight dilatation of the lateral ventricles in which tumor (T) can be faintly seen. The posterior portion of the third ventricle (T.V.) remains uninvolved.

ably owing to the neoplastic destruction of the centres concerned in the normal reaction.

A similar experience, though in the absence of a post-mortem examination somewhat less telling, was had with another Russian woman, fifty-seven years of age, with a tumor of the third ventricle similarly demonstrated by ventriculography. She had progressive symptoms over a period of twelve months, characterized by somnolence, mental deterioration, incontinence, and unsteadiness of gait, which were long ascribed to cerebral arteriosclerosis. In this case there was a moderate choked disc and ventriculograms showed a fairly marked expansion of the lateral ventricles, air passing freely between them, with an upward and

forward displacement of the third ventricle as from a suprasellar tumor or a tumor of the ventricle itself.

In this patient also an osteoplastic flap with decompression was made, but here again no especial evidence of pressure was found nor was there a subsequent tendency for the ventricles to fill or the flap to become elevated.

An intraventricular injection of one cubic centimeter of surgical pituitrin caused no reaction whatsoever except a moderate rise in blood-pressure from 110/65 to 140/85 which persisted for the next two hours, accompanied by

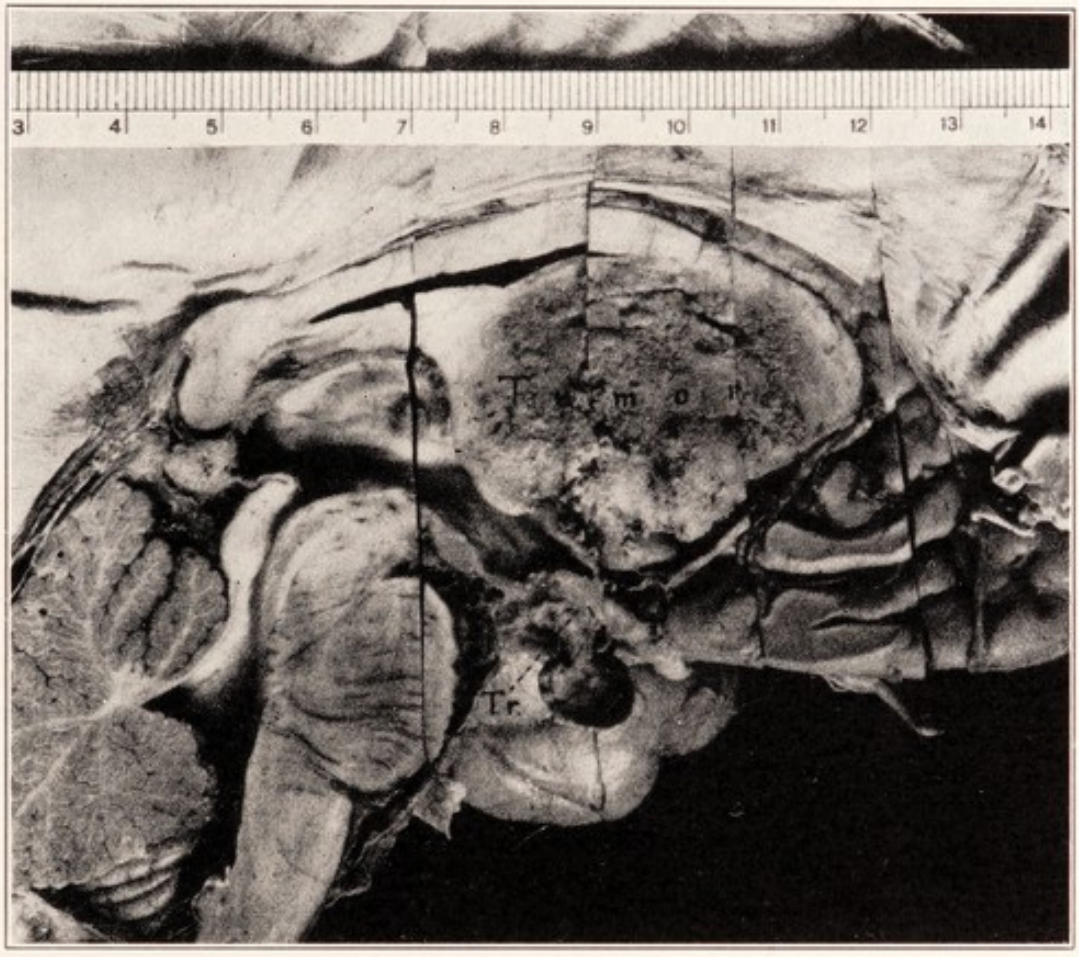

FIG. 30.—Mesial section of brain (natural size) for comparison with Figures 28 and 29, showing the situation of the primary tumor with implantation involvement of infundibular cavity and complete destruction of tuber, (Tr) the posterior part of the third ventricle remaining free.

slight acceleration of the pulse from 65 to 75 over the same period of time. There was no change in temperature, no flushing or sweating; a single attack of vomiting with a bowel movement occurred two hours after the injection.

It has been shown by Cannon and his co-workers[1] that an animal may survive after complete removal of its thoraco-lumbar sympathetic chain of ganglia. Similarly, it would appear that in man life may be maintained after apparent destruction of the diencephalic centers for parasympathetic action. It has been found possible on two occasions to remove

extensive tumors from the third ventricle, the walls of which must have been seriously damaged in the process. Recovery in each instance nevertheless took place and the patients continue to lead essentially normal lives. It would appear, therefore, that complete paralysis of either sympathetic or parasympathetic system is less serious in its effects than abnormal or perverted stimulatory disorders affecting either system.

In contrast to these supposedly paralytic pathological conditions affecting the interbrain and which we have herein described, one may occasionally encounter irritative ones which cause stimulatory responses on the part of the autonomic system. No better example of this has appeared in the literature than that reported by Penfield[2] of what he calls diencephalic autonomic epilepsy. The case was that of a middle-aged woman who had a small cholesteatoma of the third ventricle which supposedly caused periodical irritation of the adjacent hypothalamus provoking peculiar seizures characterized by sudden sweating, flushing, salivation, lachrymation, hiccoughing, respiratory disturbances and fall in temperature which were regarded as evidences of autonomic stimulation. That they were essentially parasympathetic phenomena and, apart from the absence of vomiting, fully comparable to those which the intraventricular injection of a cubic centimeter of pituitrin produces is quite obvious.

CONCLUSIONS

Negative responses to the intraventricular injection of pituitrin may occur naturally enough when the dose is insufficient and there may of course be individual variations in susceptibility to its effects. The customary responses may also fail to occur when a marked degree of hydrocephalus serves to balloon the walls of the third ventricle and also when the ventricular walls are involved by a tumor. Both of these conditions presumably serve to throw out of action the anterior hypothalamic nuclei whose stimulation is assumed to call forth the typical reaction.

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V. THE COUNTERACTIVE EFFECT OF TRIBROMETHANOL (AVERTIN)* ON THE STIMULATORY RESPONSE TO PITUITRIN INJECTED IN THE VENTRICLE

IN THE foregoing discussion of the method and place of action of pituitrin and pilocarpine when put into the ventricle, one of the arguments favouring the stimulation of hypothalamic nuclei was based on the negative responses shown by patients with pathological lesions in-

* This commercial product is a combination of tribromethyl alcohol dissolved in amylene hydrate customarily given in a dose of one hundred milligrams per kilogram body weight.

volving the interbrain (tumor and hydrocephalus). Interpretations of physiological responses in the normal subject are difficult enough, and to bolster an argument by the absence of responses in pathological states, however suggestive they may be, is unconvincing.

Were there some certain method of experimentally inhibiting the diencephalic centres before the injections were made, their locus of action might be more definitely determined. The preliminary injection of atropine, to be sure, has been shown to be counteractive, but the known antidotal effect of atropine on pilocarpine, however given, and its apparent antidotal effect on pituitrin intraventricularly administered serves possibly to exclude it from consideration. Procaine ("novocaine") immediately suggests itself but its effect as a respiratory depressant when injected into the ventricles of animals precludes its employment in man on the ground of unjustifiable risk, though the drug given by the lumbar subarachnoid routes is employed daily for abdominal operations or, in some clinics, even for operations on the chest and neck.

To these objections of undue risk the narcotics are reasonably free though there is no unanimity among pharmacologists as to how and where hypnotic drugs of various kinds act in the production of unconsciousness or sleep. Those who have studied the effects of cortical stimulation, whether experimentally on laboratory animals, or for purposes of delimiting the motor cortex during the course of operations on the brain of man, have long known that, when the subject is under deep inhalation narcosis from ether or chloroform, cortical responses are not obtainable. Not until the twilight stage of awakening from the effects of the anaesthetic is reached does the motor cortex regain its electrical excitability.

The barbituric acid derivatives, of which several are employed for the production of surgical narcosis, are generally assumed to exercise their effect on the interbrain. From two of these substances, known respectively as diallyl barbituric acid and phenylaethylic barbituric acid, E. and J. Keeser[1] succeeded in preparing stable iron and silver salts without altering the hypnotic property of the original compounds. These substances when given intravenously to rabbits were found subsequently to be recoverable only from the thalamus (presumably including the hypothalamus) and to a lesser degree from the corpus striatum, no trace being found in the rest of the brain. In view of this, it is highly interesting that Fulton, Liddell and Rioch[2] have recently found that "Dial" (the commercial preparation of diallyl barbituric acid) administered to monkeys in amounts sufficient to produce deep surgical anaesthesia leaves the electrical excitability of the cortex unimpaired. They assume consequently that its locus of action is chiefly on sub-cortical centres, i.e., thalamus, hypothalamus, midbrain and upper medulla.

Tribromethanol ("Avertin"), though chemically unrelated to the barbituric acid combinations, nevertheless appears to act in precisely the same way on man that Fulton, Liddell and Rioch found "Dial" to act in the ape, in so far as it fails to diminish the electrical excitability of the cortex in the way that ether and chloroform do. A personal experience follows:

A doctor's son had been victimized by repeated attacks of Jacksonian epilepsy invariably beginning in the right hand and occasionally passing on to unconsciousness. An osteoplastic exploration of the left hemisphere was made in the hope of finding a focal lesion that might be surgically dealt with, or, in its absence, with the intent of extirpating the pre-Rolandic hand-area. The operation was begun under local anaesthesia but the boy was so restless and uncoöperative that avertin was given per rectum, and he quickly passed into the usual profound sleep. The cortex when exposed was found hyperaemic but otherwise normal. Though the pre-central area for the upper extremity was fairly evident, to exclude any possible topographical error the cortex was stimulated by the unipolar method with a faradic current barely strong enough to cause contraction of a bundle of exposed temporal muscle. The area for the hand was thus certified, the motor responses in thumb and fingers being as sharp and easily elicited as if no anaesthetic had been used.

My personal familiarity with the numerous barbituric acid compounds as anaesthetics has been negligible, but tribromethanol has come to be used with sufficient frequency in the clinic so that we have a fairly definite understanding of its physiological reactions other than that producing unconsciousness. Sleep ordinarily comes on with surprizing promptitude, a few minutes after the drug has been introduced into the rectum. At the same time an extreme contraction of the pupils occurs, soon followed by: (1) a definite fall in blood-pressure often as much as 30 to 50 points; (2) a slight rise in pulse in certain cases amounting to 20 to 30 beats; (3) some slight increase in respiratory rate; and (4) a slight fall in body temperature of 1 to 2 degrees. At the end of 60 to 90 minutes there is usually a fairly abrupt termination of these reactions, though fluctuation in size of the pupils and in the depth of the somnolence may persist for varying lengths of time. We have also observed a drop in blood-sugar, a considerable diminution in the erythrocyte count, and other minor changes which scarcely deserve mention, as the data regarding them are insufficient.

The most striking effects of the drug are three: the *deep, apparently natural sleep,* the *pupillary contraction,* and the *fall in blood pressure.* If these are actually central and diencephalic in origin, the hypnosis may be accounted for on the basis of stimulation of the "sleep center" assumed on experimental grounds (Hess) as well as on clinico-pathological ones (postencephalitic hypersomnia) to lie somewhere in the interbrain. It has no apparent relation to the autonomic nervous system.

Pupillary reactions, on the other hand, supposedly have such a relation and the disclosure by Karplus and Kreidl[3] that electrical stimulation of the lateral wall of the hypothalamus causes dilatation of the pupils was what first led to the belief that there must be a higher "sympathetic centre" in the interbrain. Just how one is to explain the prolonged fall in blood pressure and the drop in erythrocytes unless by an expansion of the spleen is not clear, but it is at least evident that the reaction is the reverse of that which customarily follows the injection of pituitrin and pilocarpine into the ventricles. What is more, the most notable difference between the hypnotic state produced by avertin and the narcosis due to ether or chloroform is the absence of any subsequent vagal effect from the

former, postanaesthetic vomiting being most unusual. This, again, runs counter to what we have found to occur after the intraventricular injection of pituitrin, the presumably vagal effect of which in the production of repeated retching and vomiting is striking. Another contrast lies in the dryness of the skin and mouth under avertin and the sweating and salivation that follow the intraventricular injection of the extract.

All things considered then, tribromethanol (should it really act on the hypothalamus when given rectally) and pituitrin (should it similarly thus act when given intraventricularly) are so definitely opposed in their effects one would expect them to be antidotal. The truth of this conjecture appears to be substantiated by the experiences cited in the following two protocols, A and B:

Protocol A. (1) A typical reaction to 1 c.c. surgical pituitrin injected in the ventricle. (2) No reaction to the same injection with the patient under avertin. (3) A typical reaction to 2.5 mgm. pilocarpine in the ventricle.

The patient, a man fifty-three years of age, was satisfactorily convalescing from an operation performed *December 2, 1930*, for a glioma of the temporal lobe which had not served to cause hydrocephalus. At the time of the test he was wholly free from symptoms relating either to the lesion or his operation.

On *December 18, 1930*, after the usual preliminaries, at 10:03 A.M., 1 c.c. of *pituitrin was introduced into the ventricle* with prompt moderate cutaneous flush, sweating, and salivation, but with only a slight fall in rectal temperature of less than one degree. The most striking effect, though it was unusually delayed, was the vomiting which set in suddenly about an hour after the injection and which, accompanied by hiccoughing, continued off and on for the next three hours. It was estimated that he must have vomited 500 c.c. of gastric secretion. This at first was clear, serous fluid but subsequently contained thick, tenacious mucus, finally became bile-stained and had a normal gastric acidity. The frothy character of the secretions suggested some hypersecretion from the lungs but no râles were heard on auscultation.

The erythrocytes, which before the pituitrin injection numbered 4,040,000, were counted 90 minutes later at 4,300,000; and at the end of three and one-half hours they were 4,170,000. The temperature began to drop in 35 minutes but fell only 1.1° and the basal metabolic rate remained unaffected. Blood-sugar before and after the injection showed no essential change. There was the usual slight rise in blood-pressure from 110/60 to 130/80 which endured for three hours together with a slight increase in pulse rate instead of the customary slowing.

The vomiting had been so persistent and disturbing that at 1:40 P.M. it was checked by a hypodermic injection of 0.5 mgm. of atropine with 5 mgm. of morphia.

This patient, then, showed to intraventricular pituitrin a definite reaction in which retching and vomiting, though delayed, were unusually pronounced. The type of reaction therefore was eminently suitable for a test to determine whether it would be abolished or modified by avertin anaesthesia.

Accordingly, on *December 23*, after the usual preliminaries with the patient fasting, the standard dose of avertin per kilogram body weight was slowly intro-

duced per rectum at 9:35 A.M. with an almost immediate profound sleep, a fall in blood-pressure from 130/70 to 80/60, immediate contraction of the pupils to pinpoint size, increase in pulse rate from 90 to 120, an increase in respiration from 20 to 30. These characteristic reactions were practically over at the expiration of an hour and forty minutes by which time the patient had begun to show some signs of returning consciousness.

At 11:30 A.M., two hours after the avertin administration, 1 c.c. of *pituitrin was injected into the ventricle* and so far as could be seen this had not the slightest effect. The skin and mucous membrane remained dry. The rectal temperature, which under avertin had dropped from 99° to 96.2°, had begun to rise at 10:50 A.M. and the curve was not affected by the injection of pituitrin forty minutes later. An insignificant fall in blood-sugar was detected when the temperature was at its lowest. The erythrocyte count remained constant within limits of error. *The excessive bouts of retching and vomiting, which had previously been produced by intraventricular pituitrin when given independently, were completely counteracted by the action of avertin.*

Three days later, on *December 26*, an intraventricular injection of 2 mgm. of pilocarpine, without preceding avertin hypnosis, produced a typical reaction very similar to that caused by pituitrin alone.

The counteractive effect of avertin in the second case to follow was even more striking in that 1.5 c.c. of surgical pituitrin was injected, an amount of the extract which from a previous experience with the same patient had given an excessive reaction at a time when the effects of intraventricular pilocarpine and pituitrin were being compared.

Protocol B. A severe reaction to 1.5 c.c. intraventricular pituitrin. Under avertin hypnosis the reaction to the same dose of the extract almost completely counteracted.

John S., fifty-eight years of age, convalescent from an operation for the removal of a temporal glioma and at the time of the tests free from symptoms, had been found to give a typical but mild reaction to 1 c.c. of surgical pituitrin and a severe reaction to 2.5 mgm. of pilocarpine. Consequently, the better to contrast the effect of the drug and the extract, he was then given 1.5 c.c. of surgical pituitrin in the ventricles with the results recorded in another connection (*cf.* pg. 68) viz., prompt flushing, sweating, salivation, lachrymation, retching and vomiting, rise in blood-pressure, slowing of pulse, and a drop of 6°F. in body temperature accompanied by an astonishing rise in metabolism of +43 per cent associated with shivering.

The effect of avertin on this patient was known from two previous experiences. The drug caused a prompt and deep hypnosis, marked pupillary contraction, a drop in the erythrocytes of 400,000, and a fall in blood-pressure from 110/70 to 70/40 with fairly abrupt return to normal on first signs of waking at the expiration of 90 minutes.

On *March 5, 1931*, after the usual preliminaries, 6.9 c.c. of avertin in 280 c.c. of water were introduced into the rectum at 10:12 A.M. Within ten minutes the pupils had contracted to pinpoints and he was in a profound sleep. By 10:35 the blood-pressure had fallen from 135/80 to 90/65 and the erythrocytes had dropped from 5,650,000 to 5,080,000. The rectal temperature remained level at 98°F. The skin was warm and dry. At 10:42 A.M. the ventricle was tapped and 1.5 c.c. of *surgical pituitrin was introduced.* This had no apparent effect what-

soever. At 11:37 the patient began to arouse, the pupils dilated, and he asked for a drink of water.

At 11:45 he was sufficiently awake to respond to commands and the blood-pressure had begun to rise, 110/70. At this time, 93 minutes after the avertin was given and 63 minutes after the pituitrin was injected, the previously dry mucous membrane of the mouth began to show some moisture and visible beads of perspiration appeared on the skin. This mild reaction lasted for 45 minutes before it had wholly disappeared. Meanwhile the temperature dropped from 98° to 96.4°. At 12:50 when the temperature was at its lowest level, the metabolism which at the outset was zero was found to be −2, in other words, it was unchanged within the limit of error. There was no nausea or vomiting or discomfort of any kind and on returning to the ward he took his dinner with appetite.

In the first of these cases, therefore, avertin served completely to offset the patient's known reaction to 1 c.c. of intraventricular pituitrin (vomiting, retching, salivation, flushing, sweating, rise in blood pressure, etc.) when given by itself. In the second case, the larger dose of 1.5 c.c., which had at a previous session caused a severe reaction with an unusually marked fall in temperature, gave evidence of a trifling and much delayed pituitrin effect shown by transient sweating and a slight fall in temperature after the inhibitory influence of the avertin had begun to wear away.

It can be concluded therefore that the pharmacological action on hypothalamic centres of intraventricular pituitrin and of avertin is definitely antagonistic. The chief discord lies in the pupillary contraction under the blood-borne avertin and the absence of any notable pupillary effect from pituitrin which is assumed to act by diffusion through the ependyma. This, however, may well be accounted for on the grounds that the pupillary centre lies too deep to be acted upon by resorption, and it may be noted that no pupillary dilatation was observed when atropine was injected into the ventricle. In the recent experiments of Karplus and Peczenik[4] previously referred to, it was shown that in the cat electrical stimulation of the tuber cinereum does not cause enlargement of the pupil, but that it occurs only when the outer walls of the anterior hypothalamus are stimulated. Stimulation at either point nevertheless apparently serves to discharge the posterior lobe and thereby to increase the oxytocic and melanophore-expanding properties of the cerebrospinal fluid.

CONCLUSION

The hypnotic, tribromethanol (avertin), presumably causes its effects by action on centres in the diencephalon, and serves to counteract the stimulatory responses to pituitrin injected into the ventricles.

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VI. CONCERNING A POSSIBLE "PARASYMPATHETIC CENTRE" IN THE DIENCEPHALON

IN THIS series of papers it has been shown: (1) That the injection of commercial pituitrin into the cerebral ventricles produces a prompt and characteristic reaction presumably stimulatory in character; (2) that pilocarpine similarly introduced gives a wholly comparable response; (3) that an antecedent subcutaneous or intraventricular injection of atropine counteracts the action both of the extract and of the drug; (4) that the effector responses do not occur in the presence of lesions which either have destroyed or which appear to have impaired the functional activity of the interbrain, more particularly its hypothalamo-tuberal portion; and (5) that with patients under the influence of tribromethanol, a hypnotic which presumably acts upon diencephalic centres, intraventricular pituitrin has either no effect or one which is slight and much delayed.

While the clinical tests which have been described have been under way, efforts have been made to supplement and check them by corresponding observations in the experimental laboratory. Though there is no belittling the greater difficulty both of carrying out and of interpreting similar pharmacological tests conducted on the lower animals, some progress has nevertheless been made by my junior co-workers, Drs. Light, Lawrence, Dial, Boyes and Strayer, who will have some reports of their own to make on the subject. It may suffice at this time to say that the responses to intravenous and to intraventricular pituitrin in the dog are similar to those seen in man. The intravenous injection causes, as others have shown,[1] what appears to be chiefly a sympathetic effect, namely, an extreme pallor of skin and mucous membrane with contraction of the spleen from a vascular rather than capsular constriction. The intraventricular injection on the other hand causes a wholly different and apparently a parasympathetic reaction, namely, vascular dilatation, excessive panting, salivation, signs of pulmonary oedema and gastrointestinal hypertonicity.

Corresponding studies on primates have been made by J. F. Fulton and his co-workers in the Physiological Laboratory at Yale; and I am permitted to state that they find the intraventricular injection of pituitrin in monkeys to have an effect corresponding in a general way to that which occurs in man, though no comparable antipyretic reactions have been observed. Much labour necessarily lies ahead before the finer details of the responses and their differences from those observed in man can be thoroughly worked out.

In seeking to correlate and explain these observations both on man and animals, it has been assumed that pituitrin and pilocarpine are capable

of stimulating hypothalamic nuclei which preside over important so-called vegetative functions. And since many of the responses like vasodilatation, sweating, salivation, lachrymation, and gastric hypersecretion with retching and vomiting are suggestive of a parasympathetic effect, the existence of a "parasympathetic centre" in the interbrain has naturally been postulated.

For a surgeon to suggest an interpretation of matters so complicated and so far removed from his legimate field would savour of impudence were it not that the surgery of the autonomic nervous system, though still in its infancy, has made rapid strides since the periarterial sympathectomy of Leriche, and Royle's operation of ramisection came into vogue. And even should the interpretation of the effects that have been observed to follow the intraventricular injections as described, prove to be wrong, it may, like the ardently combated views of Hunter and Royle, be provocative of new investigations of old problems, not without profit; and the neurosurgeon unquestionably will come to take part in them.

HISTORICAL REVIEW

The delicate neurones composing the vegetative nervous system play upon structures and organs that are wholly or in large part automatically controlled. Based chiefly on the discovery of the preganglionic relay of fibres to the paravertebral chain of ganglia, the involuntary nervous system has come to be divided into two structurally distinguishable divisions: namely, the sympathetic or thoraco-lumbar division; which serves to separate the cranial and the sacral components of the other division. These cranial and sacral components which have been found to act more or less in definite opposition to the thoraco-lumbar or sympathetic division, have been variously designated, but the term "parasympathetic" has come to be commonly employed for them.

Known by whatever name, these two divisions of the autonomic system, unlike the sensorimotor apparatus, which up to the time of Gaskell, Langley and Anderson had largely dominated neurophysiological research, supposedly act upon the glandular structures and smooth muscle of the blood-vessels and viscera through involuntary reflex arcs. The reflex centres for the preganglionic sympathetic fibres came to be anatomically identified in the lateral horn of the gray matter of the cord, whereas those for the cranial autonomic were experimentally located somewhere in midbrain and medulla.

But however independent of volition and the cerebral cortex these two parts of the involuntary nervous system may be, ever since Karplus and Kreidl[2] found in 1909 that electrical stimulation of the hypothalamus (*Zwischenhirnbasis*) gave a sympathetic effect in dilating the pupils, contracting blood-vessels, and accelerating secretions, there has been a growing tendency among physiologists to accept the probability of a higher centre at least for the sympathetic division of the system. The Vienna school, indeed, has been largely responsible for the promulgation of this idea to which not only Karplus and Kreidl, but Aschner and Erd-

heim contributed in their attribution of presupposed pituitary symptoms to lesions of the hypothalamus or tuber. The matter was soon taken up from a pharmacological standpoint by Hans Horst Meyer[3] (1912) who with Gottlieb in the successive editions of their *Experimentelle Pharmakologie* have accepted the existence of special higher centres for parasympathetic as well as sympathetic systems, both of which are specifically acted upon by drugs.

Whereas adrenalin supposedly acts on the sympathetic nerve endings in precisely the same manner as does a general sympathetic stimulation, the effect of poisons of the pilocarpine group, which are effectively counteracted by atropine, corresponds in the opinion of Meyer and Gottlieb to a parasympathetic stimulation. They, however, are obliged to admit that the striking effect of these poisons in the cutaneous glands has not as yet been proved to be wholly parasympathetic, though this exception to the general rule of opposite action of sympathetic and parasympathetic stimulation is, they believe, only an apparent one which will come to be explained by further investigation of the method of innervation.

Though the opportunity of testing the intraventricular action of drugs that influence one or another division of the autonomic nervous system has not been grasped by pharmacologists, Meyer and Gottlieb make certain statements that are highly pertinent to the subject at hand. They state for example (*loc. cit.*, IV. Auflage, pg. 158), that irritation of the sympathetic system increases metabolism and body temperature, whereas the parasympathetic system appears—without its being possible as yet precisely to prove the matter—to lead to the opposite effect. Since a similar pharmacological reaction implies a similar chemical structure, all sympathetic end organs must be chemically alike and all parasympathetic ones equally so. And in illustration of this pharmacological law they point out that picrotoxin, for example, stimulates the parasympathetic system throughout "sometimes not only in the end organs but centrally" and that tetrahydro-β-naphthylamin similarly excites both centrally and peripherally the sympathetic (thoraco-lumbar) apparatus. Whether by "centrally" the authors mean anything higher than the brain stem is not clear, but they may well enough have had the diencephalon in mind.

From the physiologist's point of view, no one in later years has given a more vivid account than Cannon[4] of the manner of action of the involuntary nervous system, more particularly of its intermediary thoraco-lumbar division. In his more recent papers in which the general features of his many contributions have been summarized, he chooses to introduce these new terms: "exterofective" for the voluntary sensorimotor nervous system, and "interofective" for the involuntary or autonomic system. The chief function of this latter system, through its action chiefly on smooth muscle and glands, is to preserve stability ("homeostasis") of the internal economy. Cannon particularly stresses the importance of the thoraco-lumbar division of this interofective system, for through its ability to mobilize the body reserves it may properly be regarded as the special and immediate agency of homeostasis. He emphasizes, too, that the

principal effect of the morphological arrangement of relayed neurones in the thoraco-lumbar region is to make possible a diffuse discharge of nerve impulses which constrict blood-vessels, inhibit the activity of the digestive canal, etc., and at the same time lead to a discharge of adrenalin, the hormone and the nervous impulses working together as a sympathico-adrenal system to produce throughout the organism widespread changes in smooth muscle and glands which are largely defensive in their purport.

Now at the same time it is recognized that the cranial and sacral or parasympathetic division of this interofective or autonomic system work more or less in antagonism to the sympathetic (thoraco-lumbar) division. Thus, to give some familiar examples, stimulation of the sympathetic inhibits the muscular tone of the stomach, stimulation of the vagus, which is part of the cranial parasympathetic, increases it; stimulation of the sympathetic dilates the pupil, of the parasympathetic fibres in the oculomotorius contracts it, etc. But this principle of antagonism in the two systems begins to be somewhat less definite in the matter of vaso-constriction and vaso-dilatation; and when we come to the question of sweating, the rule of opposite action appears to have entirely fallen down.

Still another difference in the two systems, as emphasized by Cannon, lies in the fact that the parasympathetic fibres are anatomically so distributed as to favour more or less independent or discriminating activities in contrast to the diffuse action of the sympathico-adrenal system. This is shown in the contraction of the pupils by light, in salivation at the sight of food, in lachrymation, in gastric secretion, and so on, all of these reactions occurring normally quite independently of one another. But this, it seems to me, may merely be a question of strength of stimulus, for the effects we have observed from the injection of pituitrin into the ventricle indicate an apparent diffuse discharge of the parasympathetic system (at least of its cranial portion) as definite as the diffuse discharge of the thoraco-lumbar system which has been the chief object of Cannon's studies.

In thus assuming that the retching and vomiting, salivation, lachrymation, vaso-dilatation and sweating, as well as the effect on the metabolism of water and of fat and also the extraordinary loss of body heat called out by intraventricular pituitrin, represent a diffuse parasympathetic discharge, the posterior lobe hormone may be looked upon as playing by central action very much the same rôle that adrenalin plays by peripheral action in prolonging and intensifying the diffuse discharge of the sympathetic division. Of the two systems, indeed, the parasympathetic, in view of its evident close relation to diencephalo-hypophysial mechanisms, would seem to be far the more important. But this would be difficult to prove, for the cranial autonomic system does not lend itself to experimental extirpation as does the thoraco-lumbar division, the complete removal of which has been so brilliantly accomplished by Cannon[5] and his associates with the surprizing disclosure that completely sympathectomized animals may survive for an indefinite time if protected from undue

exposure to cold and rendered exempt from the stresses and strains which the struggle for existence would ordinarily call for.

In spite of Cannon's emphasis on the peripheral sympathico-adrenal apparatus, he at the same time has done more than any other to show how it is influenced centrally by primitive emotions; and his studies,[6] supplemented by those of his pupil, Philip Bard,[7] on what they call "sham rage" in decorticated animals, have served to prove the existence of an emotional centre in the diencephalon which ordinarily is under some inhibitory influence by the frontal cortex. In short, emotions such as pain, fear, rage, or a strong excitement of any kind instantly abolish the secretion of saliva, of gastric juice, of pancreatic juice, and of bile, the action apparently (if Cannon is rightly understood) occurring through central stimulation of the sympathico-adrenal (thoraco-lumbar) apparatus. But it would appear that an equally strong case might be presented in favour of the inhibition of the parasympathetic apparatus by these emotional states if a centre for this apparatus in the interbrain has any basis in fact.

Since pituitrin when given subcutaneously or intravenously appears to act much like adrenalin as a vaso-constrictor, whereas its effects when put into the ventricle appear to be parasympathetic, it is not unlikely that the posterior-lobe hormone may exercise a far greater influence on the two divisions of the autonomic system than has been heretofore suspected. It is possible, too, that its cleavage products, vasopressin (pitressin) and oxytocin (pitocin) isolated by Kamm and his co-workers[8] may not act in the ventricle but only peripherally; and further tests in this direction may throw light on the controversial theories of unitary *versus* multiple hormones for the posterior pituitary.[9]

THE ANTIPYRETIC, VASO-DILATOR AND DIAPHORETIC EFFECTS

Since the lowering of body temperature, vaso-dilatation and diaphoresis are the three most striking phenomena of the intraventricular-pituitrin reaction, they may deserve brief separate consideration.

THE ANTIPYRETIC EFFECTS

Forty years ago, Ott[10] first briefly stated that punctures of the tuber cinereum in rabbits or cats served to stimulate what he called a "thermolytic center," and since that time the possible existence of a heat centre or centres at the base of the brain has been investigated by many others who have used a variety of experimental methods. It was found by Isenschmid and Schnitzler[11] that after bilateral removal of the forebrain, the cerebral hemispheres, striatum and most of the thalamus, a rabbit is still capable of normal heat regulation; but this capacity, once the tuber cinereum is excluded, wholly disappears. Experimental cooling or warming of the region by altering the temperature of the arterial blood vessels, carotid and vertebral, which supply it (Kahn) or by artificially cooling or warming the region by direct irrigation (Barbour) have been shown to have marked effects on the thermo-regulatory mechanism. Hans Meyer, indeed, has postulated the existence of a "heating" as well as a "cooling"

centre which, though opposed in action, work hand in hand as a regulating apparatus; fever toxins, for example, acting on the one, antipyretics acting on the other. What is more, it is appreciated that these centres not only lie in the interbrain but send impulses through the autonomic nervous system; and Meyer goes so far as to say that the *Wärmcentrum* acts through the sympathetic and that the *Kühlcentrum* acts through the parasympathetic. Whether or not this hypothesis is actually open to proof, it at least offers an explanation of the extraordinary antipyretic effect of intraventricular pituitrin which accords with the other responses that are interpreted as being definitely parasympathetic in character.

Barbour and his co-workers have called attention to the fact that heating the carotid blood and cooling the vertebral blood have very similar effects; and they believe their experiments indicate the existence of two functionally opposed nervous fields, the cooling centre being located in the hypothalamic centre, the heating centre in the medullo-pontine region.

Though the "centres" which govern shivering, at least in the rabbit, have been shown by Dworkin[12] to be rather diffuse, he regards them as an integral part of the heat-regulating mechanism and believes that they are coördinated for service by a superior presiding centre in the interbrain. Shivering has only been observed after one of the many tests with intraventricular injection of pituitrin or pilocarpine even when there was a marked fall in temperature, this particular reaction having occurred in a patient who showed, contrary to the usual rule, a marked increase rather than the usual decrease in basal metabolic rate. Apart from this particular case, there has been no exception to the rule that intraventricular pituitrin when it has an effect at all marked either inhibits the mechanisms involved in heat production or, what is more probable, stimulates those involved in heat loss, and these latter are regarded as predominantly parasympathetic in nature.

Stimulation of the sympathetic (thoraco-lumbar) system is known to increase body temperature, and Cannon has shown that animals experimentally deprived of this apparatus are prone to lose heat on exposure to cold. What is more, when excited, sympathectomized animals have a tendency to lose heat—an antipyretic effect which might conceivably be explained on the basis of stimulation of an unopposed and still intact parasympathetic apparatus.

VASO-DILATATION AND SWEATING

In the patients whose responses to intraventricular pituitrin and pilocarpine have been described, not only have the extremities felt warm to the touch, but the patients themselves have felt subjectively warm even when the rectal temperature has been at its lowest. Conversely, patients with hyperthermia, such as occurs after certain intracranial operations, may have a rectal temperature of 106°F. even though their extremities possess a death-like coldness and clamminess to the touch. Though this, from the standpoint of sweating, sounds somewhat confusing and con-

tradictory, it is safe to say that vaso-dilatation, sweating and the regulation of body temperature are closely related processes even though opinions concerning them, which are largely built up from observations on lower animals, are highly controversial.

Vaso-constriction being admittedly the outstanding effect of sympathico-adrenal stimulation, one would assume on the principle of functional antagonism between sympathetic and parasympathetic systems that vaso-dilatation would be the normal response to parasympathetic stimulation. But the relation of sweating to these two parts of the involuntary nervous system is highly obscure, it being generally believed by physiologists and clinicians that the sweat glands—at least those of the face and neck—can be activated by either of the opposed divisions.

The pharmacological effects of muscarine, histamine, pilocarpine, physostigmine and acetylcholine when given systemically are essentially sudorific and vaso-dilator, and to these better-known diaphoretic drugs intraventricular pituitrin must now be added. Though the intraventricular effect of the other substances remains to be studied, pilocarpine at least, as has been made clear, causes generalized flushing and sweating, together with a more marked fall in body temperature than could well be accounted for by the effect of evaporation alone.

Sweating and vaso-dilatation, though they customarily go hand in hand, do not necessarily do so, and they have usually been studied independently of one another. Since 1876 when Ostroumoff and Luchsinger showed that faradic stimulation of the severed sciatic nerve could produce sweating in the amputated leg of a cat, the foot-pads of this animal have been the locus, favoured by physiologists and pharmacologists alike, for estimating the effect of procedures and of drugs that influence sweating. From the classical paper of Max Levy[13] in 1892 to the studies of Hasama[14] nearly forty years later, it has been the chief method of estimating sudorific responses.

Burn's investigations,[15] which were limited to a consideration of the peripheral mechanisms in animals and which carried the subject about as far as laboratory methods permit, led to the conclusions: That pilocarpine has a dilator action on the vessels; that after denervation of the leg a sweat response to pilocarpine persists only so long as vaso-dilatation persists; that the loss of the sweating and dilator response is not due to degeneration of the sympathetic or sensory nerve fibres but rather to degeneration of the motor fibres of the leg muscles; that the amount of sweat secretion produced by a central stimulus depends upon the blood-flow through the foot-pads; that the exaggeration of the sweat responses to pilocarpine after sympathetic degeneration is due mainly to removal of sympathetic control of the blood-vessels.

In contrast to Burn's laboratory observations, in which the possible active participation of the parasympathetic system in the phenomenon of sweating does not seem to have been considered, one may turn to the observations on man which have already been made and which are likely to be made in still greater number in the future now that the involuntary

nervous system has come to be the object of attack by surgeons. The most informing and most detailed studies so far reported are those by Otfrid Foerster and by his co-workers, Guttmann and List,[16] the results of which are assembled in the concluding sections of Foerster's elaborate treatise on the effect of gunshot wounds on the peripheral nerves.[17]

Foerster assumes the existence, for the diaphoretic mechanism, of a higher diencephalic and a lower bulbar centre whence the fibres descend in the cord to emerge by way of the anterior spinal roots. He has found that stimulation of a posterior root after its division causes vaso-dilatation confined to the spinal dermatome concerned, whereas subsequent stimulation of the corresponding anterior root causes sweating and a pilomotor response without vaso-dilatation over a much wider field, the central strip which previously showed vaso-dilatation from posterior root division remaining dry. Thus sweat fibres unquestionably leave the cord by the anterior root and active efferent vaso-dilator fibres by the posterior root, the two acting quite independently.

Foerster has further shown: That stimulation of purely sensory peripheral nerves causes both sweating and vaso-dilatation in the area of cutaneous distribution; that total division of a mixed nerve leads to significant vaso-dilatation over the area of its cutaneous distribution, and though in some cases pilocarpine may continue to cause sweating in this area, it soon loses this effect with resultant total anhidrosis; and that division of the sympathetic paths completely checks the hyperhidrosis produced by external heat, but does not in any way affect that induced by pilocarpine. In other words, sweating produced by external heat and by pilocarpine act somewhat differently. From these and other observations Foerster had been led to conclude that in the peripheral nerves there are two sets of sweat fibres, one sympathetic and the other set, which reacts to pilocarpine, parasympathetic. Where the latter have their higher centres and how the fibres run in the peripheral nerves he does not pretend to say.*

The investigations by Burn on animals and by Foerster on man which have thus been briefly reviewed have been restricted, as we have seen, to the peripheral mechanisms concerned in vaso-dilatation and sweating; and though Foerster at least predicated the existence of higher centres of control, these had not been made the particular object of a detailed study until the matter was taken up by Hasama, the Japanese pharmacologist. In his three important papers[14] Hasama has shown elaborately and conclusively that mechanical, thermic, chemical and electrical methods will all serve to affect both sweating and the thermo-regulatory apparatus, whether the stimulus is applied to centres in the interbrain or to others which presumably are directly subsidiary and which lie in the floor of the fourth ventricle, more especially the dorsal nucleus of the vagus. As

* By electrically stimulating the surfaces of the serially transected brain and medulla of the cat, Langworthy and Richter, (*Brain*, 1930, LIII, 178), have traced the autonomic paths for sudorific impulses from the frontal cortex through the diencephalon to the spinal cord.

Hans Meyer was led to predicate the existence of separate warming and cooling centres, one sympathetic and the other parasympathetic, so Hasama has concluded from his studies that there are two kinds of centrally induced sweating, one parasympathetic associated with vaso-dilatation, and the other sympathetic or "cold" sweating.

But it is fair to say that neither mechanical, thermic, chemical nor pharmacological excitation, however much information may be gained thereby, represents the natural way of affecting the diencephalic centres with which we are concerned; and reasons have been advanced whereby it may be at least assumed that the posterior-lobe hormone may actually be the normal excitant, albeit the extract must be administered in a far larger dose than normally is present in order that we may unmistakably recognize its effects. And one striking feature of this vaso-dilator and diaphoretic response called forth by pituitrin is the surprizing coincidental antipyretic effect, the like of which does not seem to have been observed in and apparently does not occur in animals.

CONCLUSIONS

The information in this series of papers, on which an hypothesis has been built up regarding the action of the posterior pituitary hormone on an assumed parasympathetic centre in the interbrain, may be briefly summarized as follows:

A. The active principle of the neurohypophysis is in part excreted into the blood-stream and in part into the cerebrospinal fluid. The hormone when experimentally introduced into the blood-stream causes pallor from vaso-constriction and stimulates the musculature of the lower bowel; when introduced into the human ventricle, on the contrary, it causes flushing, sweating, salivation, lachrymation, vomiting and a pronounced fall in body temperature. The former bears resemblance to a sympathetic discharge combined with a sacral autonomic effect; the latter appears to be essentially a cranial autonomic or parasympathetic effect. Pilocarpine introduced into the ventricle gives a highly similar response. These responses to intraventricular pituitrin and pilocarpine are counteracted by atropine whether given subcutaneously or intraventricularly; they moreover appear to be abolished when the tuberal portion of the interbrain is highly distended by hydrocephalus or is the seat of tumors; and their action furthermore is checked by tribromethanol, a hypnotic that presumably acts chiefly on the interbrain.

B. A rich arborization of unmyelinated nerve fibres is known to pass from the tuberal nerve centres to ramify in the neurohypophysis. The posterior pituitary hormone, or a substance indistinguishable from it, has been shown to be increased in the cerebrospinal fluid after electrical stimulation of the tuber. It has also been shown to be increased in amount in the fluid of animals under emotional excitement. The interbrain has been found to be the "seat" of certain primitive emotions which are released from their cortical inhibitions by experimentally disconnecting the nerve paths from the frontal cortex. Theoretically animals so decorticated

should show an increase of posterior pituitary hormone in the cerebrospinal fluid.

C. As a working concept it may be assumed: (1) That under emotional stimuli the posterior lobe becomes discharged through its histologically demonstrable tubero-hypophysial fibre-paths; (2) that the active principle or a portion of it enters the cerebrospinal fluid whence presumably by diffusion through the ependyma it may come to act upon diencephalic nuclei for the parasympathetic apparatus; (3) that conditions may conceivably arise when posterior pituitary hormone is discharged into the fluid in sufficient strength to call forth a parasympathetic (cranial autonomic) response as diffuse in its character as is the response on the part of the sympathetic system brought about by the discharge of adrenalin. The neuro-hypophysis, in short, may conceivably bear a somewhat similar relation to the parasympathetic division that the adrenal medulla does to the sympathetic division of the vegetative nervous system.

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[*ADDENDA*]*

VII. THE RESPONSE TO INTRAVENTRICULARLY-INJECTED HISTAMINE

IN THE preceding papers, it was pointed out: (1) That the intraventricular injection of pituitrin, contrary to its known effects when given subcutaneously, causes a marked reaction characterized in susceptible subjects by a bright flush, sweating, salivation, lachrymation, prolonged vomiting, and fall in body temperature; (2) That intraventricular pilocarpine, in far smaller doses than was effective when given subcutaneously, causes a highly similar reaction; (3) That atropine serves to check these reactions; (4) That the reactions do not occur when the third ventricle is distended by marked hydrocephalus or when it is the seat of tumor; and (5) That the reactions are annulled when the subject is under the influence of an hypnotic drug which presumably inhibits the activity of the hypothalamic centres.

From these observations the inference was drawn that pituitrin and pilocarpine given intraventricularly acted directly upon a higher vegetative centre in the interbrain which appeared to be essentially parasympathetic in nature.

That the writer's interpretation of these reactions ran counter to certain recognized pharmacological tenets was fully realized. One of them concerns the principle that a drug wherever introduced into the body necessarily produces the same effect, differences in rate of absorption and individual susceptibility of course being taken into consideration. Another generally accepted principle, which the observations tended to discredit, is that parasympathetic stimulants like pilocarpine act on the nerve terminals rather than centrally.

Objections on these scores were fully anticipated but a serious criticism I was unprepared to meet was promptly received from my friend, Professor J. J. Abel, who struck at the very root of the matter. He expressed the conviction that the flushing effects which had been observed must certainly be due to impurities in the extract—to *histamine* in all probability. It was obvious that should this prove to be true, the entire thesis which

* Reprinted from the *Proceedings of the National Academy of Sciences*, 1932.

had been primarily built up on the reaction to intraventricular pituitrin would fall to the ground.

To meet this criticism, two courses were open: (1) to analyze commercial pituitrin for the presence of histamine or other flushing bodies; and (2) to see whether intraventricular histamine gave effects comparable to those produced by intraventricular pituitrin. Professor Abel generously volunteered to investigate the first point and, after a year's interval, I have finally got round to putting the second to clinical test.

Though the manufacturers of the posterior lobe extract which goes by the name of "pituitrin" felt certain that their product was histamine-free, Dr. Kamm of Parke, Davis and Company kindly put at Dr. Abel's disposal a large amount of the substance for his personal analysis. And I think I am correct in stating at this time that it proves to contain no recoverable histamine, though Dr. Abel remains convinced that it must hold impurities of some other sort, possibly acetylcholine, which give the flushing effects.

From time to time during the year, Dr. Abel has forwarded from Baltimore a number of extractives from pituitrin containing possible impurities as well as samples of a highly concentrated active principle which have been tested by introducing them into the ventricles of monkeys. These tests, which have been carried out in the Laboratory of Surgical Research at the Harvard Medical School by Dr. Richard Light with the assistance of Dr. Stanley Bysshe, are not only difficult to make but difficult to interpret for the reactions of animals to intraventricular injections correspond only in a general way to those observed in man, as will be gathered from their report. In regard to histamine, it may be said that five times the dose of this substance needed to produce flushing effects when given intravenously has no appreciable pharmacological effect when injected into the monkey's ventricle. And the same is true of acetylcholine.

It was fully expected that the intraventricular injection of histamine in man would give results comparable to those produced by intraventricular pilocarpine and pituitrin: namely, flushing, sweating, vomiting, and so on. As a matter of fact, much to my surprise, the customary dose of histamine employed clinically for testing the acid-producing capacity of the gastric mucosa (viz., 1 to 2 mgm. of histamine dihydrochloride), when injected into the human ventricle, gives no flushing effects. This has now been tried on three patients, all of them adults satisfactorily convalescing from operations for typical chromophobe adenomas large enough to compress the optic chiasm and destroy the posterior lobe but wholly confined within an intact diaphragma so that tuber and third ventricle were intact. The results are given in the following abbreviated protocols:

EFFECT OF INTRAVENTRICULAR HISTAMINE

CASE 1.—A woman 39 years of age with no constitutional evidences of dyspituitarism and a normal basal metabolic rate, convalescent from her operation, after the usual preliminary observations was subjected to the following com-

parative tests: (1) with *intraventricular pituitrin;* (2) with *intraventricular histamine;* (3) with *intramuscular histamine.*

First test (January 19, 1932).—One cubic centimetre of *surgical pituitrin* was injected *in the lateral ventricle.* A characteristic though somewhat delayed reaction appeared in thirty-six minutes—slight flush with sweating, followed by prolonged nausea, vomiting and evacuation of bowel. The vagal reaction was so prolonged it was ultimately checked by morphia and atropine. There was a slight fall in temperature. No change in basal metabolic rate.

Second test (January 21, 1932).—Two milligrams of *histamine* were injected *in the lateral ventricle.* Fairly prompt pallor of face despite subjective feeling of warmth and sense of fullness in head. Slightly increased moisture of skin. Belching and two attacks of vomiting—one after thirty minutes and the second after an hour. The last specimen showed 35° free acid and 44° total acid.

Third test (January 23, 1932).—Rehfuss tube with three preinjection observations with twenty minute intervals on gastric secretion. *Intramuscular injection of 1 mgm. histamine.* Within two minutes, a marked generalized flush of face and neck including the skin over the bone flap. Sense of fulness in head. No sweating or nausea. Flush beginning to fade after twenty minutes and gone at the expiration of an hour. The three pre-injection tests of gastric secretion averaged 66 c.c. in amount with free acid 12° and total acid 18°. The three post-injection tests averaged 42 c.c. in amount with 46° free acid and 45° total acid.

The tests, in short, showed a typical flushing reaction to intramuscular histamine which included the anaesthetic skin over the bone flap. Hence, the dilator effect must be blood-borne rather than through vaso-dilator fibres accompanying the sensory nerves, as appears to be the case with intraventricular pituitrin and pilocarpine (*cf.* pp. 72–73). The typical increase of gastric acidity without vomiting followed the intramuscular injection and the single test of the vomitus after intraventricular histamine suggested that in the absence of flushing the same effect had taken place. To make this point more certain, in the following case a Rehfuss tube was in place during the intraventricular tests.

CASE 2.—A man 36 years of age, six days convalescent from his operation and showing no constitutional evidences of dyspituitarism apart from a low blood-pressure and subnormal (−26) basal metabolic rate. Comparative tests were made (1) with *intraventricular pituitrin,* (2) with *intramuscular histamine,* and (3) with *intraventricular histamine.*

First test (January 29, 1932).—The usual preliminaries showed a rectal temperature 98.4°, pulse 50, blood-pressure 82/52. At 10:40 A.M., *one cubic centimetre of surgical pituitrin was introduced into the ventricle.* Within one minute the patient complained of a sense of gastric uneasiness. Within two minutes his face flushed, the bone flap being spared, and he vomited (0 free acid; total acidity 24°). There was a temporary rise in blood-pressure to 100/70 with increase in pulse rate to 76. The flush increased and mild sweating first appeared after twelve minutes. Second attack of vomiting after fifty minutes (0 free acid; total acidity 14°; guaiac +). Sweating and flushing practically disappeared after one hour twenty minutes, but nausea and belching persisted with occasional vomiting of small amounts (24 c.c., containing 0 free acid; total acidity 7°, guaiac +) until 3 P.M. when the reaction was checked by morphia and atropine. There was a fall in rectal temperature of one degree only, to 97.4°, with a subsequent thermic rebound to 101.4° at 6 P.M.

Second test (February 2, 1932).—The usual preliminaries with added introduction of a Rehfuss tube. Three 20-minute specimens of gastric juice showed an average of free acid 26° and total acid 36°. At 9:45 A.M., *0.75 mgm. of histamine* was injected into the deltoid muscle. Within one minute the patient flushed brightly, the skin over the bone-flap sharing equally with the rest of the face. There was complaint of slight headache—"like smelling amyl nitrite"—but no sweating or nausea. The flush gradually faded and was no longer appreciable after 30 minutes. Meanwhile, there had been no discernible change in pulse, respiration, temperature or blood-pressure. The post-injection gastric specimens showed: after 20 minutes (35 c.c. containing 58° free acid, 68° total acid); after 40 minutes (25 c.c. containing 74° free and 85° total acids); and after 60 minutes (22 c.c. containing 70° free and 93° total acids; no guaiac).

Third test (February 3, 1932).—The usual preliminaries. All but one of the pre-injection amounts of gastric juice withdrawn from the Rehfuss tube were too small accurately to measure. This single specimen showed 2° free and 25° total acid.

At 10:33 A.M., 1.5 mgm. *histamine* (double the dose of the second test) was *injected into the ventricle*. Almost immediately the patient complained of headache but there was no observable reaction other than a slight pallor of the face and momentary subjective uneasiness of the stomach. At 11 A.M., to check his headache he was given 0.5 mgm. of morphia. The post-injection gastric specimens showed: after 20 minutes (19° free and 40° total); after 40 minutes (50° free and 71° total); after 60 minutes (80° free and 90° total); after 80 minutes (80° free and 92° total); after 100 minutes (76° free and 83° total); after 120 minutes (46° free and 65° total acids). At no time were amounts of more than 10 c.c. of gastric juice secured; none of the specimens showed a positive guaiac test.

From the foregoing tests, it would appear that the intraventricular injection of histamine causes facial pallor rather than flushing, even in doses twice that which evokes an almost immediate and prolonged flush when injected in the muscle. Hence, the striking flushing effects produced by intraventricular pituitrin can scarcely be ascribed to the absorption into the blood-stream of associated histamine, whose molecule, if I am correctly informed, is smaller than that of pituitrin and should be absorbed more rapidly.

In a recent report by Weiss, Robb and Ellis* on the systemic effects of histamine, it has been shown that the responses to histamine in man and animals differ widely. Of particular interest is their demonstration that the transient flushing effects are particularly marked in the brain, as shown not only by increased pulsatile expansion of the cerebrospinal fluid but also by direct observation during the course of a cerebral operation. Moreover, there is customarily an increase in basal metabolic rate and a rise in blood-pressure rather than the fall which occurs in anaesthetized animals.

In the following case, the order of the injections was altered to leave the more upsetting reaction from intraventricular pituitrin to the last.

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* Weiss, S., Robb, G. P., and Ellis, L. B., "The systemic effects of histamine in man," *Arch. Int. Med.*, 1932, XLIX, 360–396.

CASE 3.—A man 46 years of age, three weeks convalescent from an operation which left him with some evidences of pituitary deficiency shown particularly by his low basal metabolic rate. Tests were made: (1) with *intramuscular histamine;* (2) with *intraventricular histamine;* (3) with *intraventricular pituitrin.*

For convenience of comparison, the effects of the histamine injections are put in tabular form and made to synchronize as though both were given at 10 A.M. As a matter of fact, the intramuscular injection was given at 10:01 A.M. and the intraventricular injection at 9:31 on the following day. On each occasion preliminary observations were made with the patient fasting, beginning with an estimation of the basal metabolic rate. The Rehfuss tube was then swallowed and gastric contents removed every twenty minutes, the last just before the injection. Pulse, respiration and blood-pressure were plotted at frequent intervals and a constant chart of rectal temperature was electrically recorded on a drum. The patient was quiet and coöperative throughout.

INTRAMUSCULAR HISTAMINE (*May 3, 1932*)	(Time)	INTAVENTRIULAR HISTAMINE (*May 4, 1932*)
Basal metabolic rate −32. Gastric juice, two preliminary observations; fluid colourless and watery (specimens averaged 15 c.c. with 47° free acid, 59° total acid). Pulse 80; respiration 20; blood-pressure 120/80. Well covered; comfortable; rectal temperature 98.5°, room temperature 76°.	8:30 A.M.	Basal metabolic rate −32. Gastric juice, colourless and watery (two specimens averaged 25 c.c. with 48.5° free acid, 60° total acid). Pulse 80; respiration 20; blood-pressure 100/80. Comfortable. Rectal temperature 98.6°; room temperature 82°.
Injection in deltoid muscle 1 mgm. histamine dihydrochloride. Prompt feeling of warmth followed by bright, dry flush including boneflap. Skin dry. Transient elevation of pulse to 110 with fall in blood-pressure to 105/70.	10:00	*Injection in ventricle 1 mgm. histamine.* Almost immediate sense of warmth with fleeting suggestion of flush and slight moisture on chin. No change in pulse, respiration or blood-pressure.
Condition stationary. Flush persists; no sweating. Gastric contents (amount 18 c.c.: 87° free acid, 96° total acid; 0 guaiac).	10:20	Comfortable; composed. Slight headache. Slight increase cutaneous moisture of face persists. Gastric juice (13 c.c.: 71° free and 80° total acid).
	10:30	Headache more severe; slight nausea.
Flush beginning to fade. Pulse 90, respiration 25. Blood-pressure stationary at 110/80. Second specimen gastric contents (12 c.c., light brown colour: 110° free acid, 115° total acid; faintly positive guaiac).	10:40	Pulse, respiration, blood-pressure remain unaltered. Gastric juice (14 c.c.: 10° free and 20° total acid; faint guaiac).
Flush still present. A slight rise in rectal temperature to 98.9°. Third gastric specimen (12 c.c., medium brown colour: 103° free acid, 106° total acid; positive guaiac).	11:00	Headache much less. Third gastric specimen (13 c.c., clear and watery: 10° free and 21° total acid; positive guaiac).

INTRAMUSCULAR HISTAMINE (*May 3, 1932*) (*Continued*)	(Time)	INTRAVENTRICULAR HISTAMINE (*May 4, 1932*) (*Continued*)
Slight flush still present. Rise of 1° rectal temperature. Fourth gastric specimen (10 c.c., coffee-brown colour: 84° free acid, 99° total acid; strongly positive guaiac). Rehfuss tube withdrawn.	11:20	Complains of feeling cold though body warm to touch. Rectal temperature 97.9°, a fall of 0.7°. Fourth gastric specimen (10 c.c. colourless fluid: 10° free, 19° total acid; guaiac ++).
Basal metabolic rate −13, a rise of 19 points. Observations discontinued.	11:40	Fifth gastric specimen (only 3–4 c.c. colourless fluid obtainable: guaiac ++). Rehfuss tube withdrawn.
	12:00	Basal metabolic rate −19, a rise of 13 points. Observations discontinued.

The foregoing comparative tests with histamine show, in accordance with what is well known, that intramuscular histamine in 1 mgm. doses gives a bright, prolonged flush with a sense of fullness in the head, a temporary rise in blood-pressure and pulse rate, and increased gastric acidity in the absence of any notable increase of secretion. On the other hand intraventricular histamine in equal amount gave a trifling momentary increase of colour scarcely to be called a flush, caused headache, some nausea, and a possible temporary increase in gastric acidity quickly followed by diminution below the pre-injection percentages.

TEST 3.—To make certain that this patient was normally susceptible to *intraventricular pituitrin*, on *May 7* he was given the customary 1 c.c. by this route. After an hour's interval (during which he showed a rapid increase in gastric acidity which rose to 100° free- and 106° total acid with positive guaiac test), a severe reaction set in culminating in a brilliant flush sparing the boneflap, drenching perspiration, vomiting, and a fall in rectal temperature of 1°, to 97.8°.

The reaction lasted for fully two hours during which time the brilliant flush and accompanying sweat would fade and reappear in waves averaging from ten to fifteen minutes in duration. The over-severe reaction was finally subdued by an injection of morphia and atropine. There was a subsequent thermic rebound four hours later to 101.4°, a rise of four degrees.

These three observations on the pharmacodynamic effect of intraventricular histamine (in patients shown to be highly susceptible to intraventricular pituitrin) in view of the negligible response would appear to exclude a histamine impurity as the cause of the pituitrin reaction. Whether pituitrin contains acetylcholine in amounts sufficient to account for its flushing effect when injected into the ventricle seems highly improbable. While animals are highly susceptible to the effects of acetylcholine, man appears to be highly resistant. Administered intravenously or subcutaneously in doses vastly greater than could possibly be carried as an impurity in a cubic centimeter of pituitrin, its parasympathetic effects prove to be exceedingly transient. It therefore has seemed unnecessary to subject patients to the test of its intraventricular effects.

VIII. THE COMPARATIVE EFFECTS ON GASTRIC MOTILITY OF INTRAMUSCULAR AND INTRAVENTRICULAR PITUITRIN AND PILOCARPINE

WHILE the tests described in the preceding section were being conducted, certain studies on gastric motility, as affected by the intramuscular or intraventricular injection of pituitrin, pilocarpine and histamine, have been made with the friendly coöperation of Dr. M. C. Sosman, roentgenologist to the Brigham Hospital, and his assistant, Dr. H. F. Hare. As the results of these tests are pertinent to the mooted point regarding the essential difference of the reaction to centrally and peripherally administered pituitrin, they may be put on record at this time, though deserving of further expansion.

The observations which have been made on a series of eleven patients, six of them after operations for chromophobe adenomas, have been almost wholly restricted to the single point of gastro-intestinal motility. Having been necessarily conducted in a dark room, the usual detailed consecutive records of pulse, temperature, blood-pressure, colour change, and so on have been impracticable and made only at irregular times.

PITUITRIN EFFECTS

It has long been known that in addition to its antidiuretic effect, intramuscular or intravenous pituitrin causes cutaneous pallor together with a slight rise in blood-pressure and pulse rate suggesting a sympathico-adrenal response. Intraventricular pituitrin, on the other hand, produces a cutaneous flush, sweating, salivation and vomiting which were looked upon as of central, parasympathetic origin.

It seemed highly improbable that the active principle of an organ of internal secretion should have a contrary action if introduced in different regions of the body, though this was the only interpretation of these effects that could be readily offered. What effect on gastric motility intramuscular pituitrin would have was unknown, though the prolonged retching and vomiting that followed its intraventricular injection suggested a central stimulation of the vagus in which, curiously enough, the fibres to the heart did not participate. We were wholly unprepared for the gastric response which actually occurred.

CASE 1.—A patient satisfactorily convalescing from an operation for the removal of a parietal glioma was given an opaque meal (90 gm. barium sulphate in 200 c.c. malted milk). Vigorous and unusually active peristalsis of three-wave type started immediately. On the third wave emptying began and the barium column shot into duodenum and jejunum. Six or eight waves were followed through from cardia to pylorus. A cubic centimeter of *surgical pituitrin* was then injected into the deltoid muscle and within thirty seconds there was *complete cessation of all peristaltic movement* in the stomach and shortly after in the intestine. After an interval of twenty minutes, sluggish movements were resumed, first in the intestine, and ten minutes later normally active gastric peristalsis was fully restored.

Precisely this same effect was observed in the case of John S., whose comparative records of intraventricular pilocarpine and pituitrin were given in the second installment in this series (*cf.* pp. 68–69). He had remained well and at work for nearly a year and had recently reëntered the hospital because of a recurrence of his tumor symptoms. A secondary operation had been performed with such satisfactory results, he in gratitude willingly submitted to another series of tests, as follows:

CASE 2 (John S.).—After a barium meal, fluoroscopic studies were made to determine: (1) the effect of *intramuscular pituitrin;* (2) of *intraventricular pituitrin;* (3) of *intramuscular pilocarpine;* and (4) of *intraventricular pilocarpine.*

Test 1 (March 24).—After ingestion of the barium, active peristalsis started immediately, deep vigorous waves progressing from the cardiac third to pylorus, the stomach emptying on the first wave. A succession of waves were timed through at an average of thirty-seven seconds.

Injection.—A c.c. of *surgical pituitrin* was then injected into the deltoid muscle and within thirty seconds all gastric movement had ceased, the jejunal peristalsis continuing for a few seconds longer. After a five-minute interval, jejunal peristalsis was resumed but twenty minutes elapsed before the slightest movement in the stomach was discernible. By this time the head of the barium column in the intestine had reached the caecum. Shortly after, he had a loose stool.

Test 2 (March 30).—While recumbent, at 10:10 A.M., a lumbar puncture needle was inserted in the ventricle and a few drops of fluid allowed to escape. At 10:12, the barium meal was given and vigorous peristalsis of three-wave type immediately started. Several waves were timed through at an average of thirty-five seconds.

Injection.—At 10:20, *surgical pituitrin* (1 c.c.) *was injected into the ventricle* and the needle withdrawn. Peristaltic waves remained active and vigorous and so rapid they were difficult to time. There was such rapid emptying that further barium was given at 10:34, some of it being regurgitated. At 10:48, no visible trace of barium remained in the stomach, most of it being in the lower ileum. At 11:35, the head of the barium column was in the hepatic flexure; no stool till following morning.

The general reaction (as the year before) to a single c.c. of intraventricular pituitrin was slight, there being a delayed flush, a moderate sweat and an attack of vomiting at 12:30 P.M. (250 c.c. with free acid 6° and total acid 36°). There was a fall in rectal temperature from 98.6° to 97.4° at 1:45, followed by a thermic rebound to 101.6° at 9 P.M.*

PILOCARPINE EFFECTS

On this same patient, for comparison with the foregoing, the following tests with pilocarpine were made:

Test 3 (April 5).—Again after the barium meal vigorous deeply cut, three-wave peristalsis began immediately with rapid emptying: waves timed at 40 seconds.

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* In the second paper in the series, in which the general reaction was described, stress was laid on the primary drop in temperature, and the fact that a thermic rebound is apt to take place was insufficiently emphasized.

Injection.—At 10:11 A.M., 12 mgm. of *pilocarpine were injected into the deltoid muscle.* At 10:16, subjective feeling of warmth with sweating; also a definite diminution in activity of peristalsis though movement was not so completely inhibited as with subcutaneous pituitrin. At 10:26, duodenal cap emptied for the first time after the injection. At 10:31, vigorous peristaltic rushes were resumed in the ileum though activity of gastric movement was still retarded and remained so until 10:44 when the observation was concluded.

Test 4 (April 7).—Again, 90 gms. barium in malted milk followed by immediate active peristalsis of three-wave type with rapid emptying. "Wave-time" averaged 40 seconds.

Injection at 11:14 A.M. of 2.5 mgm. *pilocarpine intraventricularly.* In four minutes, a subjective sensation of warmth. This was accompanied by pylorospasm and antiperistaltic waves leading to three attacks of vomiting at 11:18, 11:19 and at 11:21. Each attack was accompanied by vigorous antiperistalsis. Under the light, the patient was seen to be having a marked parasympathetic effect with bright flush, profuse sweat, and salivation such as he had shown before (*cf.* pg. 68). On the cessation of vomiting, the tone of the stomach remained markedly increased with prominent and apparently swollen rugae.

At 11:26, 0.5 mgm. of atropine was given to check the explosive reaction. It was impossible subsequently to time the waves with any accuracy. The peristalsis in the small bowel meanwhile had continued and by 11:29 the barium column had reached the ileum.

By 11:31, all visible forward movement in stomach and intestine had ceased. Strong, deep, reverse peristaltic waves associated with spasm of the lower two-thirds of the stomach, which forced the barium into the fundus and through the cardia into the oesophagus, subsequently occurred at irregular intervals, the patient being conscious of their onset even before the fluoroscopist could detect them. Some of these antiperistaltic waves were accompanied by vomiting.

Not until 11:55 did the stomach begin to relax and show an occasional wave progressing in the normal direction. Fluoroscopy was then temporarily concluded. One more attack of vomiting occurred at 12:05 P.M. At 1:25 P.M., he was again fluoroscoped and the stomach was found to be emptying normally with the head of the barium column in the caecum.

In its general features the reaction was precisely similar to that previously recorded (*cf.* pg. 68). At 1:15 P.M., the rectal temperature had dropped to 96° and from this low level there was a gradual rise to normal at 2:15 P.M. with a thermic rebound reaching 104° at 6 P.M., followed by slow subsidence to normal.

Tests for acid in the vomited fluids indicated that the increased tonus was unassociated with secretory activity as shown in the following table

STUDIES OF VOMITUS

Time obtained	Amount	Character	Acids		Guaiac
			Fatty	Total	
11:18	125 c.c.	Greyish fluid	48	60	0
11:21	35 c.c.	Reddish brown	20	43	++
11:34	40 c.c.	Reddish brown	12	31	++
12:05	15 c.c.	Brownish	18	41	+++

So far, it would appear: (1) that neither subcutaneous nor intraventricular pilocarpine or pituitrin increase gastric acidity as does histamine; (2) that intramuscular pituitrin and, to a less extent, pilocarpine inhibit gastric peristalsis whereas histamine does not notably affect it; and (3) that intraventricular pilocarpine and pituitrin increase motility to the point of pylorospasm with retrograde peristalsis and vomiting.

Delayed pilocarpine reaction.—At about this time, a chance observation had been made on a patient with an unverified tumor of the third ventricle associated with a gastric ulcer (*cf.* pg. 203), who had returned for examination. Gastro-intestinal studies under a barium meal showed the ulcer to be healed. The stomach exhibited normal peristalsis of three-wave type, the wave-time averaging 65 seconds. He was given an *intramuscular injection of 12 mgm. pilocarpine* which in six minutes provoked the customary constitutional reaction with sweating and salivation and so on. No change, however, was apparent in gastric motility until fifteen minutes had elapsed, when the peristalsis became more vigorous, a 52-second wave being timed, four minutes later a 45-second wave, in another minute a 47-second wave, and four minutes later a 46-second wave.

Knowing how prompt is the effect on the stomach of even small doses (2 mgm.) of intraventricular pilocarpine, it was thought that this delayed acceleration of peristalsis might be ascribable to the retarded action of the circulating drug on the parasympathetic or vagal centre in the brain. The same delayed effect was also observed in another patient on whom the following series of tests were made:

CASE 3.—The patient was a young man previously under observation with choked discs due to an unlocalizable tumor associated with a duodenal ulcer. A subtemporal decompression had been performed with subsidence of his choked discs and headaches together with apparent healing of the ulcer. The tests were planned to determine with the aid of a Rehfuss tube the comparative effects on gastric secretion and motility of *intramuscular pilocarpine, histamine, and adrenalin.*

First test (April 5, 1932).—The pre-injection specimens of gastric juice averaged 77 c.c. in amount with 17° free acid and 26° total acid.

8:02 A.M.—*Injection, intramuscular, of 12 mgm. pilocarpine.* Within five minutes there was flushing, generalized profuse sweating, lachrymation and salivation. There was a temporary increase in pulse rate from 68 to 90, and the blood-pressure fell for 20 minutes from 128/80 to 118/70. No change in respiration or rectal temperature. The reaction persisted for an hour and by 9:20 was practically over.

At 8:25, just 25 minutes after the injection, he had some belching and complained of a bellyache which he said was precisely like his old familiar "hunger pains." This continued intermittently with some nausea and continued belching until finally at 8.55 it culminated in an attack of unproductive retching. Some nausea persisted for ten minutes and then passed off.

A Rehfuss tube was inserted, and four samples of gastric juice were obtained consecutively. The acid content of the aspirated specimens appears in the following table:

TEST 1, CASE 3, ASPIRATED SPECIMENS OF GASTRIC JUICE

Specimen	Time	Amount	Acids	
			Free	Total
1	8:20	170 c.c.	10	20
2	8:40	170 c.c.	0	12
3	9:00	45 c.c.	0	4
4	9:20	5 c.c.	6 (?)	12 (?)

In correspondence with what others have observed, intramuscular pilocarpine in this case, therefore, diminished rather than increased the gastric acidity, acting, in other words, unlike histamine. The reaction was accompanied, however, by a delayed (23 min.) disturbance apparently affecting gastric motility. More precisely to determine the delayed effect of the injection on motility was the purpose of the next test.

Second test (April 6, 1932).—After a barium meal peristalsis again of the three-wave type promptly set in with early emptying. Three waves were timed through averaging 53 seconds.

Injection at 10:41 A.M. of *12 mgm. pilocarpine intramuscularly.* Same constitutional reaction as with test of preceding day. There was no appreciable change in peristalsis—certainly no increase in activity, the next few waves being actually timed at 10 seconds slower than before. For the next 20 minutes peristalsis of original type continued unaltered.

At 11:03 A.M., 21 minutes after the injection, he began to complain, as on the preceding day, of "hunger ache." A peristaltic wave had just been timed at 61 seconds. At 11:05, a vigorous wave was timed at 50 seconds; at 11:06, at 46 seconds; at 11:07, at 48 seconds; at 11:13, at 47 seconds. Shortly after this his "ache" wore away and at 11:36 and 11:37 waves were again timed at *circa* 54 seconds. The observation at this point was discontinued.

This test, therefore, tended to confirm the suggestion of a delayed effect of intramuscular pilocarpine in accelerating peristalsis, possibly from a tardy action on the vagal centre by the circulating drug. Comparative tests with intramuscular histamine were also on two occasions made on this same patient. They showed the usual increase in acidity and possibly a slight acceleration of motility with temporary shortening of the wave-time and a tendency to pylorospasm, but nothing striking.

Adrenalin Effects.—In view of the suggestion that intramuscular pituitrin acted as a sympathico-adrenal stimulant, it remained to be seen whether adrenalin would correspondingly inhibit gastric motility. The test was made on the same patient (Case 3) as follows:

Test 3 (April 14).—Usual preliminaries with barium meal. Immediate inauguration of active peristalsis of three-wave type, the average wave-time being 49 seconds.

10:51 A.M.—*Injection 1 mgm. adrenalin (1 c.c. solution) intramuscularly.* Usual prompt adrenalin reaction (rise in blood-pressure and slight increase in pulse

rate) with prompt inhibition of peristaltic activity. The first post-injection wave started but stopped in course. It was followed by a few shallow incomplete waves and in four minutes there was complete cessation of movement both in stomach and intestine. This inhibitory phase lasted for twenty minutes when gastric peristalsis again began to occur. The first wave capable of being followed through was caught at 11:33 A.M. and timed at 55 seconds. Normal peristalsis before this time had been resumed in the intestine.

CONCLUSIONS

If these observations are correctly interpreted, pituitrin given intramuscularly has an effect contrary to that which occurs when injected into the cerebral ventricle. The systemic reaction to the former method of administration so closely resembles that following the intramuscular injection of adrenalin it suggests excitation of the thoraco-lumbar sympathetic apparatus. The stimulatory effects of intraventricular pituitrin, on the other hand, are essentially parasympathetic in character resembling those of pilocarpine in that they produce flushing and sweating together with a hypervagotonic effect on the stomach leading to pylorospasm, retrograde peristalsis and vomiting due apparently to efferent impulses of central origin.

III. The Basophil Adenomas of the Pituitary Body and their Clinical Manifestations ("Pituitary Basophilism")[1]

INTRODUCTION

IN A long since superseded monograph* on the pituitary body and its disorders, published in 1912, a section was devoted to a group of cases which showed peculiar and sundry polyglandular syndromes. It was stated at the time that the term "polyglandular syndrome" implied nothing more than that secondary functional alterations occur in the ductless-gland series whenever the activity of one of the glands becomes primarily affected; and further, that the term, as employed, was restricted to those cases in which it was difficult to tell where the initial fault lay.

That a primary derangement of the pituitary gland, whether occurring spontaneously or experimentally induced, was particularly prone to cause widespread changes in other endocrine organs was appreciated even at that early day, and it was strongly suspected that this centrally placed and well-protected structure in all probability represented the master-gland of the endocrine series. The multiglandular hyperplasias of acromegaly, so evident in the thyroid gland and adrenal cortex, were already known, and the no less striking atrophic alterations in these same glands brought about by the counter state of pituitary insufficiency were coming to be equally well recognized. But in spite of these hopeful signs, we were still groping blindly for an explanation of many other disorders, obviously of endocrine origin, like those associated with pineal, parathyroid or suprarenal tumors. Out of this obscurity, those seriously interested in the subject have, step by step, been feeling their way in spite of pitfalls and stumbling blocks innumerable.

The usual method of progression has been somewhat as follows. A peculiar clinical syndrome has first been described by someone with a clarity sufficient to make it easily recognizable by others. This syndrome in course of time has been found to be associated either with a destructive lesion or with a tumefaction primarily involving one or another of the organs in question. These tumefactions have proved in most cases to be of an adenomatous character and it was finally recognized (first in the case of the thyroid) that adenomas of this kind were functionally active structures that produced hypersecretory effects. It then gradually came to be realized that the tumor need not necessarily be bulky but, quite to the contrary, striking clinical effects might be produced by minute, symptomatically predictable adenomas. So it is the degree of

[1] Reprinted from *Bulletin of Johns Hopkins Hospital*, Vol. L, No. 3, pp. 137–195, March 1932.

* Cushing, H., "The Pituitary Body and Its Disorders." J. B. Lippincott Co., Phila., 1912.

secretory activity of an adenoma, which may be out of all proportion to its dimensions, that evokes the recognizable symptom-complex in all hypersecretory states.

The pituitary adenomas.—The anterior-pituitary body, as distinct from the neuro-hypophysis, is a compact of cellular elements of three recognizable sorts, divided by histologists, on the basis of their staining reactions, into two principal types: (1) those having a non-granular cytoplasm, and (2) those with a cytoplasm which is distinctly granular. Cells of the former type are known as neutrophil (chromophobe) elements and of the latter—the granular type—as chromophil elements of which there are two sorts: (a) those whose granules show an affinity for acid dyes (acidophil cells); and (b) those with an affinity for basic dyes (basophil or cyanophil cells). Each of these three cellular types—chromophobe, acidophil and basophil—is capable of producing its own peculiar adenomatous formations.

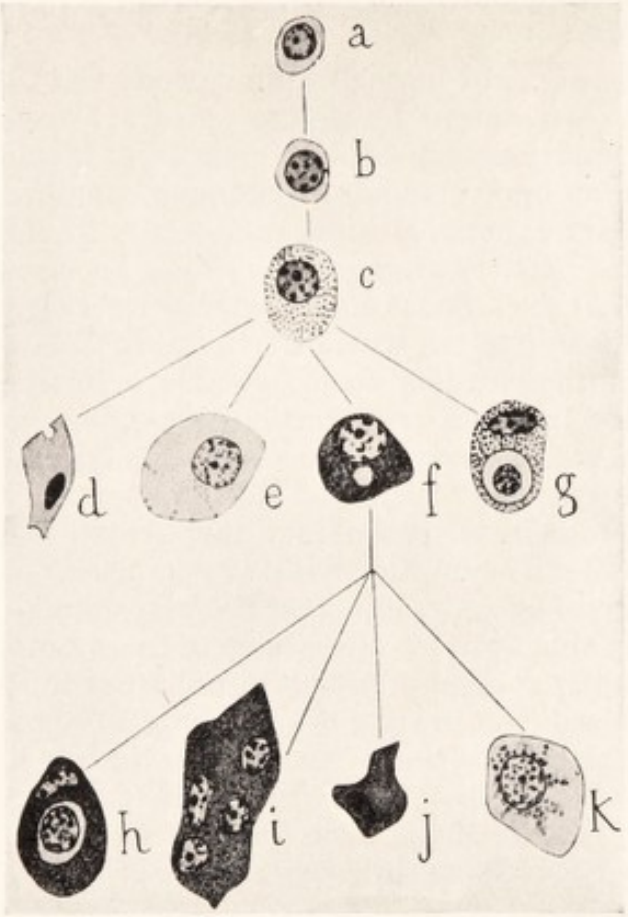

FIG. 31.—Evolution of anterior-pituitary cell (Collin): (*a*) chief cell; (*b*) eosinophil non-granular cell; (*c*) acidophil granular cell; (*f* and *i*) typical basophil forms; (*d* and *e*) degenerative eosinophil cells; (*j* and *k*) degenerative basophil cells; (*g* and *h*) endocytogenetic rebirth of chief cells.

Whether these three types of cells are fixed in character or represent different stages in activity of the same original cell is a matter of dispute. The most recent advocate of the unitarian view is Remy Collin of Nancy who, purely on anatomical grounds, presents[2] a convincing argument to show (*cf.* Fig. 31) that the non-granular cell (*cellule principale:* mother-cell) represents the primitive stage of activity of an element which in the process of ripening acquires a granular cytoplasm that is primarily acidophil (eosinophil) but which may in turn become basophil (cyanophil). When the ripened granular cytoplasm comes to be discharged, little is left but the nucleus and membrane of the cell which may then either degenerate or, in a renewed cycle, once more pass through these same

[2] Collin, R., *La Neurocrinie Hypophysaire. Etude histophysiologique du complexe tubéro-infundibulo-pituitaire.* Paris: G. Doin et Cie., 1928, 102 pp.

stages to be again discharged under proper stimulus.[3] But if this is actually what takes place, the fact that each of these varieties of cells is capable of forming adenomas whose elements appear to be of fixed rather than of a changing type is highly peculiar.[4] What is more, one would naturally expect that adenomas composed of the non-granular mother-cells (*Hauptzellen: cellules principales*) would be more likely to show evidences of cell division than would adenomas composed of elements in the more advanced stages of secretory activity. But just the opposite occurs; the elements composing the common chromophobe adenomas rarely if ever show cell division, whereas those of a chromophil adenoma, whether acidophil or basophil, are frequently multinuclear (*cf.* Figs. 32, 33, 46, 53) and show numerous mitotic figures.[5]

Meanwhile, experimental pathology has provided us with some fairly definite facts concerning the function not only of the anterior pituitary considered as a whole, but, in turn, of its different cellular constituents. When its frequent association with a pituitary tumor came to be recognized, it was at first supposed that acromegaly was an expression of glandular deficiency and theoretically should be reproducible by experimental extirpation of the gland. This, however, in the majority of cases

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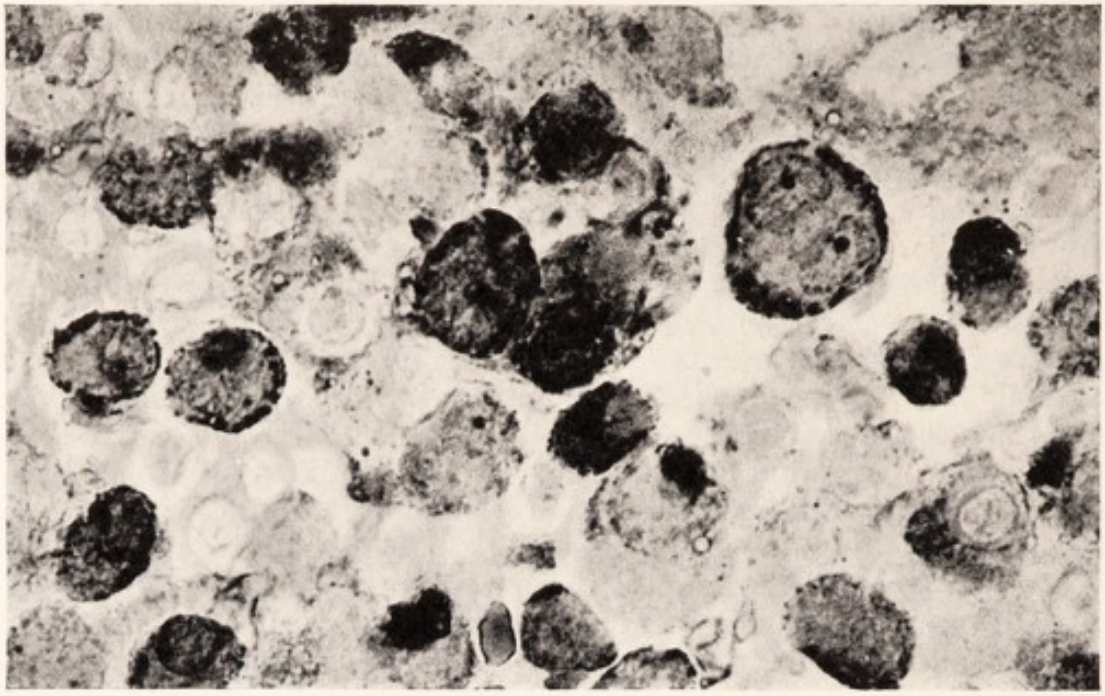
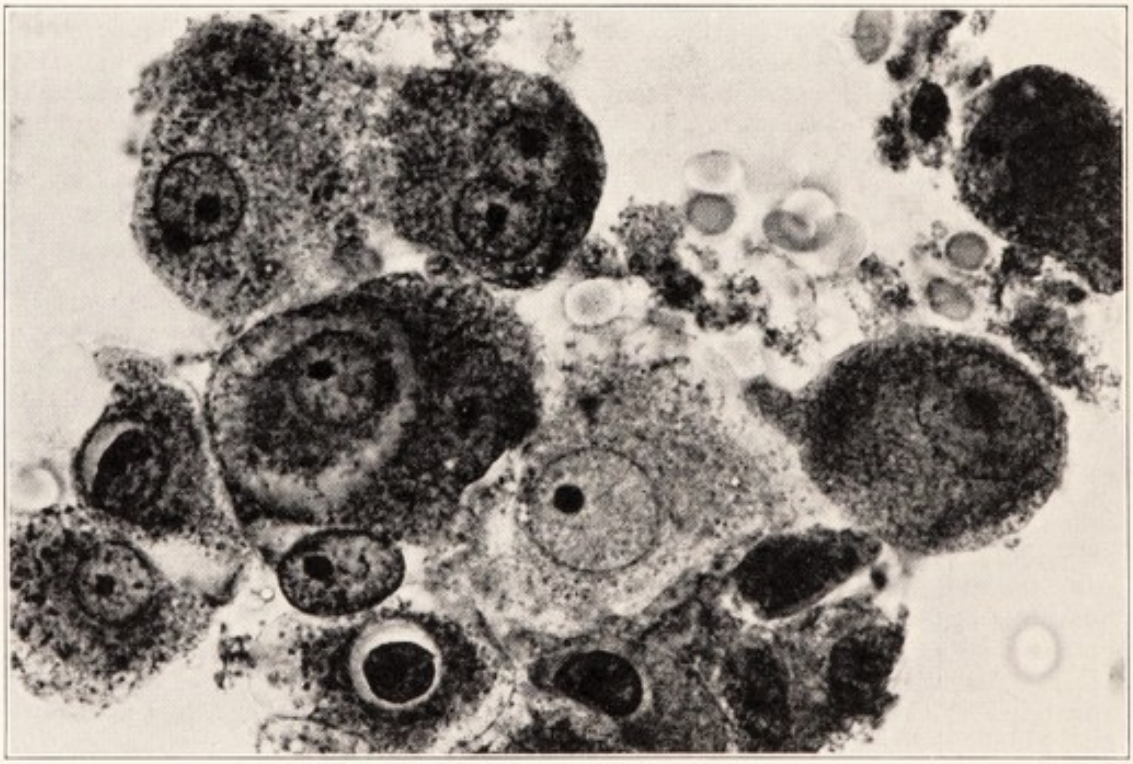
[3] Nothing of precisely this same sort, to be sure, occurs in other glands of internal secretion; but this need not unduly disturb us, for the pituitary body, whether taken from a morphological or functional aspect, is a tissue of surprizes. It is now recognized by histologists that secretory cells discharge in different ways. They may merely extrude their accumulated granules without particular change in form, as in gastric secretion; they may wholly disgorge their ripened cytoplasm, as in mammary secretion; or the entire cell may be cast off, as in sebaceous secretion—and this apparently is what takes place more particularly in the neurohypophysis from whose epithelial envelope (pars intermedia) degenerating cells are cast off which migrate through the pars nervosa where they become transformed into the hyaline bodies that presumably represent the active principle of this part of the gland.

[4] Professor A. E. Severinghaus of Columbia University has made the highly interesting discovery in the rat that basophil and acidophil cells in addition to their differing affinity for dyes are distinguishable by the character of the Golgi apparatus which they contain. The Golgi apparatus of the basophil cell has its stainable lipoid substance arranged in the form of a hollow sphere whereas in the acidophil cell it forms a characteristic network. These same differences in arrangement of the lipoids in the Golgi apparatus are traceable to the mother-cells, so that a differentiation into cells which are to become basophil and others which are to become acidophil is present at an early age. How early this distinction can be made has not yet been determined but the observations demonstrate the independent origin of basophils and acidophils from mother-cells and make unlikely any interchange between the fully differentiated chromophil types (*Anat. Record.* 1932, Suppl. No. LII 35). Dr. Eisenhardt has been able to identify in her fresh smears of pituitary adenomas the circular spot which represents the position of the Golgi apparatus and which we had formerly looked upon as a vacuolated area.

[5] It would seem that the only possible way this question of fixity or changeableness of the elements composing pituitary adenomas could be conclusively answered would be by cultivating the cells of the different types to determine whether they breed true to their original form or whether their cytoplasm undergoes progressive alteration. Efforts in this direction have so far proved unconvincing owing largely to technical difficulties due to want of experience with the artificial growth of neoplastic tissues.





FIGS. 32 and 33.—Supravital preparation (Eisenhardt) of two chromophil adenomas (×850) above from an acromegalic showing peripheral distribution of self-stained granules; below a cluster of huge granular cells from a case of fugitive acromegaly.

led to early death, at least of adult animals (chiefly dogs), whereas younger animals when hypophysectomized, though they might recover for long periods, ceased to grow and remained sexually infantile.

It had already been observed that tumors, grossly indistinguishable in situation and type from those associated with acromegaly, were of far greater frequency and provoked a syndrome, so far as its constitutional manifestations were concerned, of a wholly different character. Individuals affected by these tumors when of adult age, instead of a tendency to overgrowth, showed on the contrary a tendency to become adipose, to lose their secondary sex-characters, and to become impotent, in company with recognizable atrophic changes in the sexual organs. When altogether comparable changes were seen occasionally to occur in animals (dogs) after incomplete experimental hypophysectomy, it became evident that the syndrome represented a deficiency state which was termed *hypopituitarism;* and this furnished an added reason to assume—what had already been conjectured—that acromegaly almost certainly represented the counter state of *hyperpituitarism.*[6]

The final experimental proof of the correctness of this assumption was delayed until Evans and Long,[7] succeeded in producing experimental overgrowth (gigantism) in the rat, an animal whose epiphyses do not close throughout life; and subsequently in the dog, whose epiphyses like those of man normally do unite, Putnam, Benedict and Teel[8] produced a condition of overgrowth comparable in all respects to that characterizing acromegaly.

But this is only half the story. There was evidently a complicating element in these experiments. If only a single pituitary principle (hormone) had been involved in experimental hyperpituitarism of this kind, one might well enough have expected increased growth to go hand in hand with increased activation of the reproductive functions. Quite to the contrary, while the injections unmistakably served to promote growth they at the same time checked the normal ovulatory cycle of the animals. In consequence of this observation, Dr. Evans was led to suspect the presence of dual glandular hormones and he came to believe, indeed, that they were in some peculiar way opposed in their action.

At another time and place a review has been given[9] of the steps leading to the disclosure that the growth-provoking and sex-maturing principles —the former almost certainly elaborated by the acidophil and the latter

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[6] Cushing, H., "The hypophysis cerebri: clinical aspects of hyperpituitarism and of hypopituitarism," *J. Am. M. Ass.*, 1909, LIII, 249–255.

[7] Evans, H. M., and J. A. Long, "The effect of the anterior lobe administered intraperitoneally upon growth, maturity, and oestrous cycle of the rat," *Anat. Record*, 1921, XXI, 62–63.

[8] Putnam, T. J., Benedict, E. B., and H. M. Teel, "Studies in acromegaly. VIII. Experimental canine acromegaly produced by injection of anterior lobe pituitary extract" *Arch. Surg.*, 1929, XVIII, 1708–1736.

[9] Teel, H. M., and H. Cushing, "The separate growth-promoting and gonad-stimulating hormones of the anterior hypophysis: an historical review," *Endokrinologie* (Leipzig), 1930, VI, 401–420.

presumably[10] by the basophil elements of the lobe—are chemically separable hormones. Hence the former working conception of hyperpituitarism *versus* hypopituitarism as an indication on the one hand of secretory overactivity leading to acromegaly or gigantism, and on the other hand of secretory underactivity leading to a counterposed syndrome, wholly falls to the ground. Or, if not quite so bad as this, it at least must be replaced by hyperpituitary *versus* hypopituitary states due to excessive or insufficient secretion not only of the acidophil elements concerned with growth but also of the basophil elements chiefly concerned, presumably, with the ovulatory mechanism.[11]

In an attempt to interpret in terms of human pathology the highly informing latter-day disclosures of experimental biologists, we may properly review, with necessary brevity, the development of the idea that the adenomas which affect the organs of internal secretion are not mere static conglomerations of cells, but represent lesions possessing an incredible degree of physiological activity, those which have most recently attracted attention being the tiny adenomas of the parathyroid glandules and those of the pancreatic islets.

The common tumors of the anterior pituitary—first looked upon merely as a local expression of acromegalic overgrowth, and subsequently as sarcomas or "strumas" of the gland—were first clearly differentiated by Benda in 1900 as varieties of adenoma; and we have slowly come to understand with some degree of definiteness the clinical pictures produced by those whose cells possess a granular and acidophil cytoplasm and those with a non-granular or chromophobe cytoplasm. The former, even when so small that they may easily escape post-mortem detection, are productive of unmistakable acromegaly or gigantism or a combination of the two. The more common chromophobe adenomas, on the other hand, usually attain a size sufficient to distort the chiasm before they give appreciable clinical symptoms, and it is quite probable that the cells which comprise them possess no secretory activity—that is, produce no hormone. They nevertheless cause their own peculiar constitutional disorder, this being a deprivation syndrome[12] brought about in all probability

[10] The evidence of this is suggestive rather than conclusive. It is based on the facts: (1) that following castration, at least in the rat though not definitely in other species, there is an increase in the basophil elements; and (2) that the extracts of the pituitary glands of castrates of all species are more active than normal glands in their gonad-stimulating properties. P. E. Smith showed, moreover, that the central portion of the bovine anterior-pituitary which is particularly rich in basophil elements has a more pronounced effect in stimulating the thyroid to activity than the more eosinophil cortical portion of the gland. The effect of these injections on the adrenal cortex and the genital system unfortunately was not noted.

[11] Time has shown that *hyperpituitarism* and *hypopituitarism* are long words whose distinguishing syllable is easily misread and misprinted. And now that it becomes necessary or advisable to recognize two hypersecretory states, the terms *pituitary acidophilism* and *pituitary basophilism* are suggested as less unwieldy and more easily interpreted than acidophil hyperpituitarism (for acromegaly) and basophil hyperpituitarism (for the syndrome under discussion).

[12] *Cf.* Henderson, W. R., "Sexual dysfunction in adenomas of the pituitary body," *Endocrinology*, 1931, xv, 111–127.

through compression of the residual acidophil and basophil elements which no longer are able to produce their peculiar secretory product (*cf.* Fig. 8).

This in general terms at least approximates the truth. It must, however, be admitted that there are certain borderline syndromes in which a primary wave of pathological overgrowth appears to have been succeeded by a hypopituitary state—a condition which for lack of a better term has been called "fugitive acromegaly,"[13] the adenoma in these states proving to be of a mixed cellular type. Though the cells of these mixed adenomas are predominantly chromophobe, a few of them show a peripheral disposition of acidophil granules suggesting the functional retrogression of previously mature acidophil elements; and since these cells resemble the hypo-acidophil ("hypo-eosinophil") stage of development as described by Collin, the observation might be construed as an argument favouring his views. In other words, the supposed functional immutability of the cells of an anterior-pituitary adenoma may prove to be a misconception; but this need not particularly concern us here.

Two examples of a third type of anterior-pituitary adenoma, composed of basophil elements, were first described twenty years ago by Erdheim,[14] the tiny lesions having been looked upon as curiosities of morbid anatomy rather than as findings of any conceivable clinical significance. In one instance a small basophil adenoma, 1.5 mm. in diameter, was found in a woman forty years of age supposedly the victim of Basedow's disease. The other example was found in a forty-three-year-old acromegalic whose relatively small pituitary body was chiefly occupied by a fair-sized eosinophil adenoma, the minute basophil adenoma measuring only 1 mm. in diameter having been regarded as an accessory finding.[15]

PRESUMPTIVE EXAMPLES OF BASOPHIL HYPERPITUITARISM

After this explanatory digression, let us return to a consideration of the peculiar polyglandular syndrome to which allusion was made in the introductory paragraph. The original example of the syndrome around which the present discussion hinges was described in my monograph* (Case 45, pg. 217) as having shown *a syndrome of painful obesity, hypertrichosis and amenorrhoea with overdevelopment of secondary sexual characteristics.* Whether these symptoms were chiefly attributable to disordered pituitary, adrenal, pineal or ovarian influences was uncertain.

[13] Bailey, P., and H. Cushing, "Studies in acromegaly. VII. The microscopical structure of the adenomas in acromegalic dyspituitarism (fugitive acromegaly)," *Am. J. Path.*, 1928, IV, 545–564.

[14] Erdheim, J.: "Zur normalen und pathologischen Histologie der Glandula thyreoidea, parathyreoidea und Hypophysis," *Beitr. z. path. Anat. u. Path.*, 1903, XXXIII, 158–234.

[15] It is quite conceivable that acidophil and basophil adenomas may not infrequently coexist in cases of acromegaly, but I know of no other example than this in the literature. Such a coincidence might account for the differing syndromes shown by acromegalic patients some of whom exhibit disturbances which in the past we have been inclined to ascribe to the effects of secondary hyperplasia or adenoma-formation in the adrenal cortex.

*"The Pituitary Body and Its Disorders." J. B. Lippincott Co., Phila., 1912.

Case 1.—(J. H. H. Surgical No. 27140) Minnie G., an unmarried Russian Jewess, aged 23, referred by Dr. Stetten of New York, was admitted to the Johns Hopkins Hospital on *December 29, 1910.*

Clinical history.—One of a numerous and healthy family, though slight and undersized, she was well until sixteen years of age, having escaped the customary children's ailments.

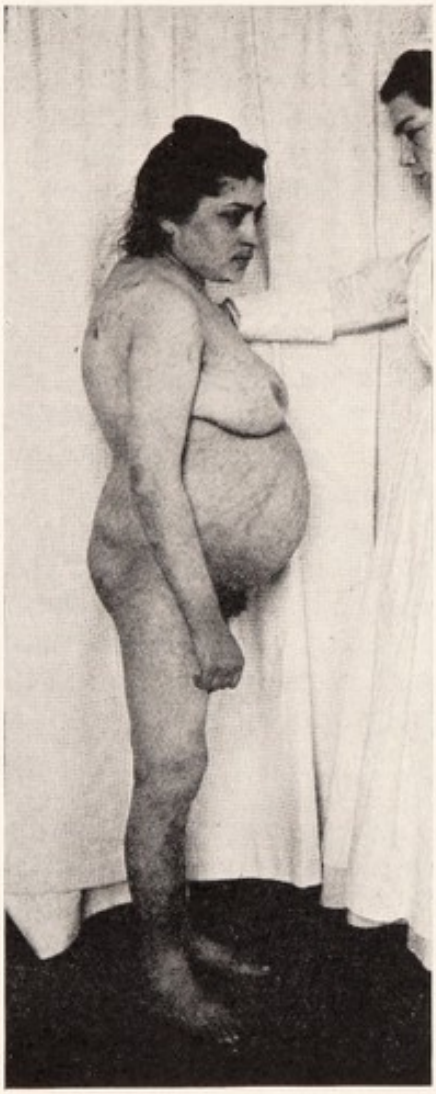


FIG. 34.—Case 1. The original example (1902) of basophil (unverified) obesity.

Her menses which started at the age of fourteen were regular for two years and then suddenly ceased. She began to grow stout and in the two years prior to admission her weight had increased from 112 to 137 pounds. She suffered greatly from headaches, nausea and vomiting sometimes accompanying the more severe attacks. She complained also of aching pains in the eyes which latterly had become prominent, and there had been occasional periods of seeing double.

Other noteworthy symptoms were insomnia, tinnitus, extreme dryness of the skin, frequent sore throats, shortness of breath, palpitation, purpuric outbreaks, recurring nose-bleeds, and marked constipation accompanied by bleeding piles. A definite growth of hair had appeared on the face with thinning of hair on the scalp. She had become increasingly round-shouldered having lost at least 4 inches in height. Muscular weakness had become extreme and there was constant complaint of backache and epigastric pains.

Physical examination.—This showed an undersized, kyphotic young woman 4 feet 9 inches in height (145 cm.), of most extraordinary appearance (Fig. 34). Her round face was dusky and cyanosed and there was an abnormal growth of hair, particularly noticeable on the sides of the forehead, upper lip and chin. The mucous membranes were of bright colour despite her history of frequent bleedings. Her abdominous body had the appearance of a full-term pregnancy.The breasts were hypertrophic and pendulous and there were pads of fat over the supra-clavicular and posterior cervical regions. The cyanotic appearance of the skin was particularly apparent over the body and lower extremities (Fig. 35) which were "marbled" and spotted by subcutaneous ecchymoses. Numerous purplish striae were present over the stretched skin of the lower abdomen and also over shoulders, breasts and hips; and a fine hirsuties was present over the back, hips and around the umbilicus. The skin which everywhere was rough and dry showed considerable pigmentation, particularly around the eyelids, groins, pubes and areolae of the breasts. The peculiar tense and painful adiposity affecting face, neck and trunk was in marked contrast to her comparatively spare extremities.

From a neurological aspect nothing was notable other than what at the time were taken to be signs of intracranial pressure: namely, headaches, slight exophthalmos, diplopia, puffiness of the eyelids and congestion of the optic discs (due, as would now appear, to deposition of intraorbital fat). The cranial x-ray showed what for the day was regarded as a normal sella turcica. The epiphyseal lines (radial and phalangeal) were still roentgenologically visible. Not only did the skin bruise easily but spontaneous ecchymoses frequently appeared. Lumbar puncture, pricking of ear, etc., caused subcutaneous extravasations. Blood examination showed 5,300,000 erythrocytes and 12,000 leucocytes (polymorphonuclears 77 per cent), with a haemoglobin of 85 per cent. The systolic blood pressure was consistently high, averaging 185 mm. Hg.

There were no clear therapeutic indications and she was discharged. She reëntered the hospital in *July 1911*, at which time, owing to the assumption that her continued cephalalgia might be due to intracranial pressure, an oldtime subtemporal decompression was performed, a wet brain being disclosed without subsequent protrusion at the site of the bone defect. She also at this time complained so greatly of backache and pain in the left side that an exploration of the kidney and adrenal gland was under contemplation.

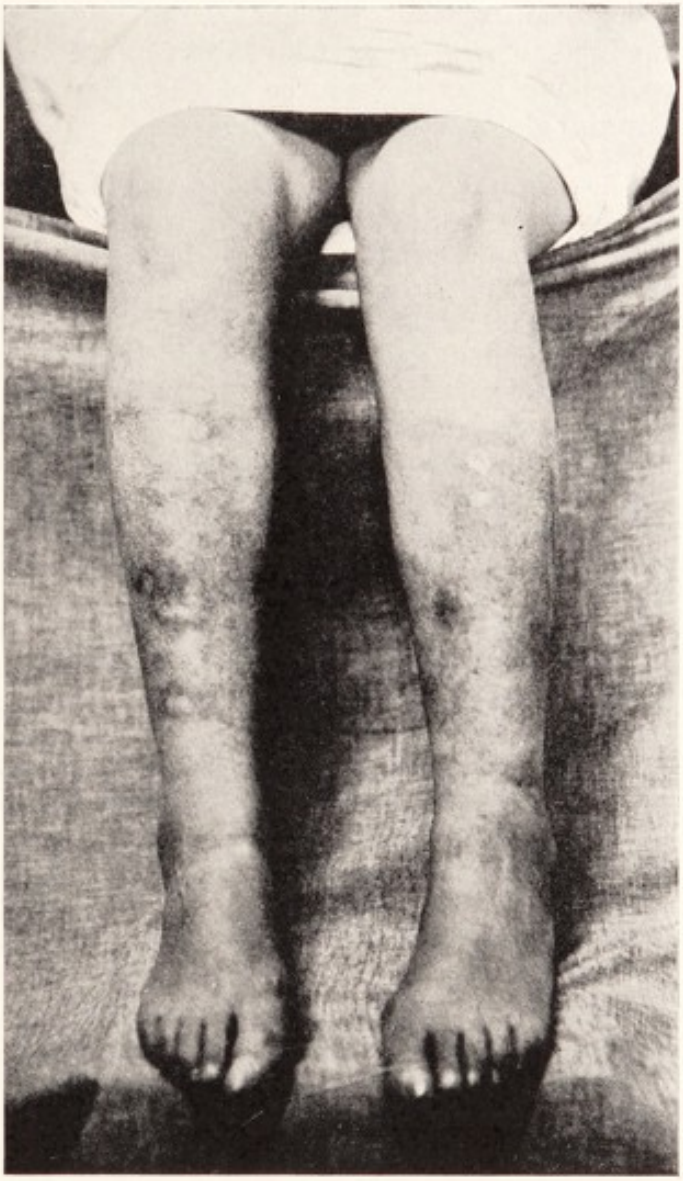


FIG. 35.—Case 1. To show acrocyanosis with scars and ecchymoses of lower limbs.

It was at this stage of the story that the case was first reported. Its most striking feature was the rapidly acquired adiposity of peculiar distribution in an amenorrhoeic young woman. At the time, Dercum's adiposis dolorosa (usually a menopausal disorder) Bartel's and Fröhlich's adiposogenital dystrophy (commonly associated with hypophysial-duct tumors) and the adipositas cerebralis of Aschner and Erdheim (due to hypothalamic lesions) were but vague terms; and the possible relation of

the basophil elements in the anterior pituitary to the reproductive functions was not even suspected.

In commenting on the case at the time, it was pointed out that a somewhat similar polyglandular syndrome had previously been recorded not only in association with pinealomas but with adenomatous or hyperplastic adrenal tumors. A chance remark that we might be on the way toward the recognition of the consequences of hyperadrenalism may possibly have inclined some of those who soon reported similar cases (*cf.* Cases 2, 3, 4), to believe that the source of the trouble in all probability lay in the adrenal gland. To this I shall return.

The case of Minnie G. further: Because of her continued complaints with an increase of weight up to 151 pounds, on Dr. Stetten's recommendation she again came under observation for a period of two months from *May* to *July 1913*, at the Brigham Hospital in Boston.

Her symptoms and general condition at this time were found to be essentially unaltered. Though there was no protrusion at the site of the old decompression, the optic discs were still hyperaemic and congested with hazy margins, while the fields of vision were contracted and the acuity considerably reduced. Her blood-pressure fluctuated around 180/110, on one occasion reaching 210/140. She was still somewhat polycythaemic, the erythrocytes slightly exceeding five million, the highest count having been 5,248,000 with a haemoglobin estimation of 105 per cent. Several differential blood counts were essentially within normal limits.

She was for a time studied by my medical colleague, Dr. Christian. On the basis of a defective excretion of phenolsulphonephthalein and the presence in the urine of a slight trace of albumin with occasional hyaline casts, he felt that a vascular type of nephritis was the probable cause of her hypertension. She was again discharged with no therapeutic recommendations.

On *November 15, 1922*, after an interval of nine years, she was for the second time admitted to the Brigham Hospital. It was then learned that her menses, after complete cessation for ten years, had late in 1913 again become irregularly reëstablished; also that in 1917 she had had an exploratory operation for a stone in the left kidney, but she was uncertain whether a calculus had actually been found.

The blood-pressure at this time averaged in the neighbourhood of 160/95; the blood-count showed 5,240,000 erythrocytes; the basal metabolism was minus nine. Her general appearance was much as before, though she had lost some weight. The cranial roentgenograms taken at this time show [as subsequently reread] an unmistakable diffuse decalcification of the bones of the vault. Renal pyelograms were made, no trace of stone or other renal abnormality being disclosed. There was no evidence of advancing nephritis and on the whole she seemed at least no worse than in 1913. She accordingly was discharged once more without further light having been thrown on the nature of her disorder.

[ADDENDUM] The patient came under observation again on *February 8, 1932*. She was in reasonably good health and had lost many of the former stigmata of her malady. The former acuteness of her malady was unquestionably in abeyance. Her weight was only 52.4 kg. (105 pounds). The metabolism was +4 and showed a pronounced rise on a specific dynamic test. Her red cells were counted at 5,190,000 and her haemoglobin was 111 per cent (Sahli). The non-protein nitrogen and cholesterol and blood were in normal limits. Differential white

count showed only 61 per cent polymorphonuclears. Her former plethora was gone and the striae in the skin were now pale instead of purplish. She no longer had any tendency to bruise. Her blood-pressure was normal. The urine showed the slightest trace of albumen but the phthalein test indicated normal elimination.

Her kyphosis had distinctly increased but the x-ray films of the spine showed no collapse of the bodies such as had been expected. The bones of the cranial vault showed a peculiar mottled porosity suggesting osteomalacia (*cf.* also Case 15, pg. 168). The aorta was markedly tortuous and multiple calcified plaques were present in the arch. There were irregularities in the ribs of the left side suggesting old fractures of which there was no clinical history.

In the intervening years six other examples of the same or a highly similar disorder have been carefully studied at the Brigham Hospital. The patients were all comparatively young women who, in association with a more or less abrupt amenorrhoea, had become rapidly obese with a peculiar tense and more or less painful adiposity chiefly affecting head, neck and trunk. They were all plethoric in appearance, all had become abnormally hirsute, all but one showed purplish cutaneous striae. Vascular hypertension with a high erythrocyte count and haemoglobin percentage was usually present; and all complained of aches and pains and general enfeeblement. In some of the patients the acuteness of the condition appeared to subside, and only one, so far as known, succumbed to her malady.

Meanwhile, soon after the case of Minnie G. had been reported in 1912, descriptions of polyglandular syndromes closely resembling hers began to appear in the literature; and in a few instances, owing to the fatal outcome of the disorder, a systematic study of the organs was made possible. Such of these cases as have come to my attention may be given in the chronological order in which they appeared in print. The first of them was recorded in 1913 by Dr. H. G. Turney of London.[16]

Case 2. [Dr. Turney's patient.] **Amenorrhoea. Acute plethoric obesity with hypertrichosis. Spinal kyphosis from skeletal decalcification. Vascular hypertension. Polycythaemia. Duration 7 years. Autopsy.**

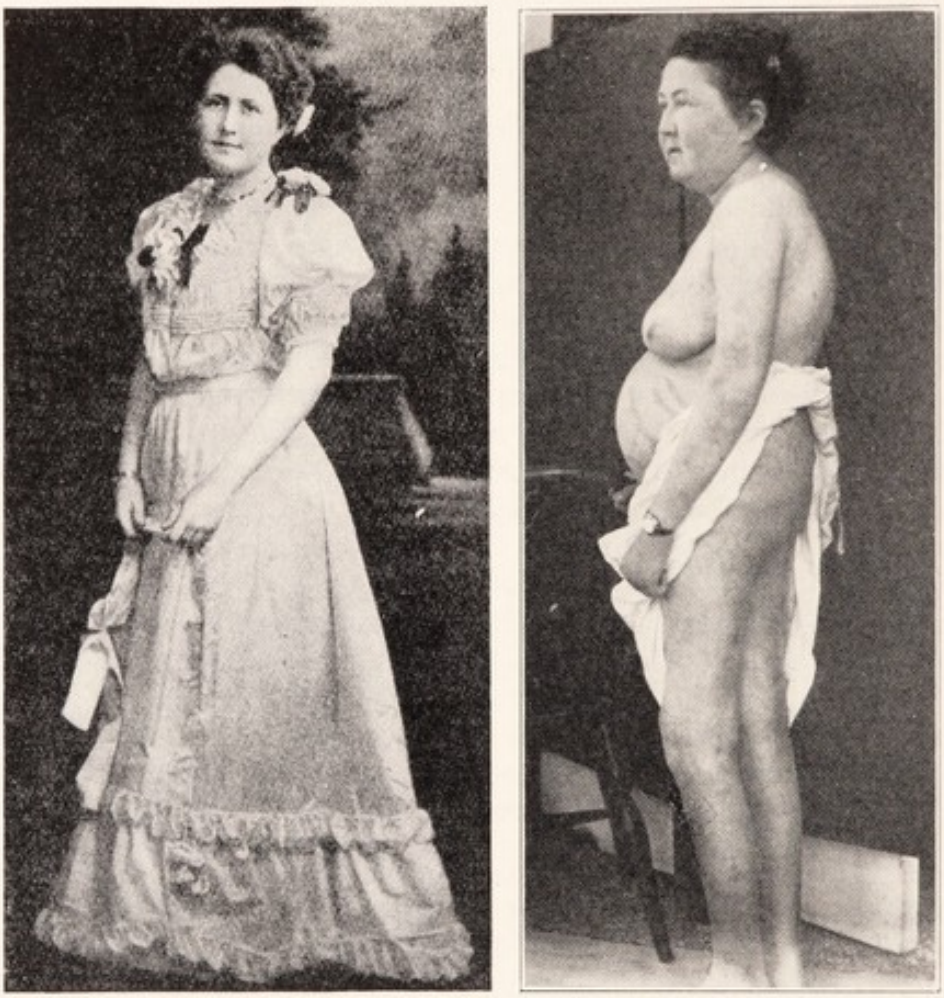
Miss A. O., a previously healthy and normal young woman, in 1907 when 20 years of age, suddenly ceased menstruating and began to grow obese. Three years later, she observed a tendency for her extremities to bruise easily. She gradually became increasingly round-shouldered (kyphotic) thereby losing two and a half inches (6.4 cm.) in height. Her chief complaints were of pain in the back.

The face was extremely fat and florid and the texture firm. The hair of the head was dry and somewhat scanty, as was the pubic and axillary hair, but there was a growth of fine short hair over the back and upper legs. Notable were the large pendulous mammae and the great obesity of the abdomen, which had the contour of a full-term pregnancy (*cf.* Figs. 36, 37).

The obesity of the trunk was in marked contrast to the somewhat thin ex-

[16] Turney, H. G., "Discussion on disease of the pituitary body," *Proc. Roy. Soc. Med.* (Sec. Neurol. and Ophth.), 1913, VI, lxix–lxxviii.

tremities which below the knee were of a dark brownish colour, interspersed with recent ecchymoses. The skin had a parchment-like texture. Numerous broad, red, atrophic striae were present over the abdomen and thorax. An apparent partial absorption of the posterior clinoid processes was shown by cranial roentgenograms. A glistening subretinal exudate was present in the right eye, probably from an absorbed haemorrhage. The systolic blood-pressure was high, varying between 200 and 185 mm. Hg. There had been a tendency to polycythaemia, the erythrocytes on one occasion having been counted at eight million and



FIGS. 36 and 37.—Dr. Turney's patient at the age of 20 and five years later (1913) at the height of the disorder.

on another at six million. The urine contained no albumin. Carbohydrate tolerance was normal.

Subsequent history.—This was briefly given in a later article by Dr. Parkes Weber.[17] Several spontaneous fractures occurred from time to time, involving sternum, clavicle, and ribs. Multiple ulcers and subcutaneous abscesses developed, and in *May 1914*, seven years from the symptomatic onset of the disorder, death ended the story.

Autopsy.—The body was that of an hirsute woman with "abundant hair on the chin" and multiple subcutaneous abscesses and ulcers. There was found a

[17] *Cf. infra., Brit. J. Dermat.*, 1926.

chronic nephritis, an hypertrophic ventricle of the left heart, a fatty infiltrated liver, and *an enlarged left suprarenal gland* of "bulky cortex." The ovaries were small. The bones showed calcareous deficiency ("fibrous osteitis") and were so soft they could be easily cut with scissors. "Nothing abnormal was found in the *pituitary and thyroid glands*." [How thorough an examination of the former was made is not stated.]

Dr. Turney writes me that at the time of his report, while the patient was still living, he favoured an ovarian origin for the symptoms, basing this opinion on the amenorrhoea and the fragility of the bones. Dr. Parkes Weber, on the other hand, in his subsequent discussion of the case appears to have regarded the syndrome as unquestionably due to a primary adrenal disorder which the autopsy supposedly substantiated.

The next example of which I have knowledge was reported two years later (1915) by Dr. John Anderson of Glasgow.[18]

Case 3. [Dr. Anderson's patient.] **Amenorrhoea. Plethoric obesity. Hypertrichosis. Vascular hypertension. Asthenia. Duration 5 years. Autopsy: osteomalacia; adenoma of anterior pituitary and of adrenal cortex.**

A woman, at the age of 23, in association with a menstrual irregularity which in two years was followed by total amenorrhoea, became increasingly obese, the adiposity sparing the limbs. The adipose areas were tender on palpation. She suffered much from headaches, pains in the chest and eyeballs, the eyes having become somewhat exophthalmic. She acquired a reddish complexion with facial hirsuties. She developed a tendency to petechial haemorrhages and purpuric outbreaks on her arms and legs, the slightest contusion provoking ecchymoses. The systolic blood-pressure was 185 mm.; the red blood count approximated five million. Muscular weakness became extreme, and she finally died from increasing asthenia. The whole course of the malady was something over five years.

At the post-mortem examination, arteriosclerosis with "chronic interstitial nephritis" was found. The ribs were brittle and easily fractured. The *ovaries* and uterus were senile in character; the *thyroid* was slightly enlarged; the *parathyroids* were normal; the *thymus* atrophic. In the medulla of one of the *suprarenal glands* which were "slightly enlarged" was a small pea-sized tumor, microscopically resembling the structure of the zona fasciculata. The *anterior pituitary* contained a small adenoma [type unrecorded] the size of a millet-seed close to the pars intermedia. In the rest of the anterior lobe "the basophil cells were apparently increased at the expense of the eosinophil cells." [*Cf.* addendum pg. 161 and Figs. 64, 65, 66.]

In his discussion of this case, Dr. Anderson expressed the belief that it was primarily a pituitary disorder, his interpretation being that it was an example of hypopituitarism (*sic*) with secondary hyperfunctioning of the suprarenal glands (hyperadrenalism) accounting for the development of the secondary male sexual characteristics. Needless to say, it was not well known at the time that true hypopituitary states are associated with atrophy rather than hyperplasia of the adrenal cortex, a similar dystrophy likewise affecting the thyroid and reproductive organs.

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[18] Anderson, J., "A case of polyglandular syndrome with adrenal hypernephroma and adenoma in the pituitary gland—both of small size," *Glasgow M. J.*, 1915, LXXXIII, 178–192.

In 1919, another example of a syndrome which appears to be related to the disorder under discussion was reported by Dr. Reichmann[19] from the Medical Clinic of Jena. Apart from a swollen and plethoric face, the patient was not adipose but on the contrary was rather emaciated. She showed vascular hypertension with negative urine. There was bowing of the back and she had lost several centimetres in height. Because of the prominence of the eyes and fullness of the lids she was supposed to have Basedow's disease. This was excluded as was also cardio-renal hypertension; and under the belief that the condition was ascribable to a sympathico-adrenal disorder the left adrenal gland was surgically removed with a fatality a few days later from a generalized peritonitis. The autopsy showed a cardiac hypertrophy, hyperplastic arteriosclerosis and skeletal osteoporosis with spinal curvature, the bones being easily cut with a knife. The pituitary body, while macroscopically normal, was found on section to contain within a compressed mantle chiefly composed of basophil elements a tumor "resembling a small-celled sarcoma." This was found to be an adenoma composed of chromophobe cells some of which contained eosinophil (*sic*) granules. The thyroid was small; the remaining adrenal was hyperplastic; the ovaries fibrotic.

In his discussion of the case, the author, if correctly understood, was inclined to regard it as a form of acromegaly, the hyperpituitary changes being confined to the thickened and cyanotic face: the other symptoms were ascribed to a secondary adrenal origin.[20]

Chronologically the next fairly unmistakable case of which I have knowledge was described in Professor Zondek's monograph (1923) on the ductless glands[21] among other examples of so-called pluriglandular insufficiency.

Case 4. [Dr. Zondek's patient.] **Amenorrhoea. Acute adiposity. Facial hirsuties. Spinal kyphosis. Glycosuria. Duration 5 years. Autopsy: Skeletal osteoporosis; pituitary tumor (adenoma?).**

This concerned a 24-year-old Russian woman who had previously been normal in all respects and in good health. At the age of 19, amenorrhoea set in and she began rapidly to grow adipose, accumulations of fat being limited to the head and trunk, while the extremities remained thin (Figs. 38, 39). She began to lose the hair of her head, whereas on the cheeks and upper lip a somewhat definite beard began to appear; and as time passed she became increasingly round-shouldered.

Glycosuria was found and the urine at one time showed as much as 3 per cent of sugar. The skin became pigmented, suggesting an adrenal disorder. The

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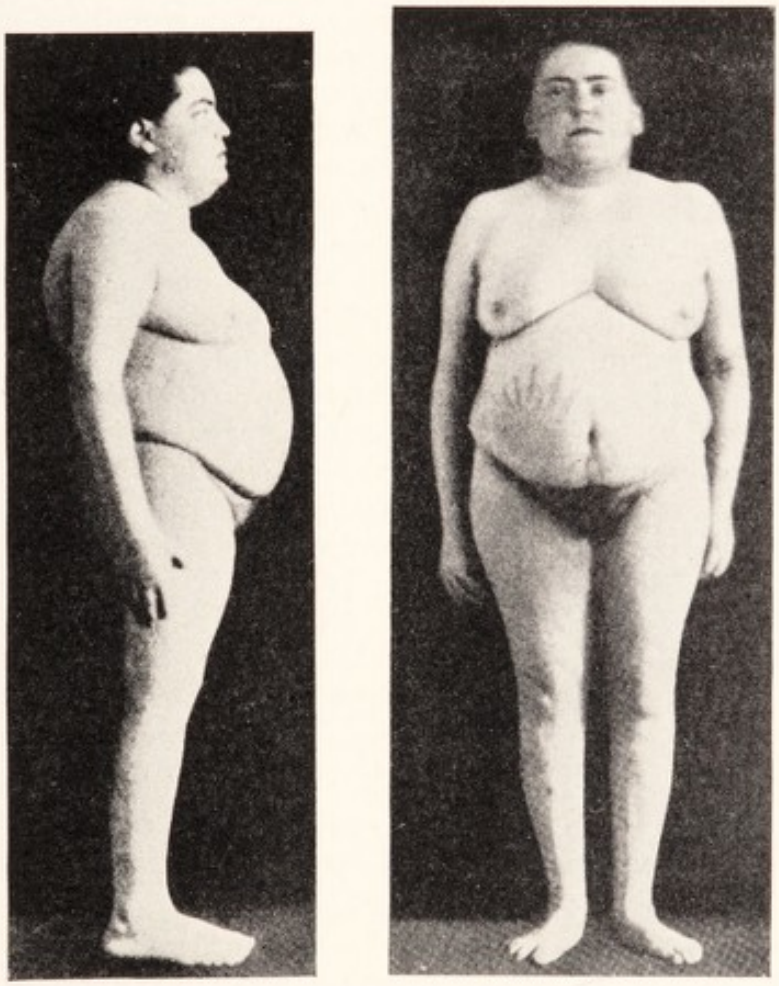
[19] Reichmann, V., "Über ein ungewöhnliches Krankheitsbild bei Hypophysenadenom," *Deutsch. Arch. f. klin. Med.*, 1919, CXXX, 133–150.

[20] It may be assumed from the post-mortem findings that this was a typical example of pituitary basophilism. The case has not been counted because of the absence of adiposity of the trunk which is so marked a feature of all the others. It suggests that the disorder may not necessarily be accompanied by abdominous obesity.

[21] Zondek, H., "Die Krankheiten der endokrinen Drüsen." Berlin: Julius Springer, 1923. 287 pp.

cutaneous dryness from lack of normal secretion strongly suggested myxoedema. Hence there were polyglandular disturbances which appeared to affect the function of the adrenals, thyroid, ovary and pancreas. She finally died of an intercurrent erysipelas.

Autopsy.—A marked osteoporosis of the skeleton was found, it being easily possible to cut the vertebral bodies with a knife, the spongy part of the bone having largely disappeared. There was follicular atresia of the *ovaries*, marked lipomatosis of the *pancreas*, an increase of colloid in the abnormally small *thyroid*, hypoplasia of the *thymus*, and capillary dilatation of the *parathyroid*



FIGS. 38 and 39.—Photographs of Dr. Zondek's case of "pituitary tumor with osteomalacia" (1923).

glandules. [The adrenal glands are not mentioned and presumably would have been had they shown any change.]

The *pituitary body* showed no apparent abnormality until examined microscopically when it was found: "that the anterior lobe was enormously reduced and diminished mesially to a narrow ledge. As contrasted with this finding, the intermediary layer, as well as the posterior lobe, was rather more than normally developed. Between the gliomatous fibres of the posterior lobe, there were enlargements of the intermediary spaces, the exact nature of which, whether hydropical enlargements or myxomatous degenerations, could not be determined. In the vicinity of the diminished anterior lobe a tremendously developed fibrous

tissue was encountered, into which the glandular elements of the anterior lobe gradually passed over. As to the kind of destroying process, involving particularly the anterior lobe, no definite decision was possible, this being the more difficult as *there were nests of an adenomatous-like structure enclosed in the masses of fibrous tissue.* The identity of these cells with the anterior-pituitary cells could not with certainty be determined, but Professor Benda, who saw the specimens, favoured more the diagnosis of a tumor arising from the hypophysial duct."

This briefly reported case, in which some clinical details are unfortunately lacking, was, properly enough, regarded as one of pluriglandular nature, the most significant post-mortem finding seemingly having been the lesion of somewhat obscure nature in the anterior pituitary. The adrenal glands at least we may assume to have shown no abnormality. Attention may be drawn to the fact that, as in the two preceding cases, the bones were described as being markedly softened and fragile, so much so indeed, that in his discussion of osteomalacia Zondek refers to this case (*loc. cit.*, pg. 235) as illustrating one type of the disease.

In the following year (1924) Drs. B. S. Oppenheimer and A. M. Fishberg of New York published a paper[22] in which the association of non-nephritic hypertension with suprarenal tumors was under discussion. Two illustrative cases were given. The first of them was that of a man said to have had an acromegalic appearance who was found after death to have had a tumor of the suprarenal cortex associated with cardiac hypertrophy. It is merely stated that the head and neck organs were negative, no specific mention being made of an histological examination of the pituitary body. It need scarcely be said that adenomas of the adrenal and cardiac hypertrophy are common in acromegaly. However, I wish rather to call attention to the authors' second case which bears a close resemblance to those under discussion. The essentials of the clinical history are as follows:

Case 5. [Patient of Drs. Oppenheimer and Fishberg.] **Plethoric obesity. Facial hirsuties. Cardiac hypertrophy. Vascular hypertension. Glycosuria. Cutaneous pigmentation and abscesses. Duration 5 years. Death without autopsy.**

S. G., an undersized child, 12 years of age, was admitted to the Montefiore Hospital complaining of weakness and adiposity. In her sixth year she suddenly began to put on flesh and became disproportionately adipose, gaining about 75 pounds (34 kg.). She was seen by many physicians and treated symptomatically with various glandular preparations. About a year prior to her admission the parents noticed a change in colouration of the skin and the patient developed a tendency to fall asleep. A routine urine examination revealed 4 per cent of sugar. Polyuria and nycturia were present at this time. At the age of 11, hair began to grow on the face, axilla and pubis. The patient had never menstruated.

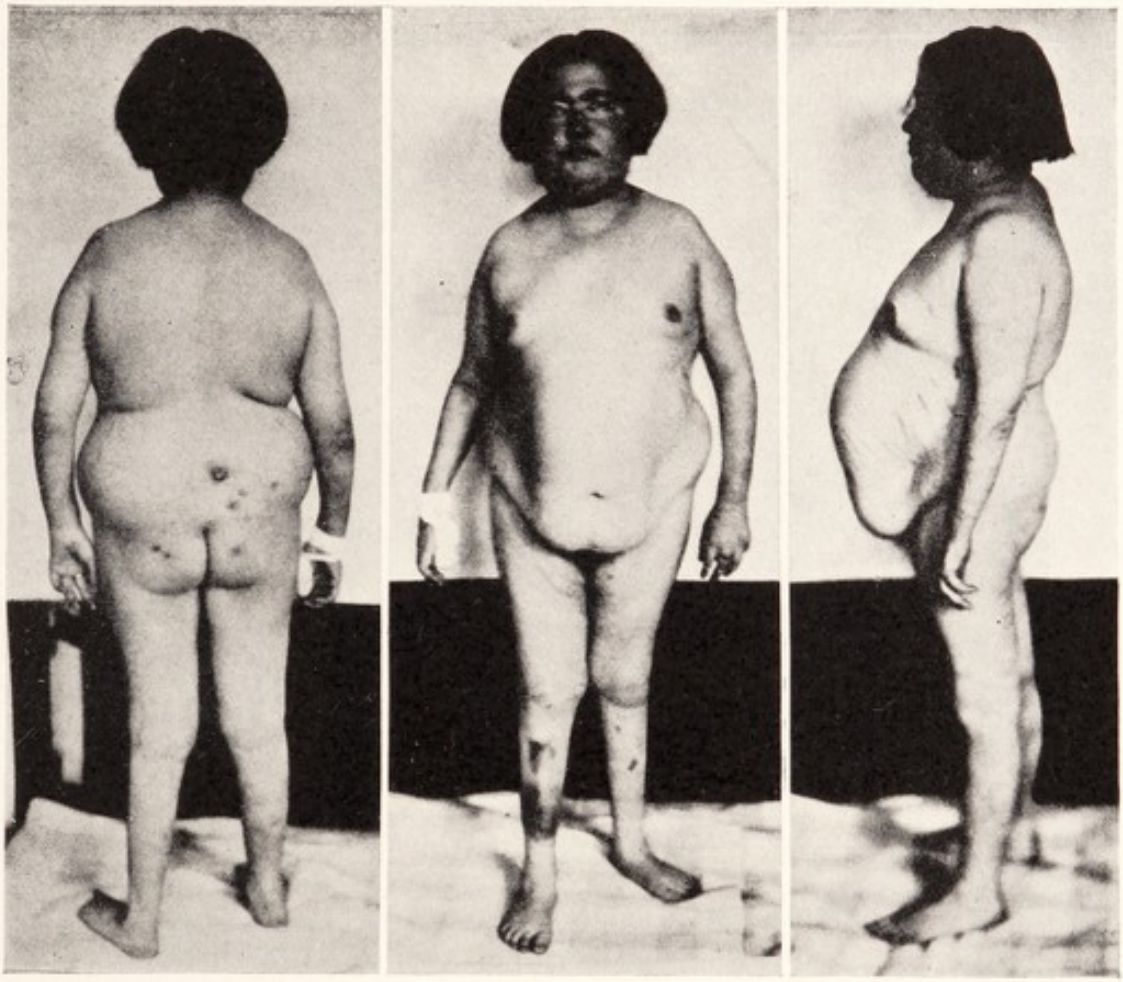
Physical examination.—An undersized child, appearing many years older than her actual age (Figs. 40–42). She was exceedingly obese and had a very red, plethoric facies. There was a well-marked growth of hair on the chin and lower cheeks; pubic and axillary hair was abundant. The skin was dry and on

[22] Oppenheimer, B. S., and A. M. Fishberg, "The association of hypertension with suprarenal tumors," *Arch. Int. Med.*, 1924, XXXIV, 631–644.

the abdomen were pigmented striae. There were abscesses on the back and neck, a mycotic infection of the nails, and ulcers on the legs. There was no oedema whatever.

The heart was enlarged to the left. The sounds were of good quality, the second sound being accentuated over the aortic area. There were no murmurs. The blood pressure was 190 systolic, 130 diastolic.

The urine contained sugar but no acetone bodies. There was a heavy cloud of albumin but neither casts nor cellular elements were found. Phenolsulphone-



FIGS. 40–42.—Drs. Oppenheimer and Fishberg's patient with "adrenal hypertension" (1924).

phthalein elimination, 45 per cent (after intravenous injection). The basal metabolic rate was normal. The blood showed 260 mg. of sugar per hundred cubic centimeters; erythrocytes, 4,500,000; white cells 11,800 with 78 per cent polymorphonuclears; haemoglobin, 90 per cent (Sahli). Roentgenologically the sella turcica was slightly larger than normal and showed bone absorption in the neighborhood.

The patient was placed on an anti-diabetic diet and digitalized. The urine rapidly became normal; the sugar and albumin disappeared completely. At one time signs and symptoms of broncho-pneumonia appeared but cleared up. The abscesses of the neck and back finally healed. At this juncture, the parents insisted on removing her from the hospital and she died three weeks later. Though

no post-mortem examination was obtained, the clinical picture, in the author's words, "was so characteristic of suprarenal hyperplasia as to leave little doubt of the diagnosis."

It can be seen that the syndrome presented by this patient, though it was of preadolescent onset, bore a close resemblance to that of the others so far presented: *viz.*, a rapidly acquired adiposity sparing the extremities, a plethoric facies with pigmented abdominal striae, an exaggeration of the secondary sexual characters accompanied by a growth of hair on cheeks and chin, vascular hypertension, and glycosuria. Her precocious

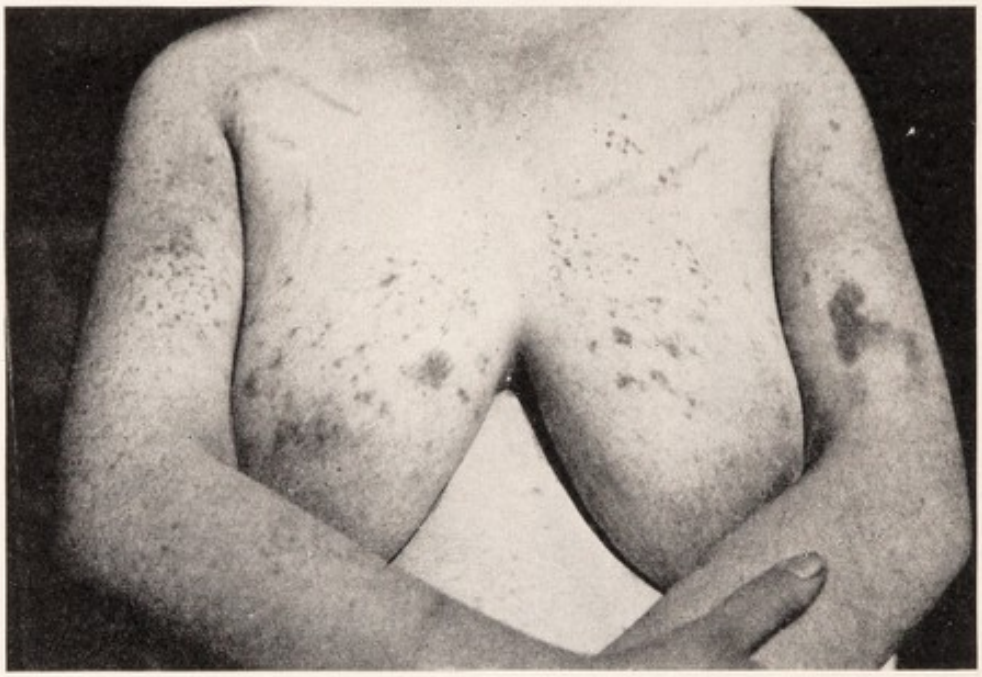


FIG. 43.—Case 6. Dr. Parkes Weber's patient (1926) showing cutaneous hemorrhages and striae ascribed to adrenal hyperplasia.

secondary sex-characters were unaccompanied by any signs of menstruation.

The close resemblance to the original case of Minnie G. shown by these last four patients, in their symptomatic history, in their physical appearance, and in their clinical findings, is unmistakable. They are examples unquestionably of a very similar polyglandular disorder the interpretation of which to this point remains highly obscure in spite of the three post-mortem examinations. A tendency to chronic nephritis with cardiac hypertrophy probably secondary to the hypertension was noted in Cases 2, 3 and 5. A peculiar softening of the bones was mentioned in all three autopsied cases. The adrenal glands showed a unilateral enlargement in Case 2, a pea-sized adenoma in Case 3, and are not mentioned in Case 4. The pituitary body was said to be normal in Case 2, to show a minute adenoma (type undesignated) in Case 3, and an "adenomatous-like structure" of undetermined nature in Case 4.

We now come to a particularly well recorded example of the disorder, published in 1926, from which something more definite can be learned. I have taken the liberty of quoting fully from the author's vivid description[23] of the case.

Case 6. [Dr. Parkes Weber's case.] **Plethoric obesity. Amenorrhoea. Purpuric ecchymoses and cutaneous striae. Facial hirsuties. Exophthalmos. Vascular hypertension. Duration 4 years. Autopsy: cardiac hypertrophy; nephritis; pituitary adenoma (basophil).**

The patient, Mrs. E. B., aged 28 years, an Englishwoman, suffers from a 'coarse' plethoric-looking type of obesity, chronic purpura (Fig. 43), and large 'striae cutis distensae' ('striae atrophicae') of the trunk and limbs. The purpura recurs from time to time in the form of 'crops' of cutaneous petechiae and ecchymoses. Constriction of the veins of the arm at once produces ecchymoses. The 'striae' are of different dates and vary correspondingly in colour the newer ones being purplish, the older ones paler. The face is coarsely hyperaemic. The obesity is shown chiefly in the trunk, by the large fatty pendulous breasts and the corpulent projecting abdomen (Fig. 44).

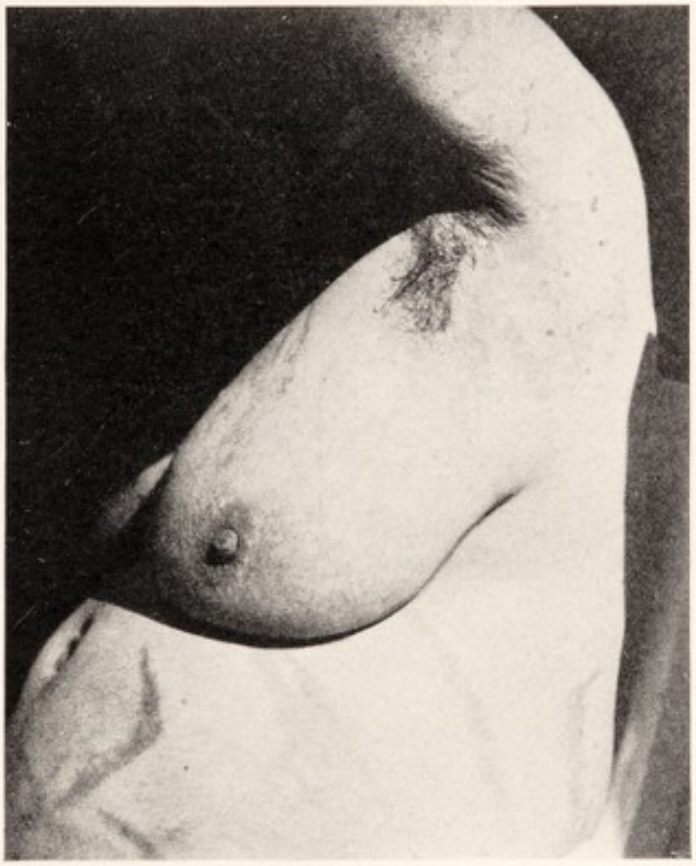


FIG. 44.—Case 6. Left side of patient's trunk showing adiposity and purple striae of abdomen and mamma.

The limbs are not specially large, and the legs below the knees are relatively thin and have a striking appearance. They show transverse 'striae' (as the thighs do), and besides petechiae and ecchymoses there is a peculiar brownish discoloration, especially over the anterior surface, resulting probably from previous multiple haemorrhages. Moreover, a good deal of the skin in front of both legs has become shiny or parchment-like owing to some atrophic change. In spite of the obese appearance of her trunk, her body-weight is actually only 54 kg. [119 pounds], her height being 159 cm. [5 ft. 3 in.].

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[23] Parkes Weber, F., "Cutaneous striae, purpura, high blood-pressure, amenorrhoea and obesity, of the type sometimes connected with cortical tumours of the adrenal glands, occurring in the absence of any such tumour—with some remarks on the morphogenetic and hormonic effects of true hypernephromata of the adrenal cortex," *Brit. J. Dermat.*, 1926, XXXVIII, 1–19.

The blood-pressure is high, the brachial systolic blood-pressure ranging from 205 to 230 mm. Hg. The urine contains a little albumin, but is practically free from tube-casts. The administration of 100 gm. of sugar causes the appearance of a little sugar in the urine. The blood-sugar, when fasting, is within normal limits, but the curve after the administration of sugar by the mouth reaches its maximum height only after two hours. The blood-count shows nothing special, excepting a moderate polymorphonuclear leucocytosis, possibly connected with pyorrhoea alveolaris; the thrombocytes are 180,000 to the c.mm. of blood. Ophthalmoscopic examination (Dr. C. Markus, *June 5, 1925*): In both eyes there is optic neuritis with white foci surrounding the optic discs; no haemorrhages; no macular changes. No tumor can be felt by abdominal palpation and no enlargement of the spleen or liver can be made out; by vaginal examination the uterus is like that of a nulli-para; there is no sign of any intra-thoracic disease. By roentgen-ray examination the *dorsum sellae turcicae* gives only an extremely faint shadow, but the pituitary fossa appears of normal size. There is slight bilateral exophthalmos. The basal metabolic rate is 20 per cent above the normal. . . . There is slight hairiness of the chin and upper lip. The Wassermann reaction is negative. . . .

The *history* is that the patient was a twin, her fellow-twin being born dead. Her father and mother are both living, aged 56 and 49 respectively, and the blood-pressure of each of them is high. They have had eleven children, of whom only four are living. . . . She was married in *December 1922*, and has never been pregnant. Her menstrual periods ceased suddenly about *September 1921*, but she had three slight periods again after her marriage. Since then (*March 1923*) there has been complete amenorrhoea. About *March 1922*, she already began to get fatter, especially in the face and abdomen. But it is only since about *March 1923, with the onset of permanent amenorrhoea*, that her chief symptoms have gradually developed: headaches, pains in her whole body, attacks of dyspnoea (accompanied by a sensation of suffocation), feelings of sickness (for which she sometimes induces vomiting by putting her finger in her mouth), frequent slight epistaxis, the 'coarse' type of obesity already mentioned, the cutaneous 'striae,' the purpura, the slight exophthalmos.

The patient died on *July 4, 1925*, in an attack clinically resembling acute pulmonary oedema. She had had a similar attack previously in the hospital, relieved apparently by blood-letting.

Autopsy.—There was no tumor in either *adrenal gland*, but the medullary substance was apparently rather in excess. The left ventricle of the heart was hypertrophied. There was slight chronic interstitial nephritis (slight renal sclerosis). In the anterior lobe of the *pituitary gland* was a minute adenoma consisting of basophil cells. There was no evidence of disease in the *thyroid gland* or in the *ovaries;* the latter were said to have been rather small but histologically normal.

Microscopical examination.—The *pituitary gland:* Its three parts can be easily distinguished. In the anterior part is a rounded nodule ($3 \times 4\frac{1}{2}$ mm. in the hardened sections) of basophil cells, in alveolar arrangement (with some minute calcareous spots), contained in a thin connective-tissue capsule; it is evidently a basophil adenoma. The remainder of the anterior part and the middle and posterior parts of the pituitary gland are of normal appearance. In the anterior lobe-spur of the pedicle of the pituitary gland there are many relatively large epithelial islands (Erdheim) [*cf.* Case 4]. This is remarkable, but must not be considered pathological. No special immigration of cells from the middle lobe into the posterior lobe can be made out.

Dr. Weber states in conclusion: "In my opinion it belongs to a group of cases characterized by complete amenorrhoea and by symptoms [given in the title of his paper] sometimes connected with cortical adrenal tumors, occurring in the absence of any such tumor. The main features cannot be explained by the small adenoma of the pituitary gland found at the post-mortem examination."

In search of further information regarding this important case, Dr.

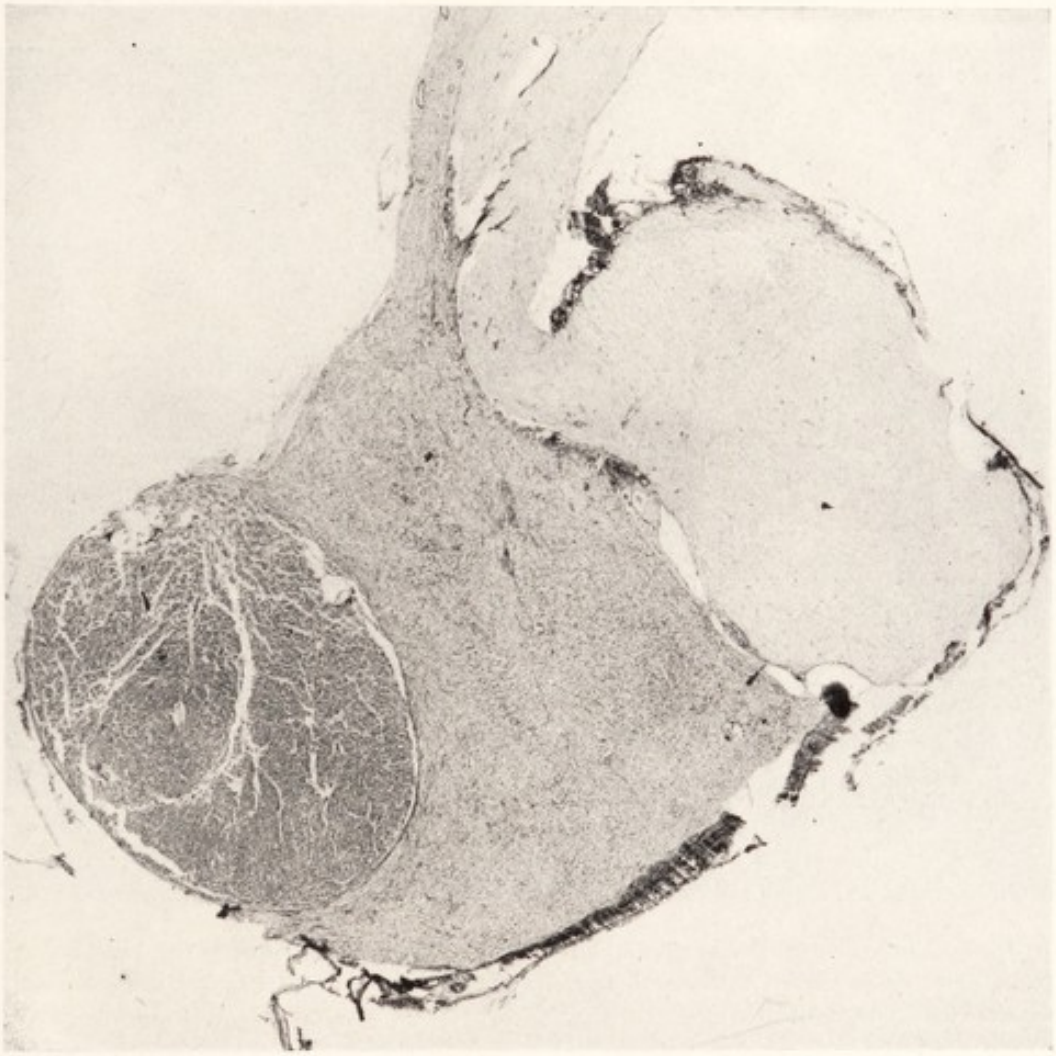

FIG. 45.—Case 6. The anterior basophil adenoma (aniline blue-fuchsin, ×10). Kindness of Professor H. M. Turnbull.

Weber was written to and he obligingly forwarded the original paraffin block from which further sections of the tumor have been made. He also referred me to Professor Herbert M. Turnbull of the London Hospital who first recognized the nature of the lesion as a basophil adenoma and who kindly sent me the accompanying photographs (Figs. 45, 46) from the single section in his possession.

Much has been learned since 1926 concerning the influence of the pituitary body on the development and regulation of the genital sys-

tem,[24] and Dr. Weber would have been more likely to-day than at that time to suspect the probable influence on his patient's syndrome of a pituitary adenoma which was then so easily explained away in favour of an adrenal influence even in the absence of any definite microscopical abnormality in these latter glands.

It was at about this time that it had become possible by crude chemical methods to separate the growth and sex hormones from bovine hypophyses and though Dott and Bailey in a study of the pituitary adenomas

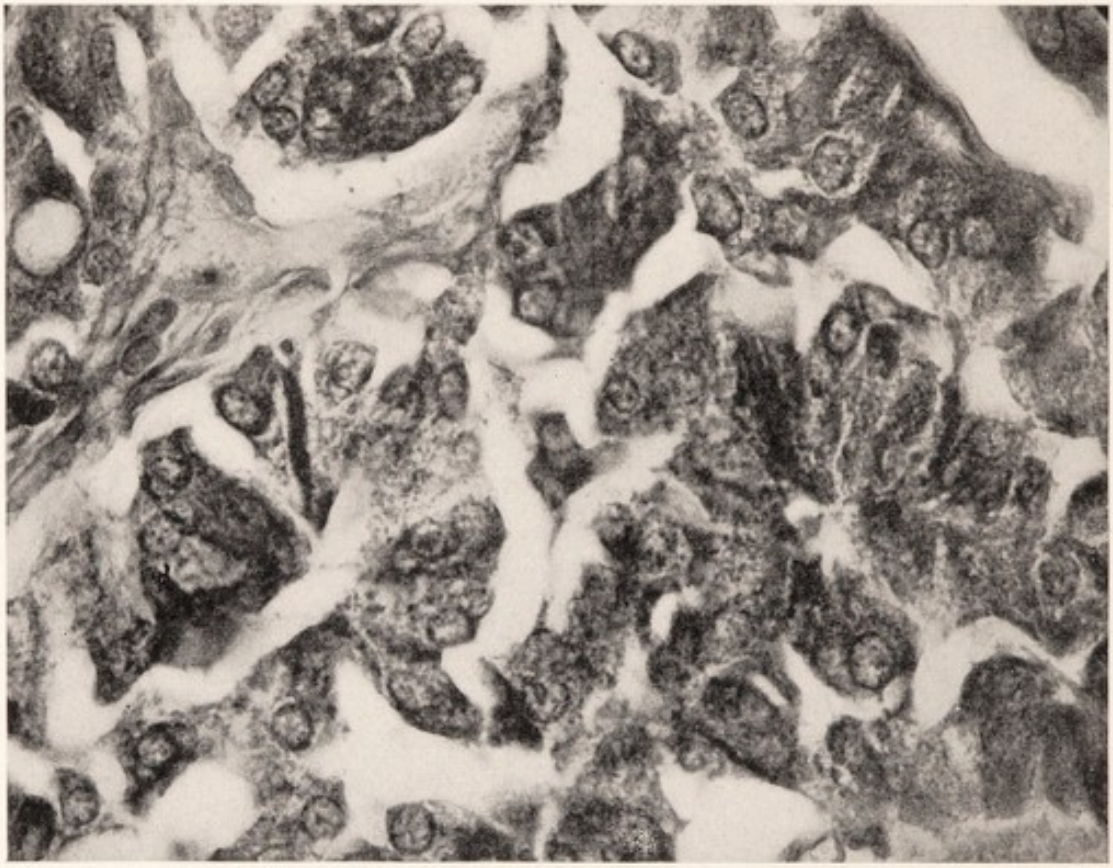

FIG. 46.—Case 6. From the centre of the basophil adenoma to show the blue basophil granules in the often multinuclear cells (aniline blue-fuchsin, ×1020). Kindness of Professor Turnbull.

in the Brigham collection had stated in 1925[25] that basophil adenomas occur only in the form of minute intra-glandular nodules that give rise to no known clinical manifestations, some of us soon began to suspect that this was probably a matter of not knowing what to look for.

This at least was the conclusion arrived at as the result of a survey of the then known facts regarding the dual anterior pituitary hormones which, chiefly for our own information, my junior co-worker, Dr. Harold

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[24] *Cf.* Smith, P. E., and E. T. Engle, *Am. J. Anat.*, 1927, XL, 159–217. *Also:* Zondek, B., and S. Aschheim, *Klin. Wchnschr.*, 1927, VI, 248–252.

[25] Dott, N. M., and P. Bailey, "Hypophysial adenomata," *Brit. J. Surg.*, 1925, XIII, 314–366.

Teel, and I shortly afterward came to put together.[26] The prepared mind was what enabled Dr. Teel during his house-officership at the Lakeside Hospital in Cleveland for the first time to predict the presence of a basophil adenoma which, as will be told, was confirmed at autopsy.[27] The case history, which unfortunately is lacking in many details, may be briefly summarized as follows:

Case 7. [Dr. Teel's patient.] **Obesity. Hypertrichosis. Menstrual irregularity. Meningitis. Autopsy: basophil adenoma.**

An exceedingly obese and abundantly hirsute young woman, 20 years of age,

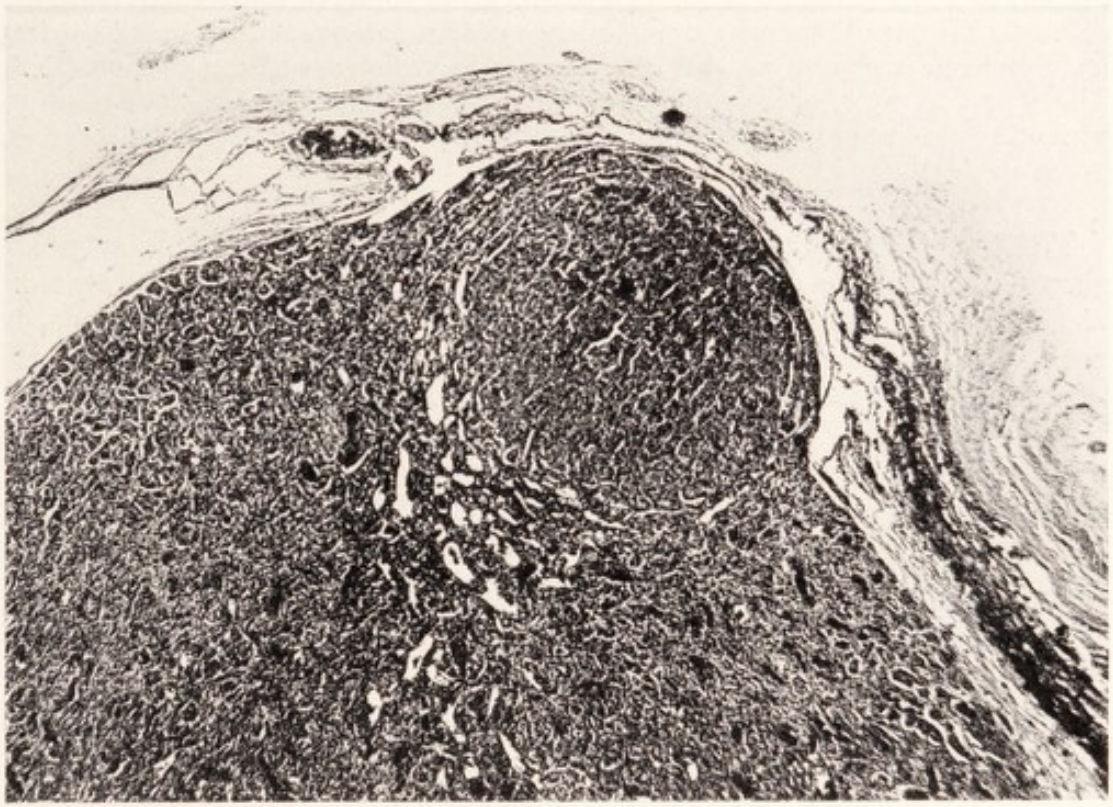

FIG. 47.—The basophil adenoma clinically predicted in Dr. Teel's case (1931).

admitted to hospital in a comatose condition due to a meningococcal meningitis, was under clinical observation for only three days before she died.

Owing to her physical condition, a personal history was not obtainable, but it was learned that at the age of nine she had a continuous menstrual flow lasting four months. Subsequently, at the age of 14, she was said to have attained a normal adolescence, but her periods were subsequently most irregular. From the age of 15 she had grown exceedingly stout, the maximum weight of 206 pounds (93.4 kg.) having been recorded seven months before her hospital admission. Because of excessive fatiguability she had consulted a physician at about that

[26] Teel, H. M., and H. Cushing, "The separate growth-promoting and gonad-stimulating hormones of the anterior hypophysis: an historical review," *Endokrinologie* (Leipzig), 1930, VI, 401–420.

[27] Teel, H. M., "Basophilic adenoma of the hypophysis with associated pluriglandular syndrome," *Arch. Neurol. and Psychiat.*, 1931, XXVI, 593–599.

time, and when he found she had a basal metabolic rate of +33, her enlarged thyroid was roentgenologically radiated. This was said to have caused little or no symptomatic improvement.

At *autopsy*, a suppurative meningococcic leptomeningitis was found to be the obvious cause of death. The *pituitary body* appeared to be of normal size, but suspecting from the patient's general appearance what might be found, Dr. Teel had the gland serially sectioned and a small but unmistakable basophil adenoma measuring 2.5 mm. in diameter was disclosed (Fig. 47). There was a persistent *thymus*, a slight enlargement of the *thyroid*, questionable enlargement of the pancreatic islets, and a definite enlargement (20 gm.) of the *suprarenals* with no histological change of structure, no definite secondary adenomas being present in any of these organs. The *ovaries* were enlarged apparently from increase in stroma; there was a single large corpus luteum with a small central haemorrhagic area and several smaller ones in various stages of organization. The only true neoplastic growth was the small anterior-pituitary adenoma to which the other endocrine changes were regarded as purely secondary.

THE SYNDROME AS IT OCCURS IN THE MALE

To this point, examples have been presented of this peculiar polyglandular syndrome as it occurs in women who seem to be more commonly victimized than do men. Why this should be so, if it is actually so, is not fully apparent. It is perhaps reasonable to assume that the combination of amenorrhoea, adiposity and heterosexual hirsuties may excite the attention of physicians and be recorded as a freakish disorder more often than would corresponding maladies in men.

However this may be, five cases of the same or a comparable disturbance, three of them with and two without autopsy, can be cited in the male. The first case, unfortunately without photographs of the patient, was briefly reported after careful study by Dr. E. D. Friedman of New York.[28] The essentials only need here be given.

Case 8. [Dr. Friedman's case.] **Obesity. Hypertrichosis. Vascular hypertension. Glycosuria.**

E. C., a student, 19 years of age, complained of obesity, hypertension and recurrent pains in the region of the spine for six months.

He was an undersized young man who at the age of ten in the course of two months had grown rapidly stout. Treatment with thyroid extract was without avail. His abdomen became pendulous and face ruddy. More recently he had been having shooting pains in the region of the spine, chest, and abdomen. He was thought to have "kidney trouble." There was shortness of breath, palpitation and tremor on exertion, dimness of vision and occasional headaches with impairment of memory. Nycturia was present; libido absent.

Physical examination.—The patient was round-shouldered and short (136.5 cm.: 4 ft. 7 in.), obese (46.4 kgm.: 102 lbs.), with an erythematous face and a pendulous, distended abdomen. The mammae were well developed, the genitals small, and the fat distribution was of feminine type. There was an overgrowth of hair at the bridge of the nose and the body was covered with a fine lanugo. The heart was somewhat enlarged to the left. The skin, which was dry, showed

[28] Friedman, E. D., "An unusual hypophysial syndrome," *N. York M. J.*, 1921, CXIV, 113.

ringworm in the axillae and pubes; erythema and telangiectasis of the face; and "striae distensae" on the abdomen and thighs.

Blood-pressure was 198/110 and there were two minute haemorrhages in the outer side of the left optic disc. The basal metabolic rate was −5 per cent. The urine showed glycosuria with a faint trace of albumin; the phenolsulphonephthalein excretion was diminished. The blood showed 95 per cent haemoglobin, 4,860,000 erythrocytes, 13,400 white cells of which 76 per cent were polynuclears. Chemical examination disclosed, in mgm. per cent, an excess of non-protein nitrogen (46.6); of cholesterin (308); and of sugar (240).

Roentgenograms: of the skull, showed markedly atrophic and thin bones of sella and sphenoid; of the hands "a development of bones such as is usually seen in persons about 13 years of age." [Dr. Friedman informs me that the patient died of pneumonia in November of the year in which his report was made: there was no autopsy.]

FIG. 48.—Case 9. Dr. Mooser's patient in 1912, aged 22.

It was recognized that this boy's syndrome had no relation to hyperpituitarism (acromegaly) nor to hypopituitarism (syndrome of Fröhlich). This condition nevertheless was thought to be of pituitary origin though the tendency to hypertrichosis and high cholesterin content of the blood suggested an involvement of the adrenals.

In the same year as the foregoing (1921) a highly suggestive example with a detailed post-mortem examination was recorded by Dr. Hermann Mooser from the Pathological Institute of Zurich then under the direction of the late Professor Busse.[29] Though the protocol specifically states that the pituitary body was normal, the case so definitely fits into the polyglandular syndrome under consideration it cannot properly be neglected any more than can examples of acromegaly without gross changes in the pituitary body be excluded in a general consideration of acromegaly.

Case 9. [Dr. Mooser's case.] **Acute painful obesity sparing extremities. Cutaneous pigmentation. Spinal deformity from osteoporosis. Duration three years. Autopsy: osteomalacia with multiple fractures; cardiac hypertrophy; atheromatous vessels; contracted kidneys; acute pancreatic necrosis; testicular atrophy. Pituitary body large but said to be normal.**

Clinical history. The patient, aged 27 (born in 1890), the eldest of eleven children, one of them a pituitary [?] dwarf, was an unmarried merchant, a polylinguist, and fond of sport. Previously spare and of slight build (Fig. 48) at the age of 24, while in military service during the autumn of 1914, he began to grow so stout as scarcely to be recognizable. The adiposity was so rapidly

[29] Mooser, Hermann, "Ein Fall von endogener Fettsucht mit hochgradiger Osteoporose. Ein Beitrag zur Pathologie der inneren Sekretion," *Virch. Arch.*, 1921, CCXXIX, 247–271.

acquired that broad striae atrophicae appeared over the trunk and extremities. The tension of the skin was such it gave the disagreeable feeling of being electrically stimulated. Before long, he began having pain in his spine, which the military surgeon thought indicated a tuberculous spondylitis and he was sent to a sanitarium. There his disorder was diagnosed as adiposogenital dystrophy of pituitary origin.

The adiposity, which was confined to face, neck and trunk (Fig. 49), progressively increased and the suffering from his tense skin which greatly disturbed his sleep became scarcely endurable. In the course of the next six months he became so weak he could scarcely hold a pencil or feed himself. He was given heliotherapy, which he bore badly, as it provoked alternating attacks of hyperaemia, cyanosis and sweating lasting from a few minutes to half an hour.

At first, there was little complaint of headache, but this for a time became more marked and later on again subsided. He was made sleepless by trembling

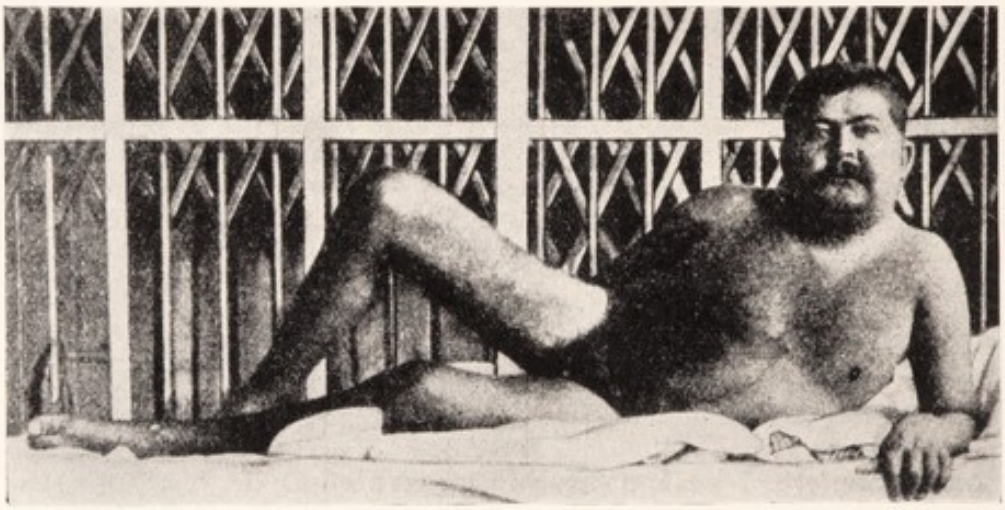

FIG. 49.—Case 9. Dr. Mooser's patient, aged 27, at height of disease three years from onset.

of the body, noises in the ears, dreams and visions. He also complained of visual disturbances on moving his head. Ophthalmoscopic investigation, apart from a slight lessening of visual acuity, showed no abnormality. He had a marked polydipsia which obliged him to get up three or four times at night. The genitalia became dystrophic. The urine examination showed during 1916–1917 a slight trace of albumin with a few hyaline casts but no sugar.

His height diminished from 165 cm. in 1914 to 158 cm. in 1917. The body circumference increased from 91 cm. in November 1915 to 96 cm. in January 1917, with a gain in weight from 52 to 63.9 kgm.

Roentgenological studies in 1916 showed that the contours of the sella turcica were scarcely visible, the bones porous. An examination a year later showed these conditions to be still more advanced. There was apparent destruction of the bodies of the mid-thoracic vertebrae associated with a gibbus which was diagnosed in 1915 as osteitis vertebralis; in 1916 as spondylitis tuberculosa; in 1917 recognized as part of a non-tuberculous generalized porosity or decalcification of the skeleton.

Following a brief period of asthmatic dyspnoea and haemoptysis, he died on *November 27, 1917*, three years from the onset of symptoms.

Post-mortem examination.[30]—The body was that of a man whose head, neck and body were exceedingly adipose in marked contrast to his relatively thin extremities. The abdomen was likened to a pillow, the circumference being 99 cm. at the level of the navel. The colour of the skin was everywhere strikingly brown, the region of the pelvis being of a lighter colour, presumably from the fact that during his periods of heliotherapy this region was protected by swimming tights. Radiating scars were present on inner surface of thigh and upper arm. The hairiness of the lower body was normal in distribution. *Head*: The inner part of the calvarium showed sharply circumscribed red spots, the largest of which had a diameter of 5.3 cm. The cerebral vessels were markedly atheromatous. The sella turcica was not enlarged. The hypophysis measured 14 by 8 by 7 mm. The neurohypophysis was plainly evident. The organ was put immediately in formalin. The base of the sella turcica was of red but smooth bone. *Thorax:* Subcutaneous fat 3.5 cm. thick. The ribs were found to be greatly softened; the upper part of the sternum greatly thickened. The heart was enlarged; the aorta atheromatous; the thymus not to be identified in the abundant mediastinal fat. The thyroid gland was fibrotic, difficult to cut, and contained but little colloid. *Abdomen:* Panniculus 4.5 cm. thick; omentum exceedingly large and fat; perirenal fat abundant. The *adrenal glands*, though buried in fat, were of average size and of normal appearance. In the *pancreas* was found an area of central necrosis. The *testes* were small.

The investigation, particularly of the bones, showed that the thickened sternum was due to the callus of a healing fracture; several ribs also showed old healed fractures. The manubrium was intensely red and soft, and contained great holes of soft marrow. The ribs were easily cut, as was true of the spinal column, part of which was removed. The greatly compressed bodies of the vertebrae, in places only 1 cm. thick, were so soft they could easily be cut with a knife.

The *gross pathological diagnosis:* lipomatosis; osteomalacia (seu rachitis tarda); multiple fractures of the ribs; vertebral collapse; hypertrophy of the cardiac ventricles; atheromatosis of aorta and of the cerebral vessels; encephalomalacia of the right occipital lobe; fibrino-purulent peritonitis; necrosis of the pancreas; hypoplasia of the thymus; granular atrophy of the kidneys.

The principal *histological findings* of note were those relating to the peculiar structure of the softened bones. The kidneys showed slight glomerular fibrosis; the cerebral vessels an endarteritis proliferans. No abnormality was found in the *adrenals*, *pineal* or *pituitary* glands.*

The small [from a Swiss standpoint] *thyroid* showed an increase of intralobar connective tissue with small and atrophic intermedial follicles; the single *parathyroid* detected was closely attached to the capsule of the thyroid, measured 4 by 3 by 2 mm., and showed an increase of connective tissue. The *thymus* could scarcely be identified in the mediastinal fat. The *pancreatic islets* were relatively few and atrophic in the part of the gland that had escaped necrosis. The *testes* also showed fibrosis with atrophic changes, though some active spermatogenesis was still present.

The outstanding symptomatic features of this remarkable case were: (1) The suddenly acquired, and peculiarly disposed, painful obesity; (2)

[30] Professor Busse's detailed protocol is herein greatly abbreviated. It deals largely with the pathology of the bones.

* [It has been learned from Zurich that the collection of tissues made during Professor Busse's lifetime has unfortunately, not been preserved.]

The softening of the bones affecting the entire skeleton but more particularly the vertebrae, leading to multiple fractures (*cf.* Case 2); (3) The ultimate enfeeblement with fatality at the expiration of three years. In view of the slightly contracted kidneys, the enlarged heart and the arteriovascular changes found after death, vascular hypertension was probably present during life. Plethora was not particularly emphasized nor purplish abdominal striae, but pigmentation of the skin was noted by the pathologist.

The author, in his analysis of the case, comes to the conclusion that the disorder represents a polyglandular deficiency, and ascribes the skeletal decalcification to sclerosis of the parathyroid glandules; the adiposity was taken to be chiefly thyroidal in origin though something was to be said in favour of a pancreatogenous insufficiency. A possible pituitary origin was discussed only in so far as to point out the lack of resemblance of the syndrome to that of adiposo-genital dystrophy. Whether the gland was scrutinized for the possible presence of an adenoma is not apparent. The gross measurements were certainly in the upper limits of normal.

The next case, also with autopsy, figures in a report made from Professor Biedl's clinic in Prague in 1924 by Dr. William Raab[31] on the general topic of hypophysial and cerebral adiposity, or what is commonly called adiposo-genital dystrophy. The subject was approached largely from its roentgenological aspects, and it was a mere chance that in 1920 when preparing for my Lister Lecture I happened to hit upon the fact in reading this paper that in the author's second case a basophil adenoma had been disclosed at autopsy. The photographs of the patient were so striking and bore such a close resemblance to the appearance of a patient at the time under observation in my own wards (*cf.* Case 11) that I felt little doubt but that they had been afflicted in all certainty with the same disorder. The translation of Dr. Raab's brief note of his case is as follows:

Case 10. [The Raab-Kraus case.]. **Acute recent plethoric obesity, sparing extremities. Purplish striae. Backache with kyphotic spine. Death from infection. Autopsy: osteoporosis of skeleton; testicular atrophy; basophil adenoma of pituitary body.**

Karel W., a man aged 31, showed gigantism of moderate degree (192 cm.), with very long extremities, externally well-developed genitalia and distribution of hair of normal masculine type. Patient complains of suffering from headaches for the past two weeks previous to his admission into the clinic and claims to have taken on 10 kgm. in weight during the same [*sic*] short period. This was confirmed by the family doctor.[32] The libido had always been rather low; he had been impotent for the past fortnight.

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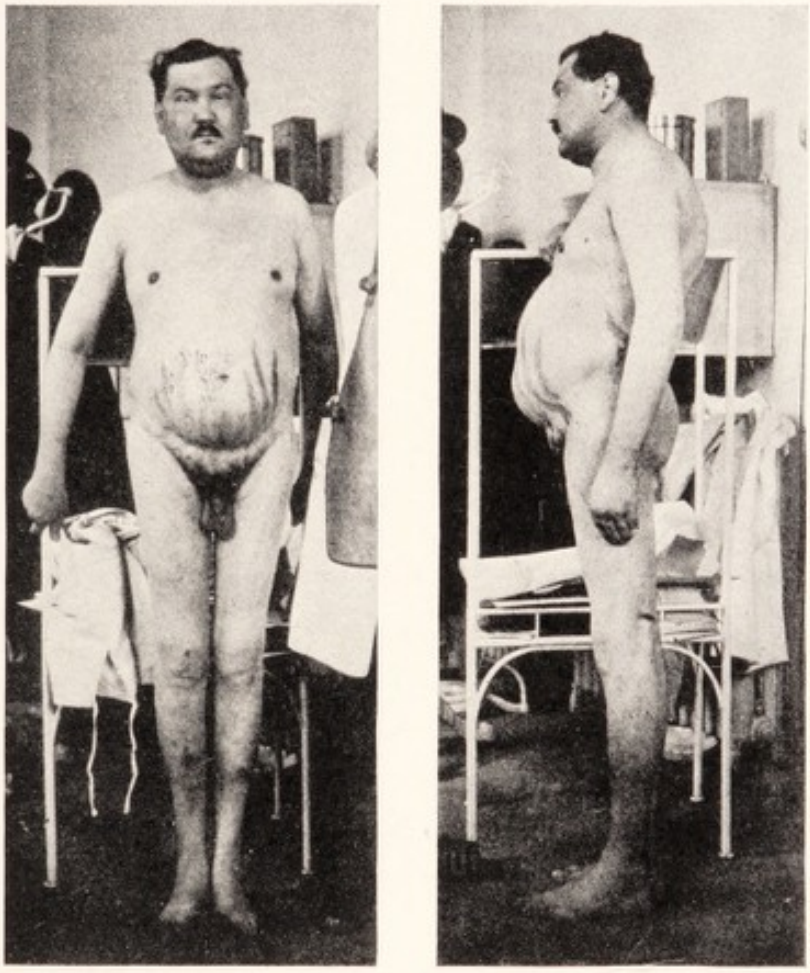
[31] Raab, W., "Klinische und röntgenologische Beiträge zur hypophysären und zerebralen Fettsucht und Genitalatrophie." (Case 2) *Wien Arch. f. inn. Med.*, 1924, VII, 443–530.

[32] In view of the post-mortem findings of advanced testicular atrophy and decalcification of the skeleton, the disease presumably was of longer duration than this statement would indicate.

There is a marked obesity of the face which appears, therefore, considerably disfigured when compared with former photographs (slit-eyes), and a marked adiposity of the abdomen (Figs. 50, 51). There is no adiposity of the long, slender extremities and of the nates. The abdomen is tremendously prominent and shows flame-shaped striae of dark-red color which are, in part, more than 2 cm. broad. The hips reveal the same feature. Weight 96 kgm. [211 pounds]. The x-ray plate shows a sella which, while not being excessively large, reveals nevertheless the characteristic deconfiguration produced by a process enlarging the intrasellar space. *Diagnosis:* tumor of hypophysis.



FIGS. 50 and 51.—Case 10. Dr. Raab's patient (1924) with verified basophil adenoma.

The headaches improving and the weight remaining unchanged, the patient left the clinic, but returned in a few weeks, feverish and suffering from excessive pains in the lumbar vertebral column. Shortly afterwards he acquired a streptococcal phlegmon of the hand and died from acute sepsis in spite of generous incisions and amputation of his arm.

The *autopsy* revealed an operculum sellae which was, as usual, concave; the pituitary body was scarcely enlarged; the posterior lobe was softened supposedly by postmortal changes. The pathologist emphatically denied the presence of a growth. Histologically, however, a small basophil adenoma was discovered which had almost entirely replaced the posterior lobe and showed

central softening—a verification of the clinical diagnosis. An osteoporosis of extreme degree involving the vertebral column and the long bones accounted for the vertebral pain.

Further details of the post-mortem examination of this case were given in a separate report in the same year (1924) by Professor E. J. Kraus[33] of Prague who has been kind enough to send me sections of the pituitary

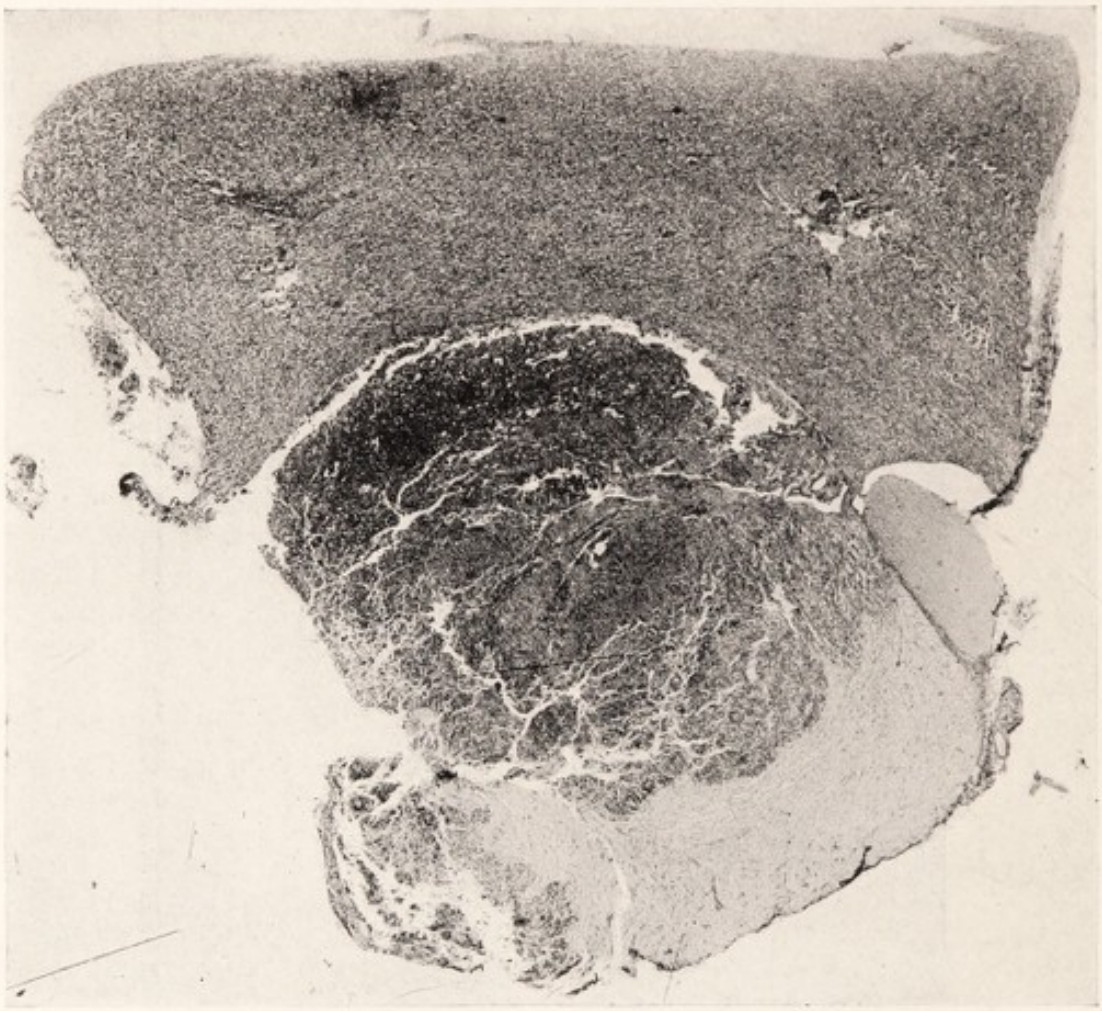


FIG. 52.—Case 10. The basophil adenoma from Dr. Raab's patient. Tumor lying between pars anterior above and pars nervosa below. (Hematoxylin and eosin, ×9). Kindness of Professor Kraus.

body (*cf.* appended Figs. 52, 53) for study, and whose personal description is translated as follows:

The *autopsy* reveals besides signs of a general septic infection a marked enlargement of the pituitary body which, however, does not protrude out of the pituitary fossa. There was, in addition to these findings, a definite osteoporosis of the vertebral column, sternum and ribs, there being a slight degree of kyphosis of the thoracic spine. There was a small diffuse colloid struma of the *thyroid*.

[33] Kraus, E. J., "Zur Pathogenese der Dystrophia adiposogenitalis." (Case 3), *Med. Klinik*, 1924, xx, 1290–1292; 1328–1330.

The *testes* were strikingly small. The thickness of the fat layer was: on the neck 1.3 cm., on the upper arm 2 cm., above the sternum 2 cm., on the abdomen 3.5 cm., and the upper leg 2 cm.

The *morphological examination* of the endocrine organs reveals: *hypophysis* 0.93 gm. In the posterior lobe there is an infiltrating basophil adenoma, situated especially in its anterior two-thirds, having destroyed about two-thirds of the adjacent substance of the anterior lobe. In the non-affected third of the lobe there are several small cysts as big as hemp-granules. The tumor, almost in its entirety, is sharply demarcated, slightly compressing the adjacent glandular

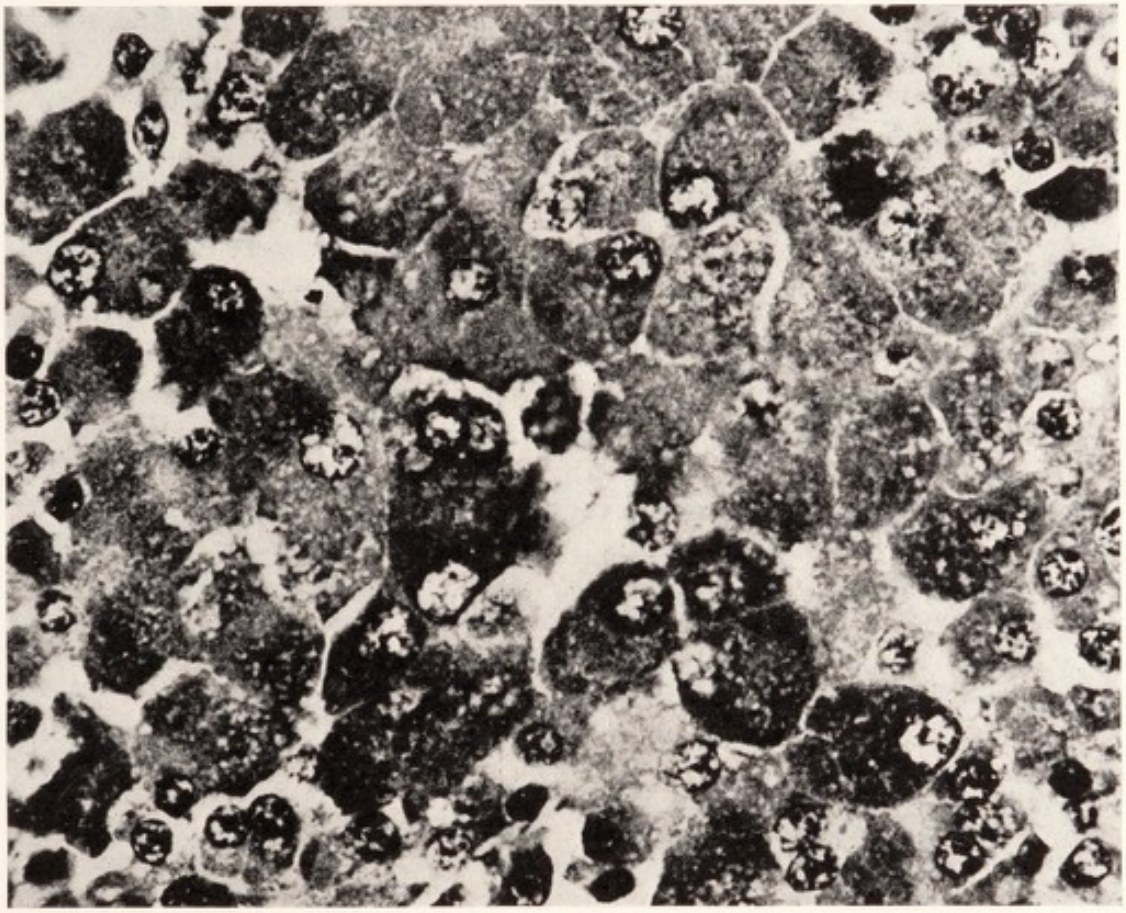


FIG. 53.—Case 10. The adenoma of the Raab-Kraus case (hematoxylin and eosin ×850) showing typical basophil cells, many of them multinuclear.

parenchyma, and infiltrating the neurohypophysis. Furthermore, the tumor sends a pointed process into the stalk of the pituitary body, thus replacing about the half of its cross-cut area. The numerous eosinophil cells on an average are somewhat smaller in size than normal. There are strikingly few ripe basophil cells. Many cells which have lost their granules (*Entgranulierte*) represent former basophil elements. There are many mother-cells (*Hauptzellen*), augmented apparently in relation to the diminished number of basophil cells. The pharyngeal-hypophysis could not be found in the many histological slides.

The *pineal body* is of normal size and also histologically normal. The slightly enlarged *thyroid gland* contains much colloid, reveals enlarged vesicles, a partly cubiod, partly flat epithelium, and a delicate interstitial tissue. Three *parathyroid glands* (weight together 9.16 gm.!) are strikingly infiltrated by fat tisssue, and

here and there occur rather large nests of oxyphil cells. The *pancreas* (weight 94 gm.) shows marked post-mortal autolysis as do also the *adrenal glands*. The two *testes* (without the epididymes) weigh 18.3 gm. The canalicules of the testes have a delicate tunica propria. Spermatides, spermatoblasts and spermatozoa are wanting; only heads of spermatozoa are found in a very few canalicules. The epithelium for the most part shows four or five rows; the amount of lipoid is somewhat diminished. The interstitial cells are definitely diminished; the epididymes histologically normal.

Professor Kraus, if I understand him correctly, looked upon the hypophysial tumor as "an incidental finding" without relation to the clinical features shown by the patient, whereas Dr. Raab believed that the adenoma in some way influenced the secretory activities of the posterior lobe, the relation of which (pituitrin) to adiposity he has made the special object of study.[34] With neither of these views do I find myself in accord; and inasmuch as Professor Kraus not only was one of the first to describe basophil adenomas,[35] but has since made other important contributions to the subject,[36] his seeming reluctance to correlate the adenoma with the clinical syndrome is the more surprizing. This may be explained by the fact that only in later years, largely through the work of P. E. Smith and his collaborators, has the functional importance of these cells been pointed out. However this may be, I quite agree with Professor Kraus' opinion that the adiposal syndrome presented by this case was something wholly different from that seen in adiposo-genital dystrophy, which is a deprivation syndrome due usually to inactivation of the hypophysis by compression. The adipose disorder under consideration, on the contrary, is almost certainly due to a hypersecretory influence of some kind, and since the adrenal glands, apart from their post-mortal change, were supposedly normal in this case whereas an adenoma was found in the pituitary body, the latter would seem to be the most probable primary seat of the trouble.[37]

We may now turn to the next of the male patients whose syndrome bears so close similarity to the foregoing case that even without a post-mortem examination it may safely be ascribed to a lesion of the same primary sort. Fortunately the somewhat meagre clinical record for the preceding case, in which many details are missing, can now be supplied:

[34] Raab, W., "Das hormonal-nervöse Regulations system des Fettstoffwechsels," *Ztschr. f. d. ges. exper. Med.*, 1926, XLIX, 179–269.

[35] Kraus, E. J., "Die Beziehungen der Zellen des Vorderlappens der menschlichen Hypophyse zueinander unter normalen Verhältnissen und in Tumoren," *Beitr. z. path. Anat. u. z. allg. Path.*, 1914, LVIII, 159–210.

[36] Kraus, E. J., "Über die Bedeutung der basophilen Zellen des menschlichen Hirnanhangs auf Grund morphologischer Studien," *Med. Klinik*, 1928, XXIV, 623, 662.

[37] Kraus has pointed out, particularly in relation to hypertension, that whenever there is an hyperplasia of the adrenal cortex an increased number of basophil cells are found in the anterior pituitary, and the reverse is true—namely, an adrenal hypoplasia is accompanied by few basophils. He suggests that the "hypercholesterinämie" of hypertension may be the common basis or at least play an important rôle.

Case 11. (P. B. B. H. Surgical No. 37076). **Rapidly acquired and painful adiposity, sparing limbs. Purplish striae. Vascular hypertension. Glycosuria with azoturia. Progressive weakness till bedfast. Clinical diagnosis: basophil adenoma. Radiotherapeusis of pituitary gland. Marked improvement.**

E. G. F., a dentist 30 years of age, referred for therapeutic recommendations by Drs. R. T. Woodyatt and A. R. Colwell of Chicago, entered the Brigham Hospital *August 11, 1930*, with the principal complaints of painful obesity, loss of strength, irritability, polyuria and polyphagia.

Family and personal history.—The patient was one of twelve children of healthy parents, both living and well, none of this large family having had any known endocrinological disorders. He had been married for ten years and was the father of two children, the first of whom died following an instrumental delivery at birth, the second being a healthy girl one year of age. Until the past year the patient had always enjoyed excellent health. He was a tall man, standing over six feet, his normal average weight having been 160 pounds.

Present illness.—This he thinks, started five years before admission, when he began slowly to grow round-shouldered and stout. In the course of the next three years he gained 25 pounds and during the fourth year there was a more rapid gain of 35 pounds, his weight reaching 220 pounds (100 kgm.) He then began limiting his diet and finally succeeded in losing a few pounds, but under this régime he soon found himself without energy, easily fatigued, unable to concentrate his mind on his work; and fits of unnatural irritability alternated with periods of depression.

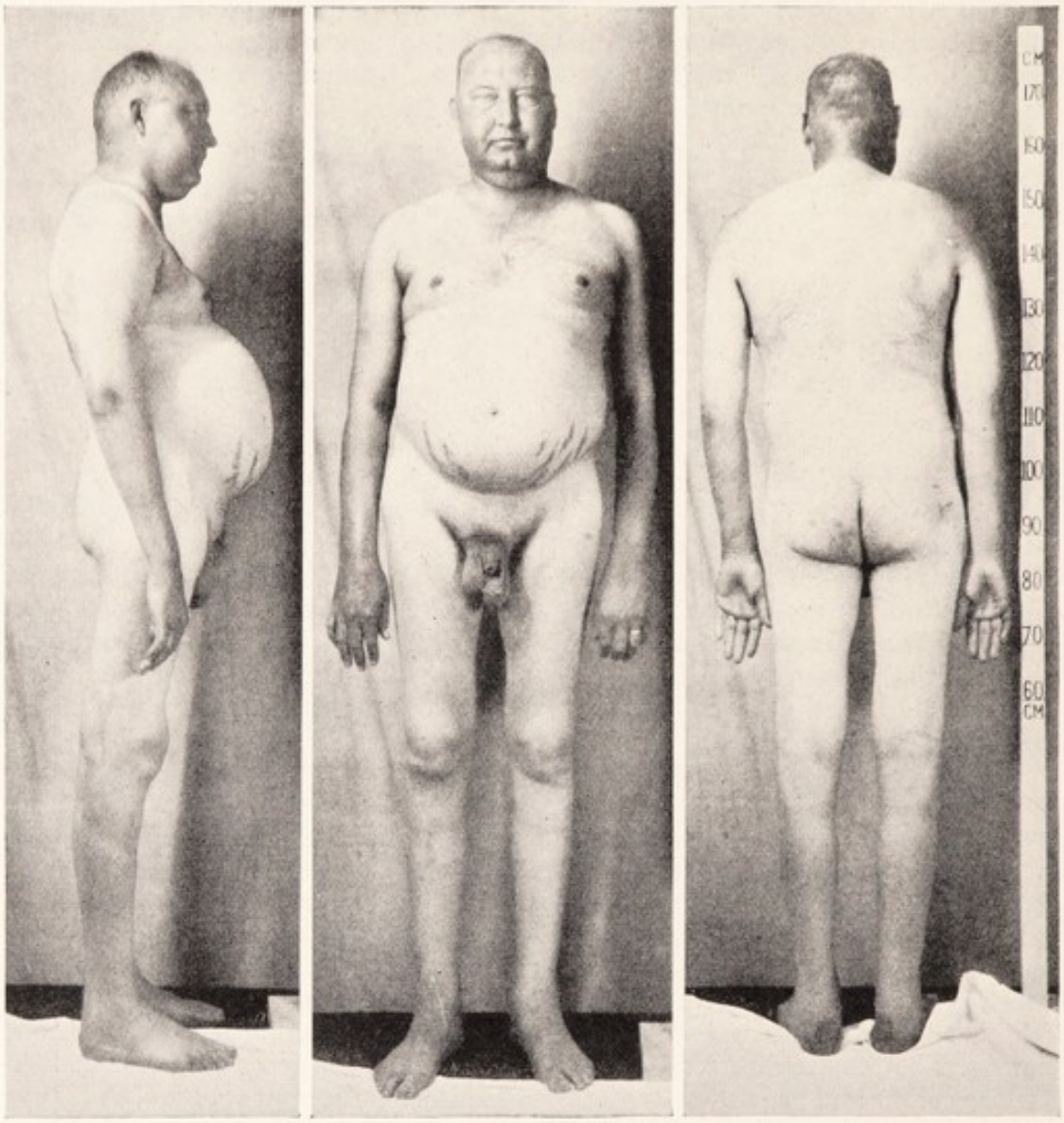
At this juncture he consulted a physician who restored some carbohydrates to his self-imposed dietary restrictions. He immediately felt better but his weight quickly increased, his abdomen became prominent, and for the first time he noticed a peculiar deposition of localized masses of fat on his face and neck. These fat deposits, which appeared in symmetrical regions over the head (cheeks, temples, orbital region, submental and suprasternal regions, as well as over the cervicodorsal spine), were at first soft, but tended to become increasingly firm and tense. They moreover were accompanied by most uncomfortable "drawing sensations," presumably from stretching of the cutaneous nerves. The tense skin over these swellings acquired a peculiar florid reddish-bronze colour and showed telangiectases so altering his appearance that he was scarcely recognizable to his friends.

At about this time (*December 1929*) he began to have an excessive thirst associated with a polyuria which was more marked at night when he would be obliged to void from four to six times. He experienced also susceptibility to fatigue, forgetfulness, restlessness, palpitation on slight exertion, swelling of the feet and ankles, generalized weakness, and impotence. A distinct loss of body hair was observed.

In *January 1930*, he was found to have a glycosuria and this led to his admission to the Presbyterian Hospital in Chicago where, by Drs. Woodyatt and Colwell, his condition was carefully investigated at various periods during the course of the next six months. They found, to make the story short:

1. "A slight *leucocytosis* of from 10 to 18 thousand, with some preponderance of neutrophilic polymorphonuclear elements; erythrocytes in normal limits.

2. "A variable *glycosuria* and hyperglycaemia, together with increased nitrogen excretion. On a diet with a daily glucose value of 201 grams, there was a daily excretion of 5.7 grams sugar (glucose) which was controlled by 50 units of insulin daily. This glycosuria was looked upon as a truly diabetic phenomenon,



FIGS. 54–56.—Case 11. To show the patient's abdominous configuration, thin extremities, plethoric face, kyphosis and striae (*cf.* Figs. 20, 21).

but it was accompanied by an unexpectedly great and wholly unrelated polydipsia and polyuria, the largest daily excretion observed having been 6,720 c.c. Attempts to modify this polyuria by pituitrin injections up to a dosage of 3 c.c. in twelve hours were wholly ineffective.

3. "*Azoturia.** On a diet containing 81 gm. of protein daily (13 gm. nitrogen), there was a daily nitrogenous excretion of 20–24 gm. despite approximate caloric

* [Of this Dr. Woodyatt writes: "The azoturia was a discovery of my own. I believe it has not been recorded in such a case (?) and that it may be of considerable theoretical interest. As the total metabolic rate was normal, the excess of nitrogen in the urine due in the main to an excess of urea, and as the nitrogen partition was otherwise normal, we may speak of an increased protein catabolism. The polyuria could be explained by the traffic in urea. The traffic in urea was sufficient to account for the polyuria, and this offers a possible and quite plausible explanation of that symptom."]

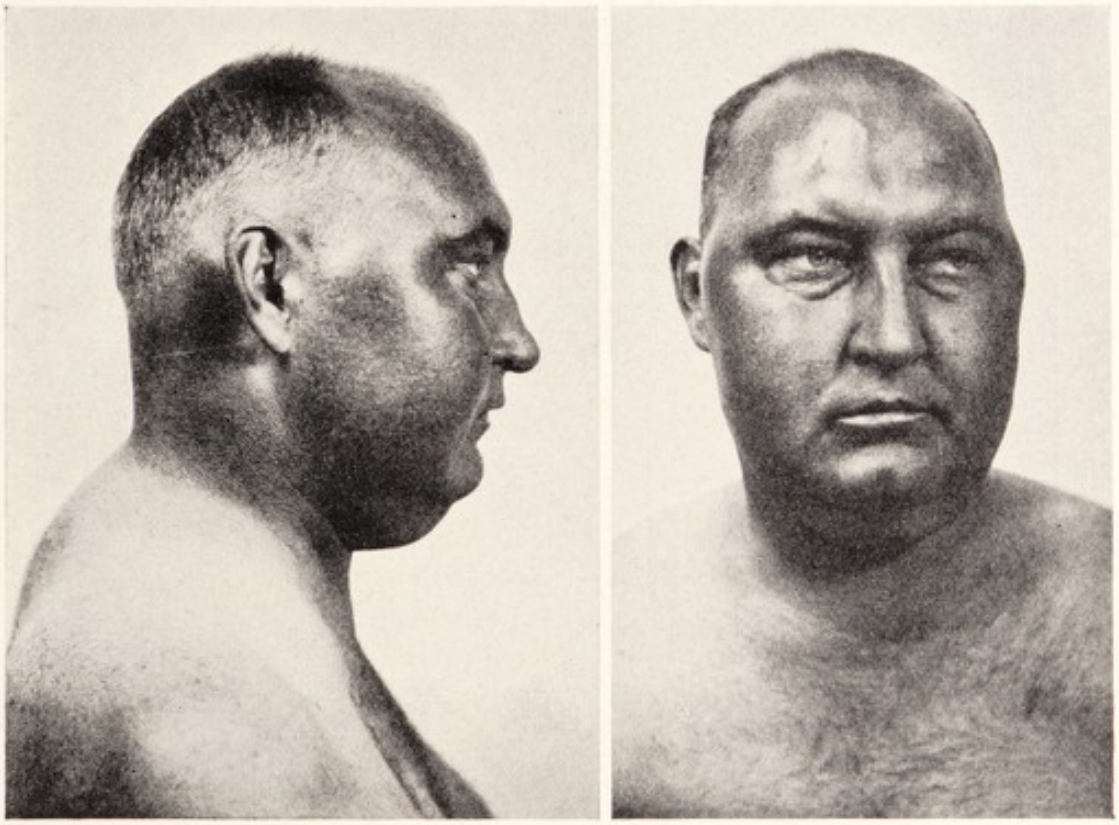
balance. This loss was later balanced by increasing the protein intake. Since then there has been a continuous excretion in the urine of 20 to 30 gm. daiiy.

4. "*Blood chemistry:* urea N. 19.0; uric acid 3.8; creatinine 1.1; total N. P. N. 36.0; chlorides 466; calcium 7.1–8.9; cholesterol 147.5 (all values in mg. per 100 c.c. blood); CO_2 77.7 vol. per cent. Wassermann reaction negative.

5. "*Basal metabolic rate:* −10 per cent to + 1 per cent on repeated readings.

6. "A moderate degree of *vascular hypertension,* from 165/70 to 178/100, without evidences of arteriosclerotic change.

7. "The administration of iodine was without effect. One of the *fat pads* on the front of the neck was removed for study and proved to be fatty tissue of customary pannicular type."



FIGS. 57 and 58.—Case 11. To show the tense, plethoric and painful adiposity of the face.

Finally, when a suspicious *enlargement of the pituitary fossa* was roentgenologically detected suggesting a possible pituitary or hypothalamic disorder, he was referred to the Brigham Hospital for an opinion.

Physical examination (on admission).—This showed (Figs. 54–56) a tall (184.2 cm.), extremely abdominous [this had been ascribed to ascites] and somewhat round-shouldered man with patchy adiposity of the face, neck and trunk, and comparatively spare extremities (weight 86.8 kgm.). All his movements, such as those incidental to rising from a chair, were obviously made with great effort, as though his limbs were scarcely strong enough to support his huge body. His face was peculiarly florid and dusky, and on forehead, cheek bones, temples, and chin were deposits of fat which were tender to the touch and covered by tense, glistening skin (Figs. 57, 58). Similar accumulations of fat were

present on the anterior aspect of the neck and over the cervico-thoracic region in the back.

Owing to the puffiness of his face and eyelids, the palpebral slits were narrow, the eyes being injected and somewhat prominent. Vessels of the fundus oculi were exceedingly tortuous and the edges of the discs were blurred, but there was no measurable swelling. The fields of vision were normal.

Wide purplish striae radiated from the groins over the abdomen and smaller striae were present over medial aspects of both thighs (Fig. 59). There was some pitting oedema about the ankles and some swelling of the hands, so that he was unable to remove a ring. He was partially bald and the hirsuties of the extremities and axillae was scanty, but there was abundant hair on the chest

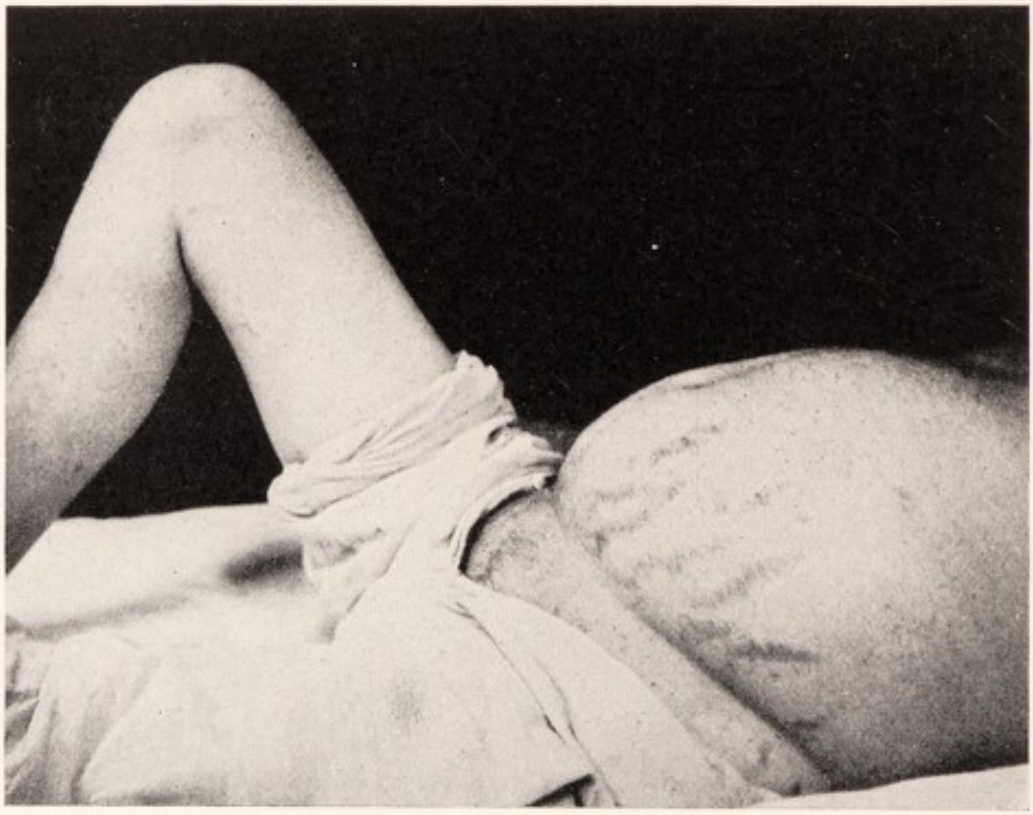


FIG. 59.—Case 11. Showing the broad purplish abdominal striae.

which was normal in deposition and texture. The skin of the axillae, groins and crotch was pigmented and scaly.

He was free from headache, but complained greatly of discomforts associated with the adiposity and also of variable pain in the back and shoulders. Roentgenograms were made of the entire skeleton, which in Dr. Sosman's opinion showed no evidence of decalcification. The pituitary fossa was not enlarged but the posterior clinoids appeared to show some absorption. No acromegalic changes were present. The spine and pelvis, so far as could be seen, were normal.

The blood examination, frequently repeated, averaged 4,600,000 red cells, 16,700 white cells, 85 per cent of them being polymorphonuclears. Haemoglobin was variously estimated at 90 to 100 per cent. The basal metabolic rate was −10 per cent; a specific-dynamic test with a 200 gm. steak-breakfast showed (possibly because of his nitrogen imbalance) a rise only to +4 per cent at the

end of a four-hour period. The systolic blood-pressure averaged over 170 mm. of Hg., indicating a moderate vascular hypertension. There were no renal elements or albumin in the urine.

When admitted to hospital, he was still on the somewhat restricted diet which finally had been worked out by Dr. Woodyatt as most effective in caring not only for the diabetes but also for the increased nitrogen output. In order to balance this and to keep up the patient's strength, it had been found necessary to increase the protein in the diet from 200 to 475 grams. He was taking in addition 65 units of insulin daily, divided into two doses, 40 in the morning and 25 at night. This, however, had been found in Chicago, as it was found here, to be most variable in its effect. His polyphagia was most striking. He was hungry all the time, and even when allowed a full meal, of which he would partake greedily, he would feel ravenous again after an hour's interval.

Laboratory studies.—During his long hospital sojourn of seventy-one days, his condition was investigated from every angle, both when under dietary restrictions and when free from them. Various authorities on diabetes and the blood, among them Dr. Reginald Fitz, Dr. W. P. Murphy and Dr. E. P. Joslin, saw him in consultation but had no therapeutic suggestion to make. Under the supervision of one or another of them frequent detailed studies were made of the blood and during the entire period daily record was kept of the total protein, total nitrogen, total uric acid and total sugar elimination in the urine, both diurnal and nocturnal.

Soon after his admission, a study of the fasting blood was made in Dr. Murphy's laboratory the morning after he had been on a wholly unrestricted diet for comparison with the findings after a period of dietary restriction, with the results shown in the subjoined table of blood studies.

Blood Studies	August 18, 1930 Diet Unrestricted	August 22, 1930 Diet Restricted
Erythrocytes	4,600,000	4,260,000
White cells	13,000	9,200
Haemoglobin	13.88 gm.	13.32 gm.
Cells	40.9 per cent	36.6 per cent
Plasma	59.1 per cent	63.4 per cent
Individual cell volume	8.8×10^{-11} cc.	8.5×10^{-11} cc.
Blood iron	43.5 mgm. per cent	41.6 mgm. per cent
Blood sugar	219 mgm. per cent	164 mgm. per cent
Non-protein nitrogen	36.8 mgm. per cent	45.8 mgm. per cent
Amino-acid nitrogen	17.0 mgm. per cent	6.8 mgm. per cent
Blood urea nitrogen	9.0 mgm. per cent	18.0 mgm. per cent
Creatinine	2.2 mgm. per cent	2.4 mgm. per cent
Uric acid	5.9 mgm. per cent	3.88 mgm. per cent
Whole-blood chlorides	255 mgm. (NaCl)	290 mgm. (NaCl)
Calcium	10.0 mgm. per cent	10.0 mgm. per cent
Cholesterol	246 mgm. per cent	190.8 mgm. per cent
Total protein	7.05 gm. per cent	6.94 gm. per cent
Albumin	3.98 gm. per cent	3.02 gm. per cent
Globulin	2.91 gm. per cent	3.53 gm. per cent
Fibrinogen	0.16 gm. per cent	0.39 gm. per cent

During the 24 hours prior to the test on the morning of *August 18*, the diet was estimated to contain 412 gm. carbohydrate, 188 gm. protein, and 256 gm. of fat with an approximate glucose value of 546 gm. The corresponding urinary output had been 5,410 c.c. containing: 58.4 gms. sugar; 20.4 gms. total nitrogen (127.5 gms. total protein); and 855 mgm. uric acid.

During the 24-hour period preceding the *August 22* test, the diet contained 92 gm. carbohydrate, 178 gm. protein, and 177 gm. fat with a glucose value of 212 gms. The corresponding urinary output had been 4,550 c.c., containing: 15.5 gm. sugar; 36.4 gm. total nitrogen (227.5 gm. total protein); and 1,595 mgm. uric acid.

During the month of August, also, acting on the assumption that a basophil adenoma might conceivably show a sex-maturing substance in the urine similar to that present during pregnancy, a series of observations was made by Dr. D. W. Gaiser to test this point. The urine was highly toxic for immature rats but the survivors showed no change in ovaries or seminal vesicles at the end of 120 hours. Similar tests on immature mice were equally without result.

On *September 12, 1930*, during a period when he was again on a restricted diet without insulin [he showed on this particular day a fasting blood sugar 0.214, with the elimination of 4,300 c.c. of urine containing 24.4 gm. sugar, 183 gm. total protein, 29.2 gm. total nitrogen, and 1,495 mgm. total uric acid], an estimation in Dr. Joslin's laboratory was made of his plasma lipids (the patient's brother and an insulinized case of diabetes of nine years' duration serving as controls), with the following results:

Plasma lipids	Cholesterol	Total Fatty acids	Lecithin	Total lipins
	mgm. per 100 c.c.	*mgm. per 100 c.c.*	*mgm. per 100 c.c.*	*mgm. per 100 c.c.*
Normal average	230	390	210	680
The patient, E. G. F.	326	575	344	901
Controls:				
Patient's brother	189	259	230	448
A 9-year diabetic	391	286	330	667

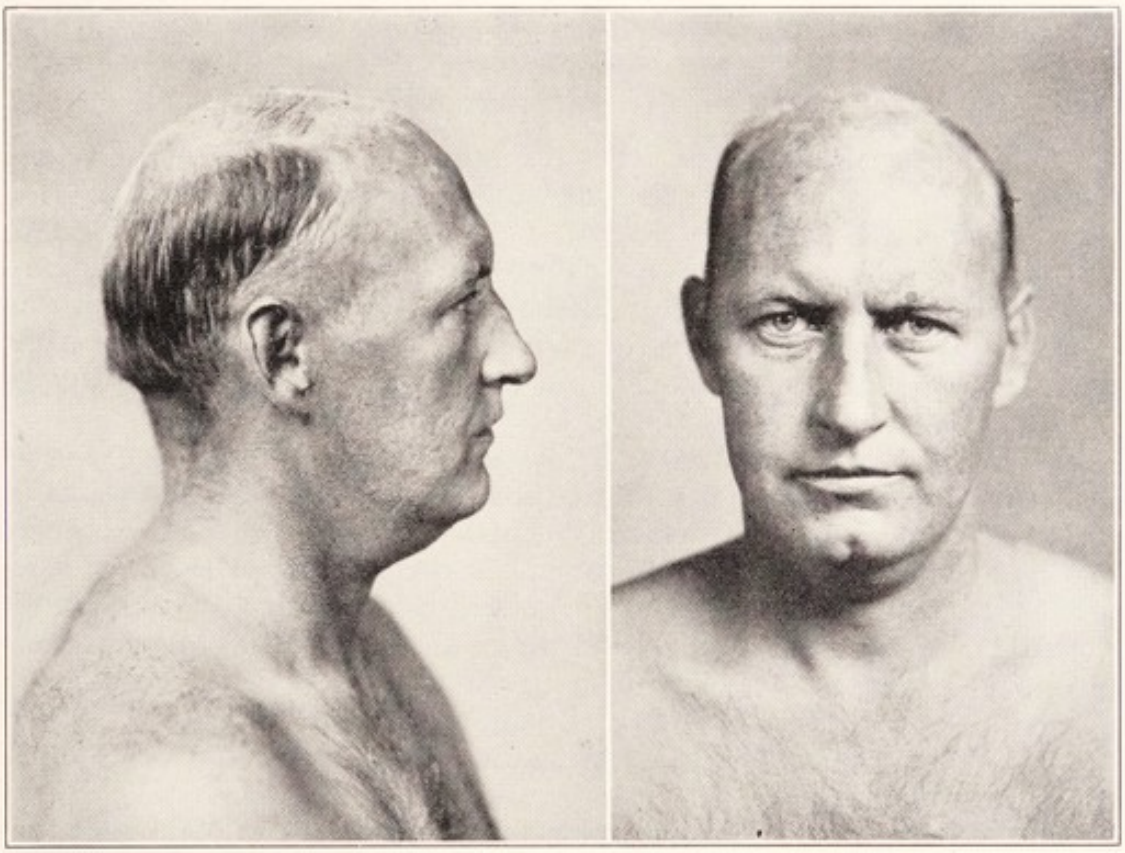
Though the patient's fatty acids and total lipins were considerably in excess of the controls, they were regarded as "approximating those seen in cases of mild or moderate diabetes in the days before the introduction of insulin."[38]

As weeks passed, he became increasingly more feeble, was reluctant to get out of bed, and appeared rapidly to be going downhill, the progressive loss of strength causing him great concern. Not only did he suffer from pain in his hips and shoulders but from such extreme sensitiveness of his face he could not bear the pressure of a pillow against it. It was very difficult to make him comfortable in bed, recourse being finally had to an air mattress. He ceased to take an interest in his surroundings; became so feeble he was unable even to turn in

[38] Attention may be drawn to two recently published papers by Anselmino and Hoffman (*Klin. Wchnschr.*, 26 Dec. 1931, pp. 2380–86) in which the presence in the anterior pituitary of what is called a metabolizing (*Stoffwechsel*) hormone is claimed. This appears to be related to but is separable from the gonad-stimulating hormone. Its injections increase the acetone-body content in the blood by accelerating fat combustion.

bed; and he finally acquired a carbuncular infection at the lower end of his spine which began rapidly to spread. Knowing that other patients with this syndrome had died either from or with ulcerative cutaneous infections (*cf.* Case 10), it was feared that his end was near.

From the outset, he had been pleading for an exploratory operation which was considered impracticable, but in view of the growing conviction that his trouble must be due to a basophil adenoma, which might conceivably be amenable to radiation, he was given, between *October 14* and *17*, four x-ray treatments. During their course, he felt particularly miserable, but *October 19* his downward progression for the preceding month was unmistakably checked. The improve-



FIGS. 60, 61.—Case 11. For contrast with Figs. 57–58 to show changed appearance of patient 14 months after hypophysial radiation.

ment in his general condition was so striking it must have been something more than coincidence. He felt stronger, began to show an interest in his surroundings, to make efforts to move himself about, was conscious of a diminution in thirst, and of lessening in his discomforts. The carbuncular infection of the lower spine began to show improvement, and though he was unable as yet to get out of bed, he at this juncture (*October 21, 1930*) insisted on being taken home.

There he again came under Dr. Woodyatt's care and was given some bone-marrow and liver feedings. He continued slowly to improve though in his frequent letters he still complained of backaches and of the painful sensations in the tense, adipose areas. On *March 6, 1931*, he reported a further gain in weight up to 235 pounds; but on the whole, he made steady progress and by *July 1931*,

was able to walk a half-mile or more at a time without overfatigue. In *October 1931*, he stated that the "tumorous growths" of his face and neck had nearly disappeared, and two months later he wrote from Florida, where he had gone for the winter, stating that he was still improving, had lost weight and no longer showed sugar on an ordinary diet, even without insulin.

[Subsequent notes.] On his return home in the latter part of February, he forwarded the accompanying views of his head (Figs. 60, 61) to show the changed appearance in his face. Though doing well, he was given, on my advice, another series of x-ray treatments. At the present time, *May 1932*, he writes that he "feels stronger and more spry," and in spite of getting easily tired, he is spending full time at his office. The blood pressure now averages 134/86 a drop of nearly 40 points since his hospitalization period. He remains sugar-free on ordinary diet, shows no tendency to gain weight, has no further polyuria, and regards himself as slowly improving in every way.

The definite improvement, following radiation of the patient's pituitary body, was looked upon as something more than mere coincidence. As will be pointed out in the next section, the average duration of life of the fatal cases had been in the neighborhood of five years and all the patients succumbed to progressive enfeeblement associated in most of the cases with terminal infections—a happening there was every reason to anticipate in this particular instance when recourse was finally had to radiotherapeusis.

The exhaustive laboratory studies of the blood and urine gave no information of value, though attention may be called to the consistently high non-protein nitrogen percentages and to the high cholesterol reading, on a single occasion, of 246 mgm. per cent. In this connection it is interesting that Professor Kraus, after the painstaking enumeration of the number and condition of the basophilic elements in the anterior pituitary in various pathological states, expresses the conclusion in a recent paper (*loc. cit.*, 1928) that a definite relationship exists between the number of these cells, those of the adrenal, the blood-pressure and cholesterin metabolism.

Another matter to which attention may be called is the fact that the patient's diabetes, like that complicating cases of acromegaly, was far more difficult to regulate and control by insulin than is the diabetes primarily of pancreatic origin. What, if anything, this may have to do with the known counter-effect of posterior lobe extract (pituitrin) on the action of insulin needs further ventilation.

Another unmistakable example of this same disorder, recently reported by Dr. Wieth-Pedersen from the Rigshospital of Cohenhagen, has been called to my attention by a Danish student in our Medical School. The author gives a detailed report[39] of two cases both of which showed marked striae distensae cutis to which factor attention is particularly drawn. One of the patients had a malignant adrenal tumor with metas-

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[39] Wieth-Pedersen, G., "Et Tilfaelde af Binyretumor og et af Hypofysetumor med Binyrehyperplasi, begge med Striae distinsae cutis," *Hospitalstidende*, 191, LXXIV, 1231–1244.

tases, the other a pituitary tumor associated with adrenal hyperplasia, the syndrome in both having been ascribed to the adrenal factor.

The first case was that of a woman, 158 cm. in height, with headaches, puffy skin (without hypertrichosis), dimness of vision, increase of 16 kg. weight, with reddish-blue striae distensae, hypertension 245/150, cardiac enlargement and polydipsia. She died a year after the onset of symptoms. An adrenal tumor 12 by 6 cm. with metastases was found at autopsy. The pituitary body was said to be normal but was not examined microscopically. An abbreviated report of the second case follows:

Case 12. [Dr. Wieth-Pedersen's patient.] **Delayed adolescence. Plethoric adiposity with striae. Albuminuria. Hyperglycaemia. Glycosuria. Vascular hypertension. Cardiac hypertrophy. Duration 4 years. Autopsy: pituitary adenoma (type unverified); adrenal hyperplasia.**

Clinical history.—A young man, 24 years of age, entered the hospital *May 6, 1930,* and died there three months later. He had always been well but his puberty was delayed until the age of 20 when he began to grow abdominous and the colour of his face and hands became bluish red. He had polyphagia, polydipsia, and polyuria. He perspired freely when at work. He needed to shave only twice weekly. There was no headache or dizziness. His vision had become impaired in later years and he had lost some weight under treatment during the nine months prior to admission.

Physical examination.—The appearance (Figs. 62, 63) was that of a man older than his age. He was of slight stature. Height 161.5 cm. (5 ft. 3 in.); weight 61.3 kg. (135 lbs.). There was quite marked adiposity, localized around abdomen, thorax and face, the extremities not being affected. No dyspnoea while resting. The teeth were carious. The thyroid gland was covered by a cushion of fat, but not enlarged. No peripheral adenitis. No cardiac enlargement was detected. There were numerous pigmented naevi on the chest.

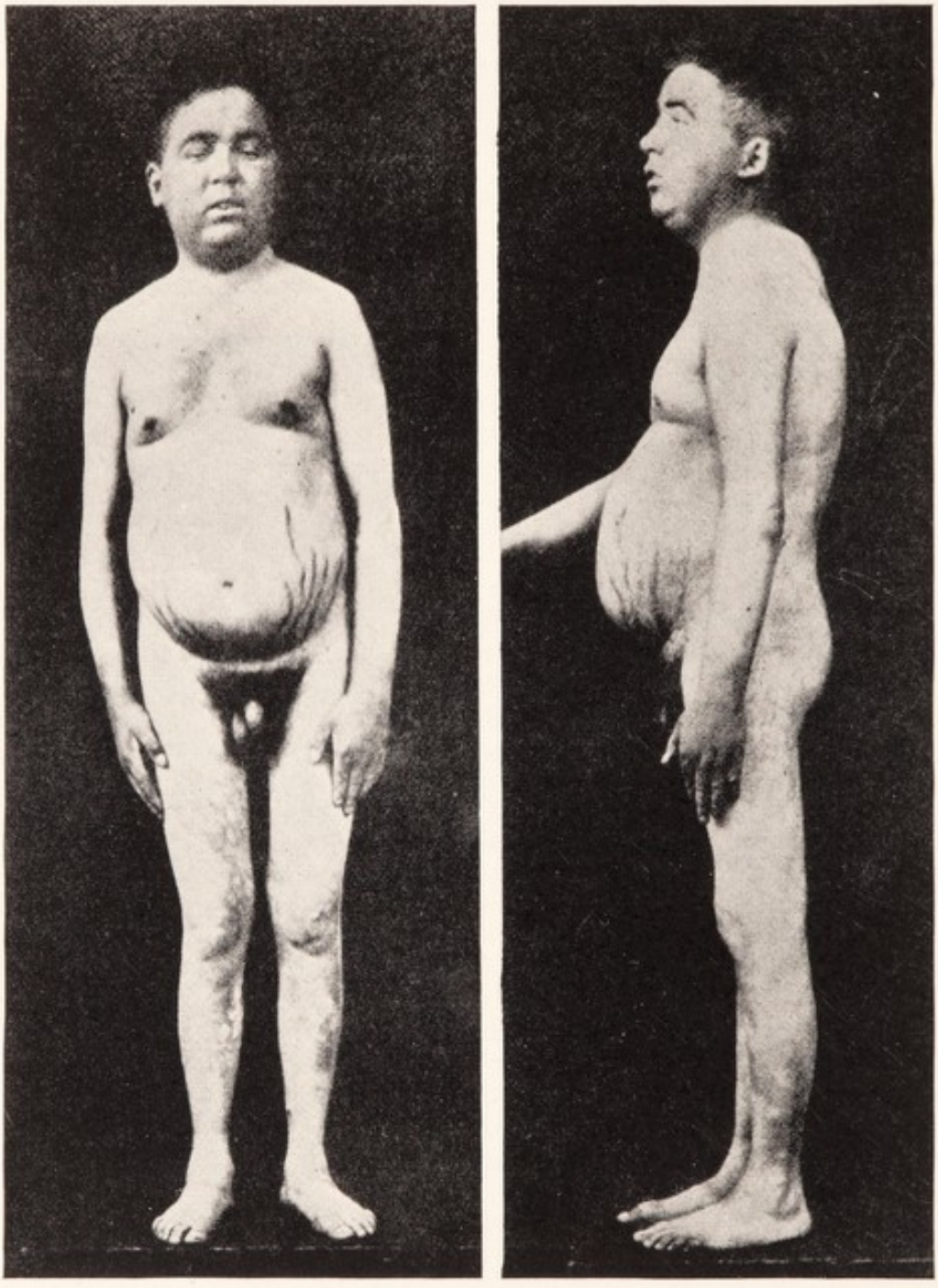
On both sides of the abdomen were reddish striae distensae, 1 cm. in width and 5 to 6 cm. in length; otherwise nothing abnormal. The external genitalia were not hypoplastic. The face and hands showed a deep red-blue colour. There was cyanosis of the lower legs with spots of light brownish pigmentation which contrasted with the varices which were present.* At the time of the examination there was a four days' growth of beard which amounted to 2 mm. at the most. The hair on the head, eyebrows, axillae and pubis was normal.

The urine contained sugar and albumin with a few hyaline casts. Blood-pressure 190/170: haemoglobin 93 per cent (Sahli). Wassermann negative. The cranial roentgenograms showed no abnormality; the sella was normal (10 by 12 mm.) with no evidence of a destructive process. The epiphyseal lines in both knees and wrists were open, corresponding with 16 to 17 years of age. No signs of atherosclerosis.

The basal metabolic rate was approximately normal. Renal function was unimpaired. The eyes were normal, except for a polar cataract visible in both of them. Blood urea [non-protein nitrogen ?] 44 mgm. per cent; fasting blood

* [The characteristic "cutis marmorata" of the lower extremities is apparent, particularly in Fig. 62. This has been a striking feature of many of these cases and is usually more evident on cold days. It is not infrequently seen also in patients with so-called essential hypertension, which suggests that pituitary basophilism may have something to do with these aetiologically obscure states.]

sugar, highest estimate 263 mgm. per cent. No ketonuria observed. Only on days of fasting was it possible to make the patient sugar-free; even on an anti-diabetic diet with greatly reduced calories the urine still showed sugar. Insulin was not used.



FIGS. 62, 63.—Case 12. Dr. Wieth-Pedersen's patient with pituitary adenoma of unrecorded type [*cf.* addendum, pg. 163].

Course of disease.—There was considerable variation from day to day, not only in the hypertension, but in the albuminuria and in the percentage of sugar in the blood. The patient complained of headache, of pains in the ears, and be-

came dull and sleepy. On one occasion, he had subjective dimness of sight, marked dizziness, and vomited, the blood-pressure registering 185/120 with a rapid pulse. The abdominal striae grew more pronounced and finally reached all the way up to the axillae on both sides. Ecchymoses occurred from time to time on the legs and arms; his left hand became oedematous. On *August 1*, the patient became dyspnoeic and cyanotic and died that evening.

Autopsy: August 2.—The extremities were lean compared with the trunk. There were striae distensae on the abdomen, running longitudinally to thorax and even to axillae. The skin was without oedema, apart from that on the left forearm and back of hand. The growth of the hair was natural, except the beard, which was scanty. Broncho-pneumonia was found, also marked hypertrophy of the left ventricle and atheroma of the aorta and common iliacs. The mesentery was exceedingly fat. The kidneys were slightly granular.

The *thyroid gland* was small (each lobe measuring 3 by 1.3 cm.) and firm. The *right adrenal* was normal, but the left was hyperplastic, weighing 27 grams; the tissue on fresh section appeared normal, but the medullary portion was oedematous and of a brownish-green colour. The *pituitary gland*, on removal of the brain, was found to be replaced by a soft tumor-like growth of reddish colour, which measured 3 by 2 by 2.5 cm. The brain itself was oedematous, the ventricles moderately dilated.

Microscopical examination.—The *thyroid gland* showed changes like those found in a colloid struma, the epithelial lining of the follicles being low cuboidal, with no proliferation and no increase of connective tissue. The *pancreas* showed slight increase of connective tissue, with an unusual number of islets. The *left adrenal gland* had a normal structure without oedematous cell proliferation. Toward its centre, there was some oedema and congestion of the vessels without cell degeneration. The hyperplasia was evenly distributed between cortex and marrow, the two structures being indefinitely contrasted with indistinct arrangement of cell columns. The *kidneys* showed no definite change, though casts were found in the tubules. *Hypophysis:* "The tumor tissue consists of a coarse network of rather delicate connective tissue, often containing thin-walled, wide, congested vessels. Although there are post-mortem changes, one is of the impression that the network of connective tissues with its branches all throughout has been covered by cells of epithelial nature. These cells are polygonal, at times somewhat extended, and containing a nucleus of varying sizes and shape with a dark nucleolus. Quite often there are seen large complexes of nuclei with a few mitoses. These cells form, as a rule, a quite dense layer and line irregularly-shaped vacuoles which are filled with granular material consisting of necrotic and degenerative cells. Thus, the tumor tissue appears papillomatous in structure. The connective tissue, which is increased in amount in the periphery of the tumor, is also infiltrated with tumor cells. There is no evidence of sarcoma. The endothelium of the vessels appears normal."

Pathological diagnosis.—Tumor of the hypophysis. Hyperplasia of the suprarenal glands, of the thyroid and of the pancreas. Hypertrophy of the left heart. Chronic granular nephritis. Compression of the left optic nerve. Hydrocephalus internus. Oedema of pia and arachnoid. Dilatation of sella turcica. Atheromatosis of mitral valve and aorta. Oedema of face and back of hand. Striae distensae cutis. Pigmentation and ecchymoses of the skin.

In his interesting discussion of the two cases, the author naturally ascribed the polyglandular disorder in the first of them to the adrenal tumor. In the second case, he laid chief emphasis (as did Dr. Parkes

Weber in Case 6) upon the unilateral adrenal hyperplasia. He however ascribed the delayed puberty, retarded ossification and the adiposity to a pituitary effect as an example of dystrophia adiposogenitalis [*sic*].

COLLATION OF SYMPTOMATIC AND PATHOLOGICAL DATA

The twelve patients whose case histories have been presented, as will have been noted, were all relatively *young adults*. Their *average age* at the onset of the malady, so far as can be estimated (Case 10 being eliminated for want of information) has been 18 years; the youngest was six (Case 5) and the oldest 25 (Case 11).

In *stature*, the female patients all appear to have been definitely undersized. Where heights were given, the tallest (Case 6) was 159 cm. (5 ft. 3 in.), the shortest (Case 1), 145 cm. (4 ft. 9 in.). Two of the male patients, on the other hand, were tall: Case 10, 192 cm. (6 ft. $3\frac{1}{2}$ in.); Case 11, 184.2 cm. (6 ft. $\frac{1}{2}$in.).

The *average duration* of the disease from onset to death in the cases where definitely stated (Case 10 again eliminated) has been slightly over five years, the extremes being three (Case 9) and seven [?] years (Case 8).

The following features are characteristic of all cases: (1) A rapidly acquired, peculiarly disposed and usually painful *adiposity* (in one instance representing a 40 per cent gain in weight) confined to face, neck and trunk, the extremities being spared; (2) A tendency to become round shouldered (kyphotic) even to the point of measurable loss of height (*Cf.* Cases 2 and 9) associated with lumbo-spinal pains; (3) A sexual dystrophy shown by early *amenorrhoea* in the females and ultimate functional *impotence* in the males; (4) An alteration in normal hirsuties shown by a tendency to *hypertrichosis* of face and trunk in all the females as well as the preadolescent males (Case 8 and 12) and possibly the reverse in the adult males; (5) A dusky or plethoric appearance of the skin with *purplish lineae atrophicae* particularly marked on the abdomen; (6) *Vascular hypertension*, present in all cases except Cases 4, 7 and 9 where no mention was made of blood-pressure; it varied from the highest recorded in Case 6 of 230/170 to the lowest in Case 11 of 178/100; (7) A tendency to *erythraemia*, a count exceeding five million having been present in five of the nine cases in which blood counts were recorded; (8) Variable *backaches, abdominal pains, fatigability* and ultimate extreme *weakness*.

Other features less consistently recorded have been as follows: *Acrocyanosis* (*e.g.*, Cases 1, 12) with cutis marmorata of the extremities (*e.g.*, Case 12); *Purpura-like ecchymoses*, whether from bruising or occurring spontaneously (Cases 1, 2, 3, 6, 12); *Aching pains in the eyes*, associated with slight exophthalmos (Cases 1, 3, 6, 11), with transient diplopia (Case 1), with suggestive papilloedema (Case 1, 6, 11), with dimness of vision (Cases 8, 9, 12), with subretinal exudate (Case 2) and retinal haemorrhage (Case 8); Extreme *dryness of skin* (*e.g.*, Cases 1, 2, 4, 6, 8), with pigmentation (*e.g.*, Cases 1, 4, 6, 11, 12); *Polyphagia*, polydipsia and polyuria (*e.g.*, Cases 11, 12); *Oedema of the lower extremities* was noted in

several cases and in Case 12, of the hand; A *susceptibility to pulmonary infections* (Cases 5, 6, 8, 9, 12); *Albuminuria* of slight degree with occasional casts was found in six patients (Cases 1, 5, 6, 8, 9, 12); A *sense of suffocation* and difficulty in swallowing were occasionally noted (Cases 1, 6); *Insomnia* was a not uncommon complaint; An increase of non-protein nitrogen and of cholesterin in the blood was recorded in the only patients (Cases 8, 11, and possibly 12) in which it was estimated; A *polymorphonuclear leucocytosis* was noted in Cases 1, 5, 6, 8, 11.

Secondary endocrine disturbances conceivably affecting the *adrenal glands* were suggested not only by the hypertension and the pigmentation (particularly noted in Cases 1, 4, 9, 12) but by the terminal extreme weakness; on the part of the *pancreatic islets*, by the glycosuria (Cases 4, 5, 8, 11, 12); conceivably on the part of the *thyroid gland*, by the increased metabolic rate (Cases 6, 7), though this was once recorded as low (Case 11) and in most instances was not noted; of the *parathyroid glandules*, possibly by the osteoporosis from decalcification, either roentgenologically apparent (Case 1) or demonstrated at autopsy, and to which the marked upper thoracic kyphosis (*e.g.*, Cases 1, 2, 4, 9, 10, 11) and the spontaneous fractures (Cases 2, 9) are attributable. There was no increase of blood calcium in Case 10; in no instance was calcium elimination estimated. [*Cf.* p. 171.]

Post-mortem findings.—The malady appears to leave the patients with a definite *susceptibility to infections*. Death in the nine fatal cases eight of which came to post-mortem examination, was ascribable to, or associated with, multiple cutaneous abscess and ulcers (Cases 2, 5), intercurrent erysipelas (Case 4), acute pulmonary complications (Cases 5, 6, 12), intercurrent meningitis (Case 7), a streptococcal phlegmon (Case 10), pancreatic necrosis (Case 9). *Chronic nephritis* of mild degree was found, in the absence of any definite clinical signs, in Cases 2, 3, 6, 9, and 12; *hypertrophy of the cardiac ventricle* in Cases 2, 6, 9, and 12; and vascular atherosclerosis, noted in Cases 3, 9 and 12, was roentgenologically apparent in Case 1. An *osteoporosis of the skeleton* most marked in the spine was specifically described in six (Cases 2, 3, 4, 6, 9, 10) of the eight autopsies, Cases 7 and 12 being the exceptions and in these it may have escaped notice.

The ductless glands.—A *basophil adenoma of the pituitary body* was found in Cases 6, 7 and 10; an undifferentiated adenoma in Cases 3 [now proven to be basophil (*Cf.* addenda)] and 12; what was described as an adenomatous-like structure in a fibrosed area of the anterior pituitary was noted in Case 4; and in Cases 2 and 9, the gland was said to be "normal." The *thyroid* was described as slightly enlarged (colloidal) in Cases 3, 7, 10, 12; as small in Case 4; as fibrotic in Case 9. The *parathyroids* were described as normal in Case 3; to have shown capillary dilatation in Case 4; to be fibrotic in Case 9; and infiltrated with fat in Case 10. The *suprarenal glands* in Cases 2 and 6 showed a cortical hyperplasia; in Case 3, a small adenoma; while in Cases 4, 7, 9, and 10, no abnormality was noted. The *ovaries* and uterus were said to be senile in Case 3; in

Case 4 to show atresia; in Case 6, to be small but normal; and in Case 7, to show hypertrophy with signs of increased functional activity. The *testes* in Cases 9 and 10 showed atrophy of the spermatogenous epithelium.

DISCUSSION AND RECAPITULATION

In ascribing this obscure polyglandular syndrome to a pituitary rather than to an adrenal source, I am aware that much might be said in favour of the latter seat of origin. Indeed, it was my original belief in the case of Minnie G. that her malady was in all probability associated with an adrenal tumor. What light the contemporary literature served to shed on the subject was strongly in favour of such an interpretation, containing, as it did, numerous examples of precocious sexual development in children or of the masculinization of women who were found to have large suprarenal tumors. A striking example was that reported in 1911 by Launois, Pinard and Gallais[40] of a bearded and amenorrhoeic woman who showed plethoric adiposity with an abundance of purplish lineae over the trunk. A suprarenal tumor of cortical type with metastases to liver and lungs was found at autopsy in association with what was said to be a normal pituitary body, though the sella turcica was said to have measured 18 mm. in its largest diameter which, to say the least, is at the upper limit of normal for her age, this being 14.4 mm. according to Erdheim and Stumme's measurements.

About this same time, twenty years ago, I had the opportunity in London to see with Dr. Gordon Holmes a striking example of masculinization or heterosexual virilism in a woman from whom an adrenal tumor was subsequently removed by Sir Percy Sargent with prompt restoration of the patient's original normal feminine appearance and reactions.[41] This woman had a lean, mannish habitus quite unlike the highly plethoric and adipose individuals herein depicted, and the case may possibly have unduly coloured my impressions of hyperadrenalism of which, to be sure, several differing types have been described. Primary adrenal tumors, therefore, may cause striking constitutional transformations, but there nevertheless is justification in again emphasizing the fact that all known primary pituitary disorders inevitably cause marked secondary changes in the adrenal cortex, a pathological observation which is amply supported by what occurs after experimental pituitary dwarfism or gigantism. And if the acidophil adenomas of acromegaly inevitably cause hyperplasia not infrequently associated with actual adenomas of the adrenal cortex,[42] it is reasonable to assume that basophil adenomas may well enough do the same.

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[40] Launois, P. E., M. Pinard, and A. Gallais, "Syndrome adiposo-génital avec hypertrichose, troubles nerveux et mentaux d'origine surrénale," *Gaz. d. hôp.*, 1911, LXXXIV, 649–654.

[41] Holmes, G., "A case of virilism associated with a suprarenal tumor: recovery after its removal," *Quart. J. Med.*, 1924–25, XVIII, 143–152.

[42] Cushing, H., and L. M. Davidoff, "The pathological findings in four autopsied cases of acromegaly with a discussion of their significance," *Monogr. Rockefeller Inst. M. Research*, No. 22, 1927, p. 109.

An excess or deficiency of anterior-pituitary hormones, in other words, secondarily affects the function of the adrenal cortex with established certainty, whereas nothing comparable to this occurs in the reverse direction. Hence, if further study should prove that adrenal tumors in the absence of any demonstrable change in the pituitary body may cause a polyglandular syndrome in many respects similar to that under discussion, it may well enough be assumed that, when the same features characterize the syndrome of a basophil adenoma, they in all probability are secondarily ascribable to a hypersecretory influence of adrenal cortex even in the absence of any histologically appreciable abnormality as exemplified by the Parkes Weber and by the Raab-Kraus cases cited above.[43]

The disorders under discussion in all probability are much more common than would appear from the present assembly of twelve examples which with four exceptions have been restricted to cases in which a post-mortem examination has been held. Acromegaly was once looked upon as a rare disease, and in its extreme form may still be so considered. However, one encounters on every hand persons with unmistakable traces of pituitary acidophilism (acromegalic overgrowth) so mild in its effects medical advice has not been sought; and the same is probably true of persons affected by transitory or mild degrees of pituitary basophilism.

I am quite aware that in ascribing the disorder to the basophil elements, even were their association with maturation and the ovulatory mechanism established beyond peradventure, many questions arise which are at present unanswerable. For example: (1) If the sex-maturing principle, which during pregnancy appears to spill over into the urine, is excreted by the basophil cells, should it not be found (*cf.* Case 11) in the urine of patients with basophil adenomas if the polyglandular disorder under consideration is actually due to the hypersecretory effect of such a lesion?[44] (2) Whereas premature sexual maturity appears to characterize the disorder in children of either sex, why, in adult women, should amenorrhoea occur together with an apparent reversal of the secondary characters of sex? (3) If, in this syndrome, we are actually dealing with an oversecretion of the gonad-stimulating factor, why should atretic ovaries be found in the females instead of over-follicularized or over-luteinized ("mulberry") ovaries such as occur in immature or adult female rats after repeated injections with extracts containing one or the other gonad-stimulating factors?[45] (4) If the polyglandular features of the dis-

[43] Smith and Engle, as may be recalled, found that pituitary transplants in the immature female rat produced precocious sexual maturity even after bilateral adrenalectomy. *Loc. cit.*, 1927.

[44] The hypophysial hyperplasia which occurs in pregnancy, described by Erdheim and Stumme (1909), is composed of modified chief cells which are nongranular. One would assume that this means the cells are not advancing to secretory maturity. The source of the gonad-stimulating substance in the urine, unless it is provided by the placenta (*Cf.* Collip), is therefore not clear.

[45] *Cf.* Fevold, H. L., F. L. Hisaw, and S. L. Leonard, "The gonad-stimulating and the luteinizing hormones of the anterior lobe of the hypophysis," *Am. J. Physiol.*, 1931, XCVII, 291–301.

order are partly due, as premised, to a secondary hyperplasia of adrenal cortex, why has this not been observed in rats after injection with the gonad-stimulating extracts whereas it is a striking effect of injecting growth-promoting extracts?[46] An answer to these and other questions will doubtless in time be forthcoming.

A *chronological recapitulation* of the facts that have chiefly served to throw light on this subject during the past twenty years are as follows: (1) Primary anterior-pituitary disorders are commonly produced by adenomas; (2) Adenomas of the endocrine series are as a whole functionally active lesions; (3) Even minute adenomatous tumors of parathyroid glandules and pancreatic islets may lead to serious constitutional derangements of hypersecretory type; (4) Pituitary adenomas are of three principal varieties—neutrophil, acidophil and basophil, no constitutional disorder heretofore having been definitely ascribed to the last; (5) There is experimental evidence to suggest that the basophil elements of the anterior pituitary secrete the sex-maturing hormone; and finally, (6) A polyglandular syndrome hitherto supposed to be of cortico-adrenal origin characterized in its full-blown state by acute plethoric adiposity, by genital dystrophy, by osteoporosis, by vascular hypertension, and so on, has been found at autopsy in six out of eight instances to be associated with a pituitary adenoma which in the three [now five (*cf.* addendum)] most carefully studied cases (Cases 6, 7, 10) has been definitely shown to be composed of basophil elements, the lesion in one instance (Case 7) having been clinically predicted before its post-mortal verification.[47]

CONCLUSIONS

Of all subjects that engage the attention of the profession at the present day, that of endocrinology particularly lends itself to the temptation of impressionistic speculation. During the past ten years, innumerable syndromes of so-called polyglandular type, some of them bearing a certain resemblance to that under consideration, have often been described in print. Examples of "diabetes in bearded women," of rapidly acquired obesity, of hypertension, of masculinization in the female and of sexual precocity in children of either sex, often associated with hyperplasias or tumors of one sort or another of the suprarenal glands, have been so many and varied as to baffle analysis.

Some of these syndromes have unquestionably been due to cortico-adrenal tumors and in not a few instances, indeed, such a tumor has been removed at operation with definite amelioration of symptoms. What is more, in similar states suprarenal tumors have been found after death in the absence of any recognizable abnormality in the pituitary body, though

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[46] *Cf.* Smith and Engle, 1927, *loc. cit.*

[47] Since Erdheim and Stumme's classical paper (Über die Schwangerschaftsveränderung der Hypophyse. [III. Adenome der Hypophyse.], *Ziegler's Beitr.*, 1909, XLVI, 1–132), no one appears to have made a systematic search for the presence of adenomata in supposedly normal pituitary glands. These authors found adenomas in approximately one out of ten of the glands that were serially sectioned.

all too often the protocol refers to the examination of this structure either in the briefest terms or not at all.

While there is every reason to concede, therefore, that a disorder of somewhat similar aspect may occur in association with pineal, with gonadal, or with adrenal tumors, the fact that the peculiar polyglandular syndrome, which pains have been taken herein conservatively to describe, may accompany a basophil adenoma in the absence of any apparent alteration in the adrenal cortex other than a possible secondary hyperplasia, will give pathologists reason in the future more carefully to scrutinize the anterior-pituitary for lesions of similar composition.

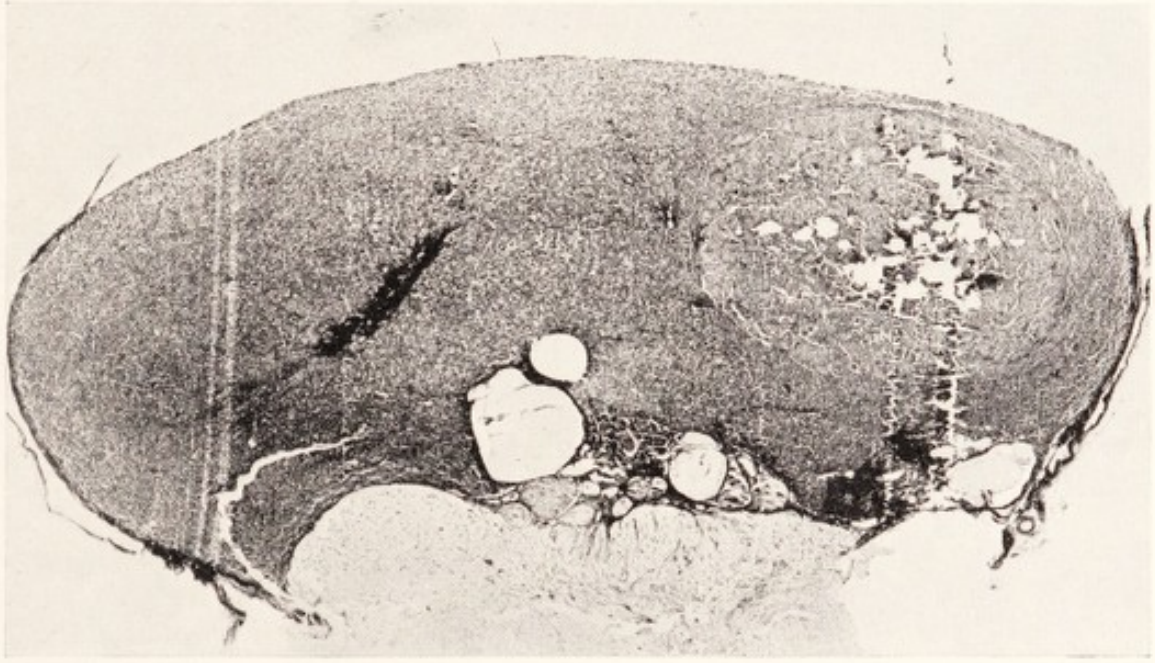


FIG. 64.—Pituitary body of Dr. Anderson's patient (Case 3) showing on coronal section the laterally situated (to right) basophilic adenoma (van Gieson, ×9). Compare Figs. 65 and 66.

[*ADDENDUM*]*

PITUITARY BASOPHILISM

Since the publication of the foregoing paper, new facts have come to hand which serve further to strengthen the views therein expressed. Through the kindness of Dr. Anderson, it has been possible to examine microscopical slides of the pituitary body of Case 3, (pg. 125), the adenoma being unmistakably of basophil type. Its size and situation as well as that of the associated adrenal adenoma are shown in the accompanying illustrations (Figs. 64–67). Had this been an isolated example of the syndrome in question, it might well enough have been ascribed to either of the tumors. It, however, is the only instance in the series in which an actual

* Reprinted in part from *Jour. Amer. Med. Assoc.* July, 1930.

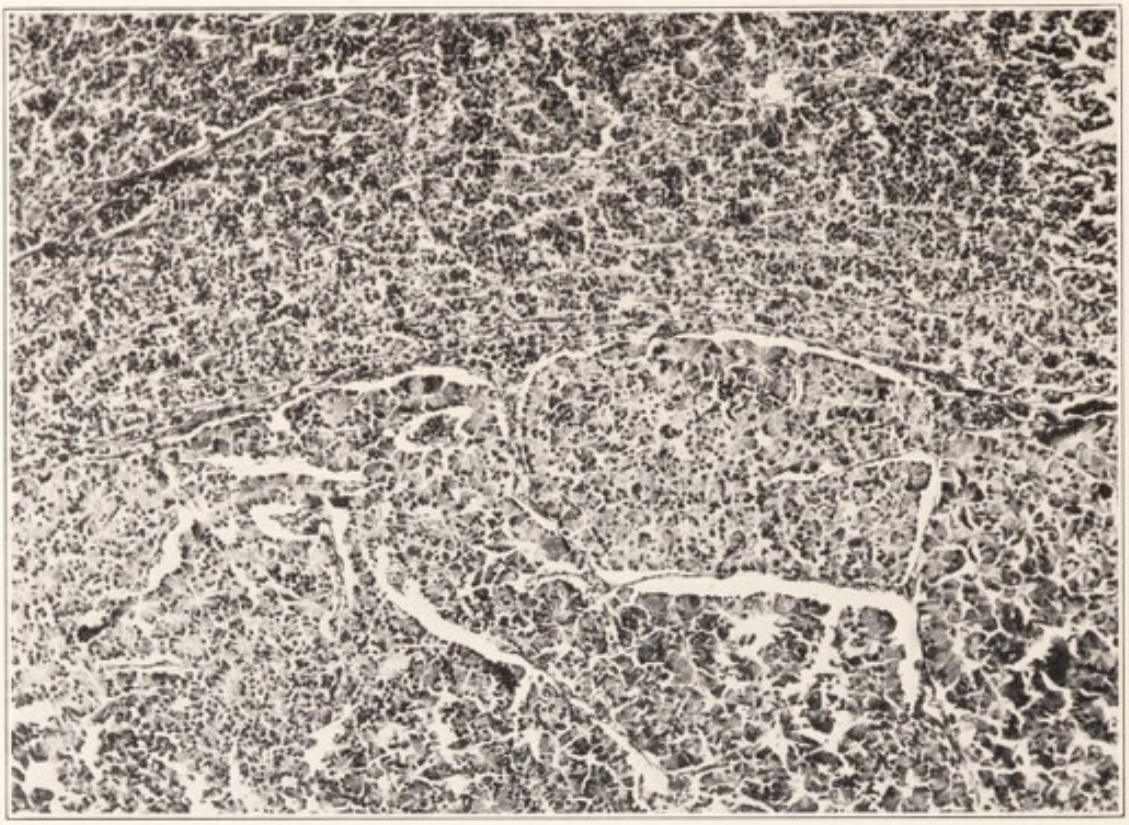


FIG. 65.—Case 3 continued: showing (mag. ×100) the margin of the adenoma below compressing the normal glandular structure above (*cf.* Fig. 64).

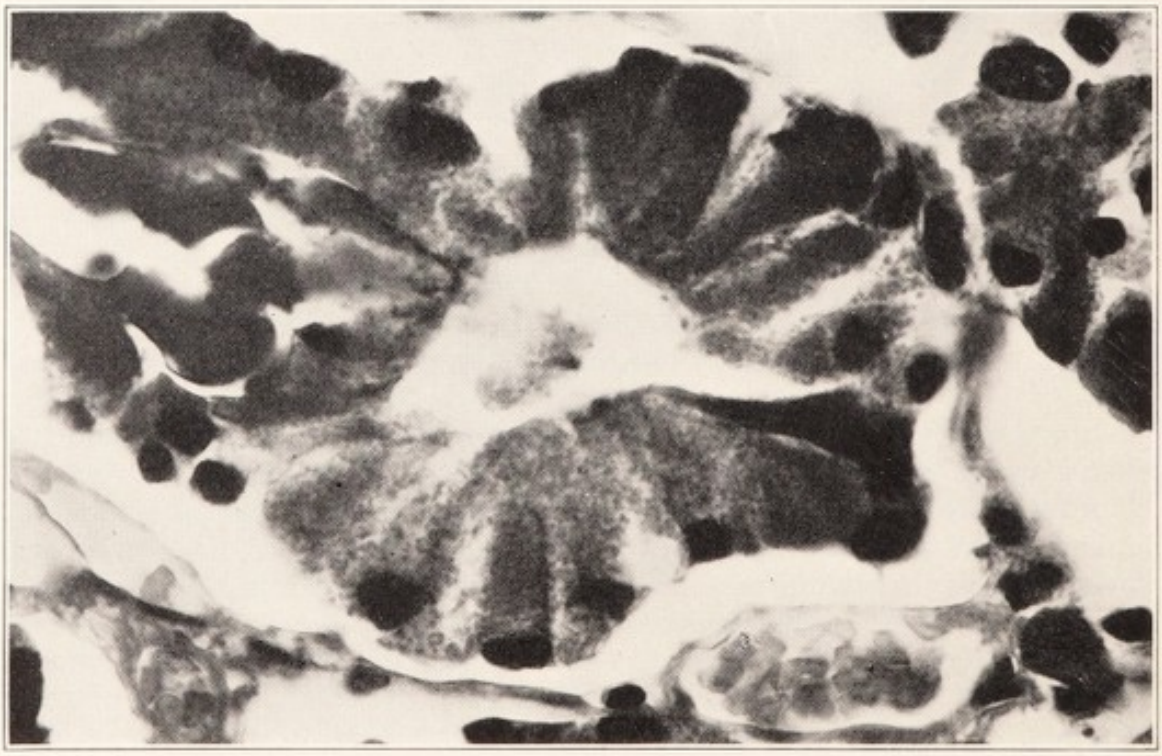


FIG. 66.—Case 3 continued: higher power (×850) of basophil adenoma, to show the alveolar arrangement of the highly granular cells. Note peripheral disposition of nuclei.

adenoma of the adrenal cortex was observed. Adenomatous tumefactions of the adrenal cortex, as is well known, are a not uncommon accompaniment of the chromophil adenomas of acromegaly, and no one regards acromegaly as primarily an adrenal disorder.

Dr. Wieth-Pedersen has also forwarded blocks of the tissues from Case 12. The pituitary tumor is a large one and, as his description indicated (*cf.* pg. 155) has none of the histological characteristics of a basophil adenoma; it appears rather to be an adenoma composed of peculiar nongranular elements. This, while disappointing, does not necessarily mean that there may not have been a minute basophil adenoma somewhere in the periphery of the intrasellar mass. To determine this would have

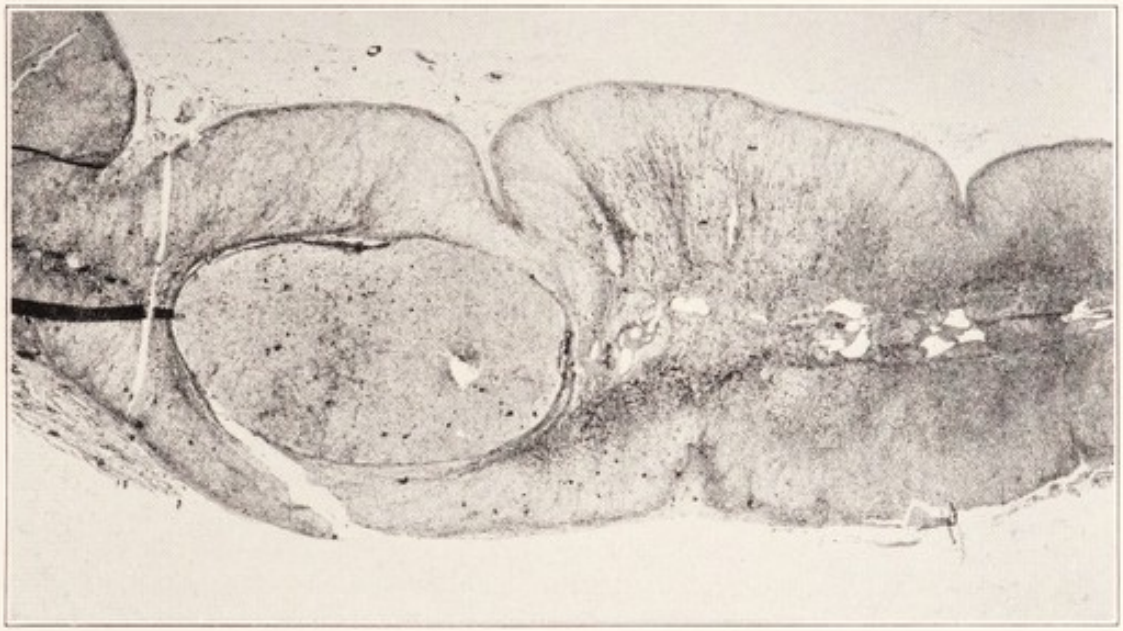


FIG. 67.—Case 3 continued: showing (×9) the adenoma of the adrenal cortex.

necessitated complete serial sections of the entire growth, only a thin slab of which had been preserved.*

Information that is of greater value has been acquired from the following additional cases. To the first of them my attention had been called while the original paper was being put together. It would have been included therein had not the photographs of the patient been somewhat unconvincing and had not the pituitary body been described as showing no abnormality. The case was reported† by Professor Julius Bauer of Vienna as an example of overfunction of the adrenal system "without anatomical findings," and I have his kind permission briefly to report it again from another angle.

* It has not been possible to get any further information regarding the pituitary body of Cases 2 and 4, and since Professor Busse's death the tissues of Dr. Mooser's patient (Case 9) have unfortunately been thrown away.

† Bauer, J., "Überfunktion des gesemten Nebennierensystems ohne anatomischen Befund," *Wien. klin. Wchnschr.*, 1930, XLIII, 582–586.

Case 13. [Professor Bauer's patient.] **Rapidly acquired plethoric obesity with hypertrichosis and amenorrhoea. Vascular hypertension. Cutaneous pigmentation. Glycosuria. Clinical diagnosis adrenal tumor; exploratory operation; fatality. Autopsy: ductless glands, apart from ovary, normal. [Predicted basophil adenoma subsequently verified].**

A married woman, 36 years of age, first came under observation in *November 1929*. For 18 months, striking changes had occurred in her appearance. She had gained 33 pounds (15 kgm.) in weight and been obliged to shave because of a growing beard. At the same time, there had been loss of hair on the scalp. Menstruation, from the age of 11 always scanty and irregular, had ceased completely for five months. She complained of pains in the lower spine.

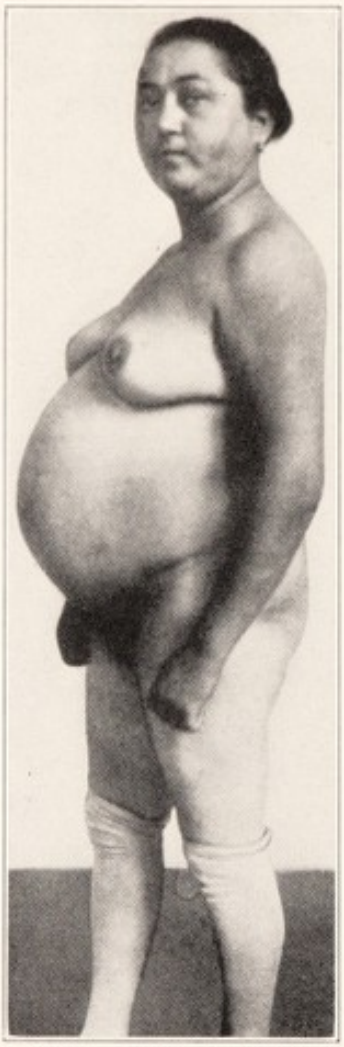


FIG. 68.—Case 13. Dr. Bauer's patient.

Status Praesens.—An adipose woman, height 155 cm. (5 ft. 1 in.), weight 71.5 kgm. (157 lbs.) with extremities disproportionately thin for her face and trunk (Fig. 68). The skin was pigmented, coarse, dry, furunculosed, and the extremities showed cutis marmorata. On both sides of the abdomen were prominent veins (*sic*). Hypertrichosis was present on lip, chin, cheeks, forearms, sacral region and breasts. There was diffuse alopecia of the scalp. The round "moon-face" was cyanotic and the conjunctivae injected.

The pulse ran between 104 and 120; the blood-pressure 175/110 to 185/120. The urine contained traces of albumin with no demonstrable renal elements; renal function was normal. The blood showed 5,290,000 erythrocytes; haemoglobin 93 per cent (Sahli); leucocytes 12,500 with 78 per cent polymorphonuclears. Blood sugar 116 mgm. per cent; nitrogen 34 mgm. per cent; cholesterin 195 mgm. per cent. A sugar tolerance test showed an exceedingly low threshold to 100 grams of dextrose with prolonged hyperglycaemia increasing to 282 mgm. per cent in two hours with persisting alimentary glycosuria for forty-eight hours. Basal metabolic rate +28.7 per cent repeated.

The case was looked upon as an example of overfunction of the adrenal system. Pyelograms (uroselectan) were taken and showed an enlarged renal pelvis on the right with normal calyces.

On *December 16*, an exploratory operation disclosed no palpable abnormality of right kidney or ureter. The right ovary was found to be slightly enlarged and was removed. The patient developed erysipelas and died ten days later.

Autopsy (Professor C. Sternberg).—This "gave not the slightest explanation for the peculiar disease." The fat deposits in the abdominal walls, omentum and mesentery were striking. The *hypophysis* was of normal size and without change (*sic*). The *thyroid gland* was not enlarged. Both *suprarenal capsules* were thin

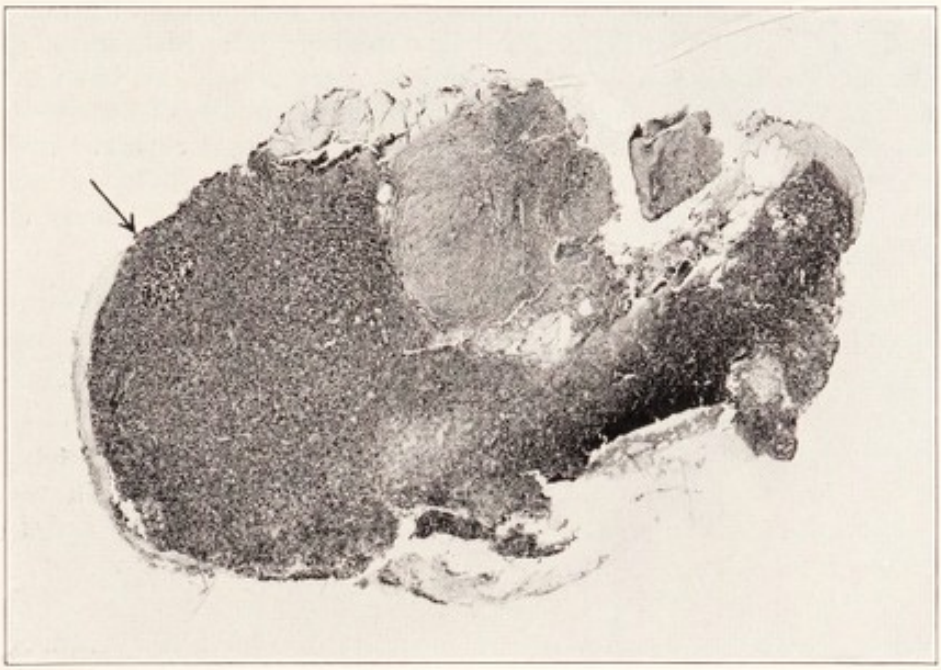


FIG. 69.—Case 13. The Bauer-Sternberg case showing (×9) the minute basophilic adenoma (arrow).

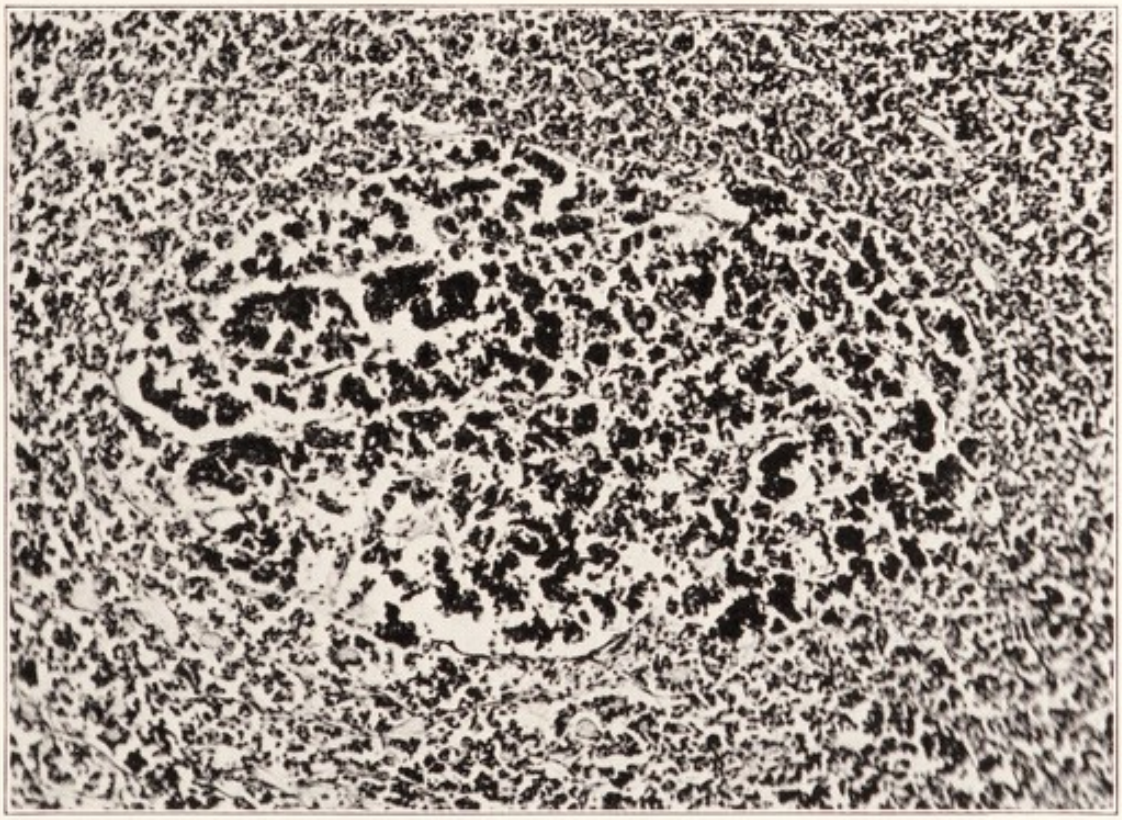


FIG. 70.—Case 13. The minute papillary adenoma of basophilic elements (*cf.* Fig. 69) from The Bauer-Sternberg case (mag. ×100). Kindness of Professor Sternberg.

and revealed a small zone of colloid. The *pancreas* was normal. The left *ovary* was the size of a cherry, the surface being nodular. The *histological findings* were essentially negative, apart from the left ovary which had been removed at operation. This showed a small, faintly yellowish nodule, of hemp-seed size, which was thought possibly to represent aberrant adrenal cortex. [The bones unfortunately were not made a particular object of study though it was subsequently learned that the patient had a cervico-dorsal kyphosis ("runde Rücken") such as is commonly seen in fat people.]

On the basis of this minute lesion in the ovary, taken in conjunction with what information the literature afforded, the case was looked upon by the author as an expression of adrenal overfunction. In response to a letter of enquiry, Professor Sternberg was kind enough serially to cut the pituitary body which fortunately had been preserved. To his expressed surprise no less than to my gratification the predicted lesion was disclosed. Though small in size, it shows a typical papillary basophil adenoma (*cf.* Figs. 69, 70).

Dr. R. C. Moehlig of Detroit has written to me in regard to an equally convincing unreported example of this malady in which he had recognized the nature of the lesion and its probable relation to the syndrome in question before my paper was published. He has kindly given me permission briefly to report the case as follows:

FIG. 71.—Dr. Moehlig's patient.

Case 14. [Dr. Moehlig's patient]. **A middle-aged, bearded woman with plethoric obesity, hypertension, purpuric ecchymoses, erythraemia, hyperglycaemia, azoturia (?), high basal metabolic rate. Thyroidectomy with fatality. Autopsy: Basophil adenoma.**

A woman, 44 years of age, came under observation at the Harper Hospital in *June 1931*. She had been operated upon nine years previously for a uterine tumor, a complete hysterectomy and bilateral oöphorectomy having been performed. Following is a description of the symptoms which she showed at the time of her hospital admission:

She was a plethoric woman of masculine appearance; her face was livid, and a real beard was present (Fig. 71). She was affected with marked nervousness, dizziness, hot flashes, acroparaesthesias, and headaches accompanied by vomiting. She had joint pains and purpuric tendencies. She weighed 135 lbs. (best weight 150 lbs.) and was 5 feet tall; pulse 140. The systolic blood-pressure ranged from 190 to 230.

She had a definite goitre of adenomatous type; the heart was enlarged to the left; she had striae atrophicae on the abdomen; her eyes were quite prominent and the hair on the abdomen was masculine in distribution. She also had marked hirsutism of the arms and legs. Ecchymotic spots would appear spontaneously under the skin. Her hands and feet were small compared with the rest of her body.

The Wassermann reaction was negative. The urine was normal except for a few pus cells. The blood showed 6,800,000 erythrocytes, 106 per cent haemoglobin; platelets 428,000; clotting time three minutes; bleeding time two minutes. Blood sugar 200; nitrogen 27.3; blood calcium 12 at one test, 9.98 at another (all figures in mgm. per cent). The cranial roentgenogram showed a normal sella without evidence of increased intracranial pressure. Basal metabolism was +31 at one test and −1 at another.

Her "goitre symptoms" were so prominent that on *June 13* a subtotal thyroidectomy was performed, the gland having been found enlarged, firm, and

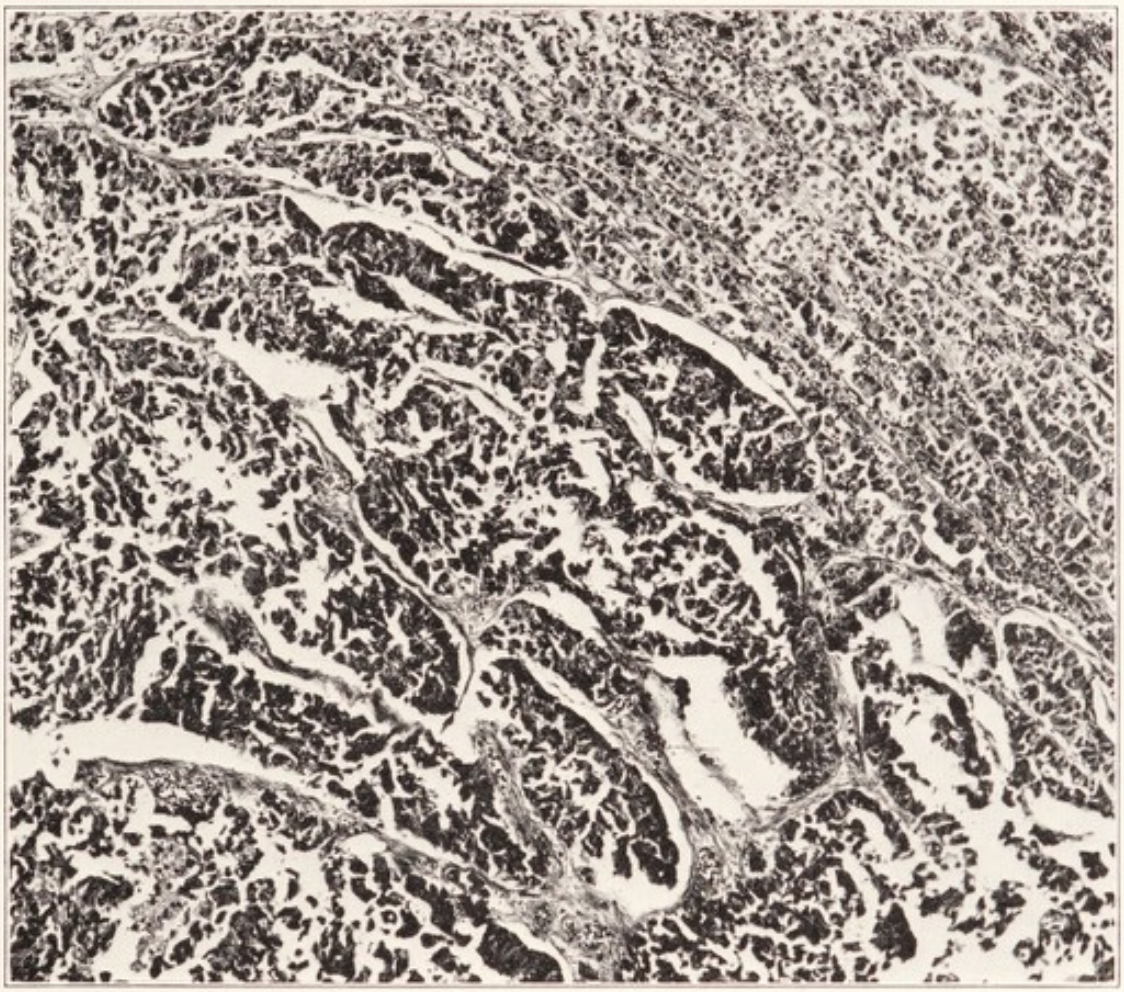


FIG. 72.—Case 14. Margin of papillary basophilic adenoma from Dr. Moehlig's patient (hematoxylin and eosin, ×100).

adenomatous. She subsequently developed a psychosis with convulsive seizures and died sixteen days later from myocardial failure. The post-mortem examination was limited to the brain. The pituitary body was found to be slightly enlarged and on section showed a small circumscribed whitish-gray adenoma about 2 mm. in diameter.

Sections of this tumor have kindly been sent to us by Dr. Moehlig and they show a typical basophil adenoma (Figs. 72, 73).

The age attained by this patient indicates that the malady is not confined, as had been assumed, to comparatively young persons. In the two

following examples, the symptoms, as in Case 5 and Case 8, had dated from preadolescence, and in neither of them has the lesion been histologically verified. Its nature nevertheless may be safely predicted from the general information so far acquired.

For calling my attention to the first of these final cases acknowledgment is due to my medical colleague, Dr. Reginald Fitz; to Dr. L. F. Davenport, the medical interne, I am indebted for his record and preliminary studies made before the young woman was transferred to the surgical service. The case is important in that it is the first (with the pos-

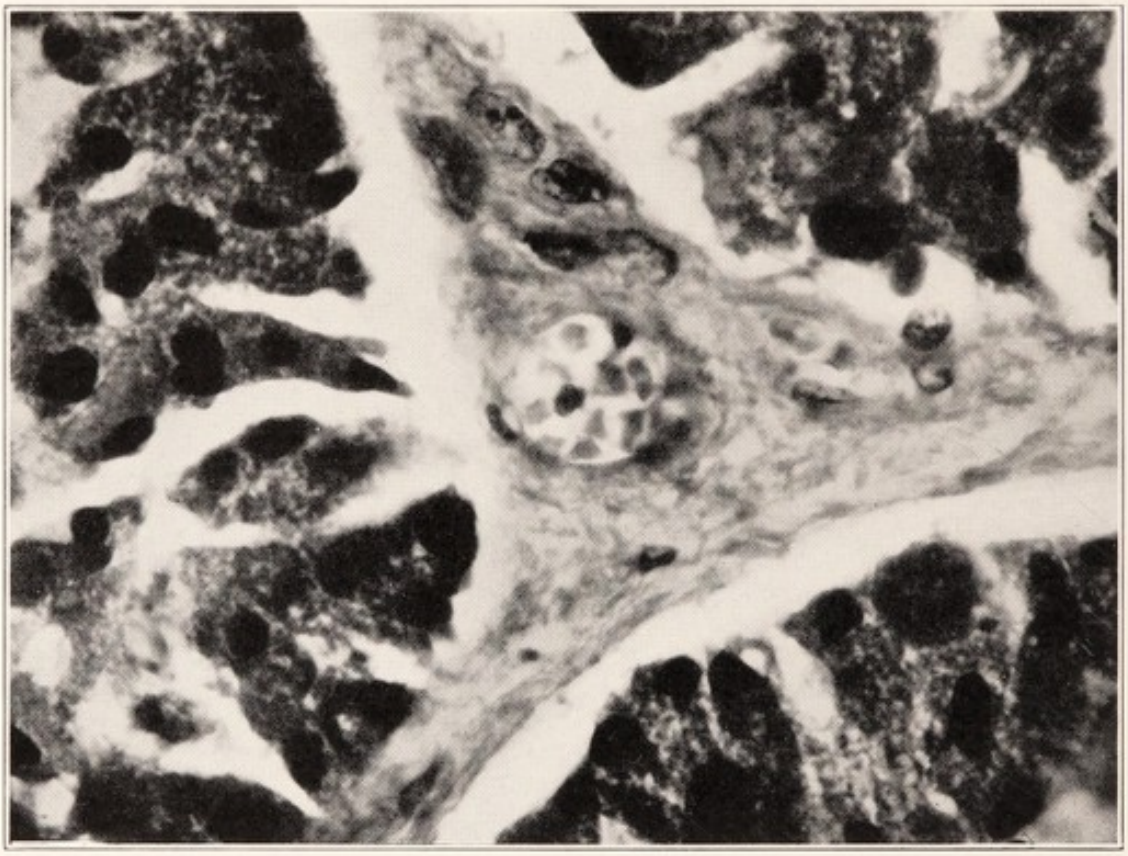


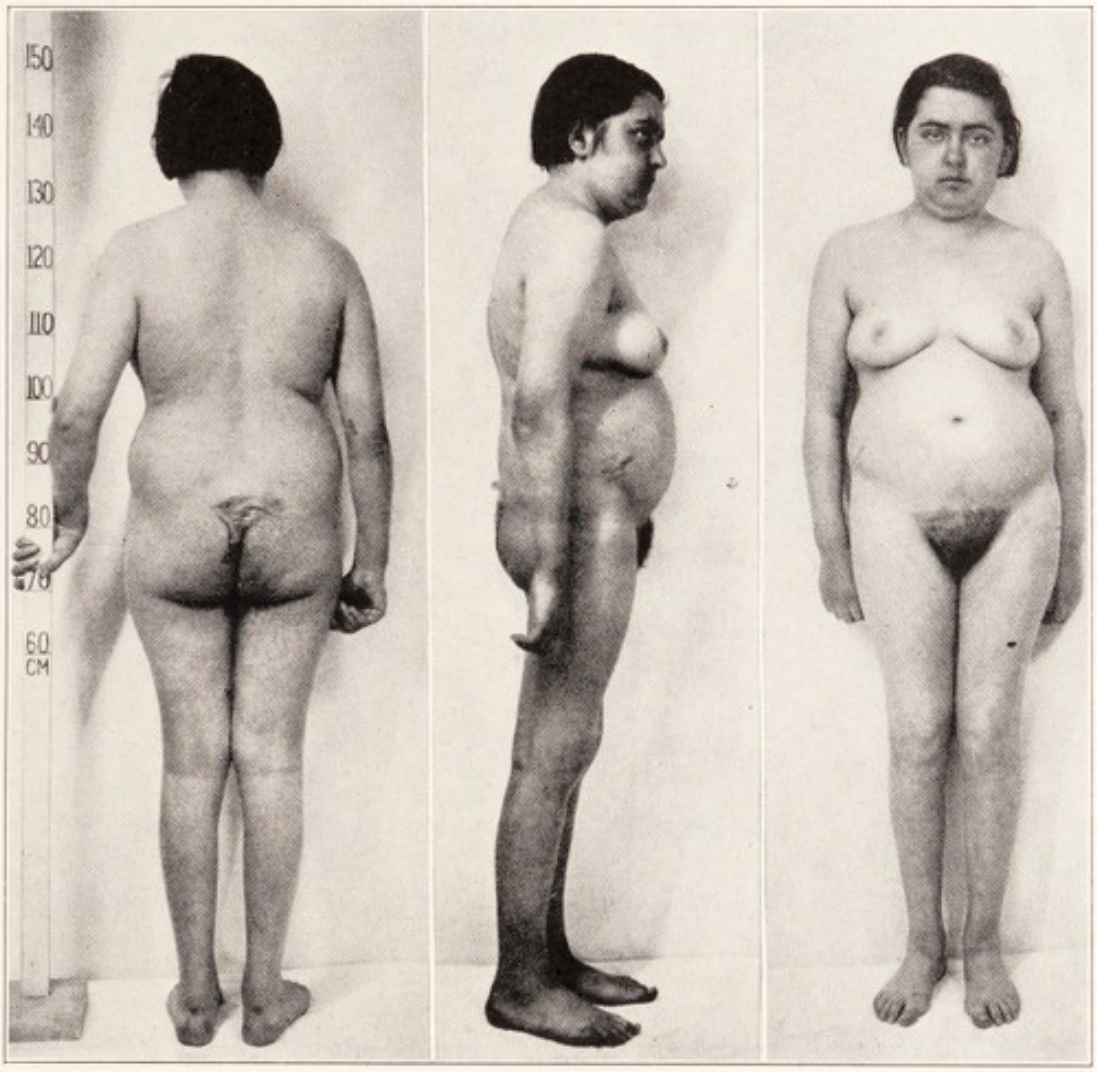
FIG. 73.—Case 14. To show on higher power (×850) the type of highly granular and vacuolated basophilic cells radiating off from a papillary stalk (*cf.* Fig. 72).

sible exception of Case 9) in which roentgenologically demonstrable changes in the vertebral bodies have been detected, accounting for loss of height and upper thoracic kyphosis.

Case 15. (P.B.B.H. Surgical No. 40886). **Precocious adolescence followed by amenorrhoea. Hypertrichosis, acrocyanosis, and purplish striae. Vascular hypertension. Recent convulsions. Roentgenological evidence of vertebral softening with collapse. Increased calcium elimination. (?) Perirectal abscess. Radiation of pituitary body. Marked improvement.**

Alice D., aged 15, was admitted to the Brigham Hospital, *March 29, 1932*, chiefly because of what was taken to be an infected pilonidal sinus. When about 8 years of age, following an appendectomy, she acquired a voracious

appetite and began to grow fat. At 10 years of age, normal menstruation set in with acquirement of secondary sex characters. In 1927, because of recurrent attacks of sore throat, a tonsillectomy had been performed. Her weight at that time was 103 pounds, height 50 inches. In 1928, she weighed 122 pounds; in 1929, 137 pounds; and in 1930, she was said to weigh 170 pounds which under a dietary régime was reduced to 137 pounds. In *April 1930*, her previously normal menstrual periods abruptly ceased. Her basal metabolic rate at the time was reported as −28 per cent.



FIGS. 74–76.—Case 15. Note plethoric adiposity sparing limbs, attitude from early kyphosis, acrocyanosis, early abdominal striae, etc.

For the prior two years, she had been under the care of a local physician. She was once put on a pituitary régime which apparently aggravated her symptoms. In *December 1931*, she had a sudden convulsion on the street and was taken home unconscious. She subsequently attended the ambulatory clinic of the Brigham Hospital where she was found to have a basal metabolic rate of −33 per cent, and she was given thyroid extract and referred to the obesity clinic. On *February 29*, a month before admission, she again had another convulsive attack and the local doctor found glycosuria.

Examination.—This showed a coöperative and intelligent girl complaining of headache, lumbar backache, and an ischiorectal infection. Her height was 5 ft. (152 cm.); she weighed on admission 132 pounds (60 kg.). There was moderate adiposity chiefly of face, neck and trunk (Figs. 74–76). She was definitely round-shouldered. Her face was rather puffy and plethoric with hirsuties over lips, cheeks and chin, and definite thinning of the hair of the scalp. There was a fine growth of hair over thighs, arms, legs and back. The skin was dry, dusky, and scaly, and there was marked acrocyanosis. Numerous short purplish

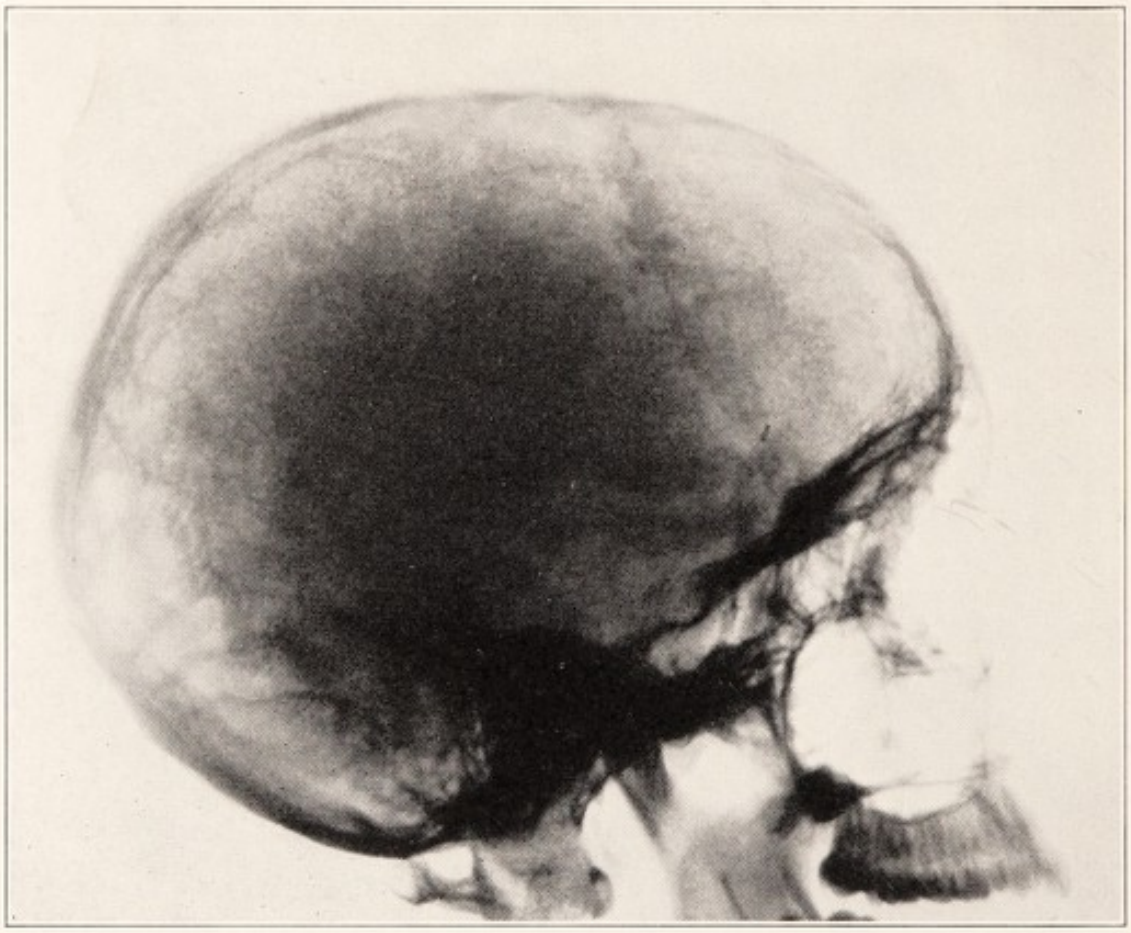


FIG. 77.—Case 15. To show characteristic mottling of skull also seen in Case 1.

striae were present, radiating from the groins onto the abdomen and there were many transverse reddish striae over the legs.

The blood-pressure averaged 140/110, the highest registration being 180/110. The ophthalmoscopical examination was negative. The basal metabolic rate was −22 per cent. She was found to have a low sugar tolerance, 100 gm. of glucose leading to a hyperglycaemia of 212.7 mgm. per cent after 60 minutes. Her fasting blood showed 4,880,000 erythrocytes; 9,400 leucocytes with 87 per cent polymorphonuclears; haemoglobin was 80 per cent; non-protein nitrogen 30.7 mgm. per cent; calcium 12.1 mgm. per cent; total protein 5.4 mgm. per cent; cholesterol 173 mgm. per cent.*

* The patient's sister used as a control showed blood cholesterol of 110 mgm. per cent.

Roentgenological studies showed (Fig. 77) a peculiar mottled atrophy of the bones, particularly apparent in the cranial vault (*cf.* also Case 1, pg. 120). The dorsal kyphosis was associated with compression of several of the vertebral bodies, more marked in the fifth and seventh thoracic (Fig. 78). There were six lumbar vertebrae, two of them, the fourth more particularly, showing definite compression (Fig. 79). In contrast to the general appearance of atrophy, the margins of the vertebral bodies appeared eburnated. The epiphyses of the long bones were normal for her age but appeared denser than normal. The humeri and radii showed mottling and enlargement of the trabeculi and thinning of the cortical portion of the bones. Similar changes were present in the ribs. The heart on measurement was definitely enlarged.

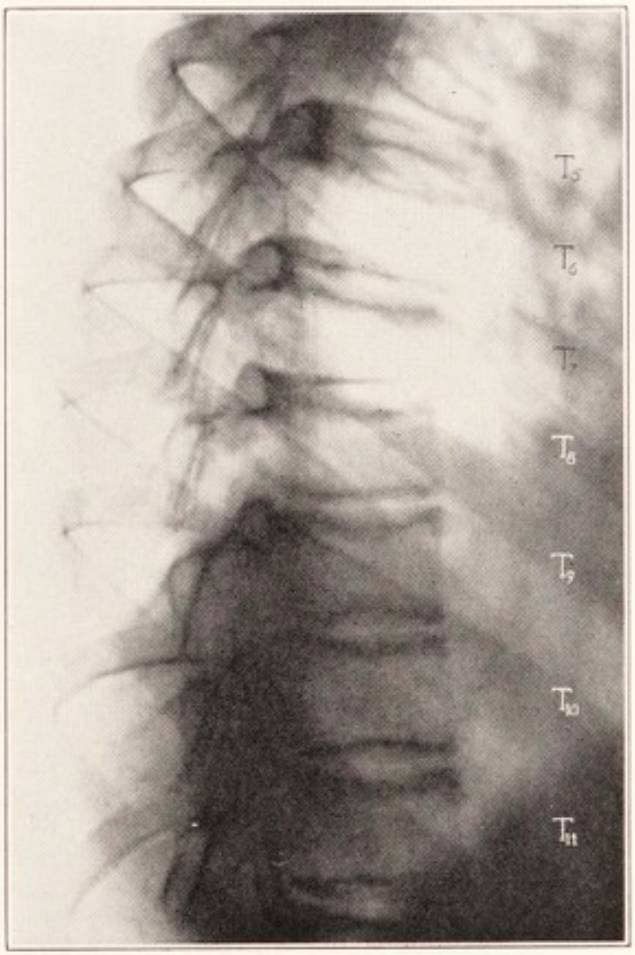


FIG. 78.—Case 15. Showing absorption and collapse of thoracic vertebral bodies more notable in Tv and Tvii.

In view of the apparent decalcification of the bones and the estimated increase in blood calcium, my colleague, Dr. J. C. Aub, kindly offered to investigate this matter in greater detail. Accordingly, on April 10, she was transferred for ten days to the Huntington Memorial Hospital where the previously estimated increase in blood calcium was not substantiated, the serum calcium being 9.8 mgm. and serum phosphorus 2.7 mgm. per cent. However, a surprizing increase in calcium output was found. Dr. Aub's personal note follows:

She was given a neutral diet containing only 100 mg. of calcium daily. After a preliminary equilibrium was established, we studied her excreta for two periods of three days each. She showed herself to be in nitrogen and phosphorus balance. Her calcium output, however [*viz.*, 840 mg. in the urine and 480 in the faeces], was far in excess of our normal figures for this diet, which are 186 mg. of calcium in the urine and 386 mg. in the faeces per period.

In the course of these tests, it was observed that an abnormal amount of fat was being excreted, and though this deserved more thorough study the patient was becoming restive over her prolonged hospitalization and she was readmitted to the Brigham Hospital.

On *April 21, 23, 25* and *26*, she was given a series of deep x-ray treatments with prompt improvement in her general condition. From constant complaints of headache, lumbar pains and general indisposition, she became alert and interested and soon was engaged in helping the nurses in their ward work. She remained under observation until *May 7*, no striking change having been observed other than an apparent tendency to a lowered blood-pressure, and a definite diminution of her former plethora both of face and extremities.

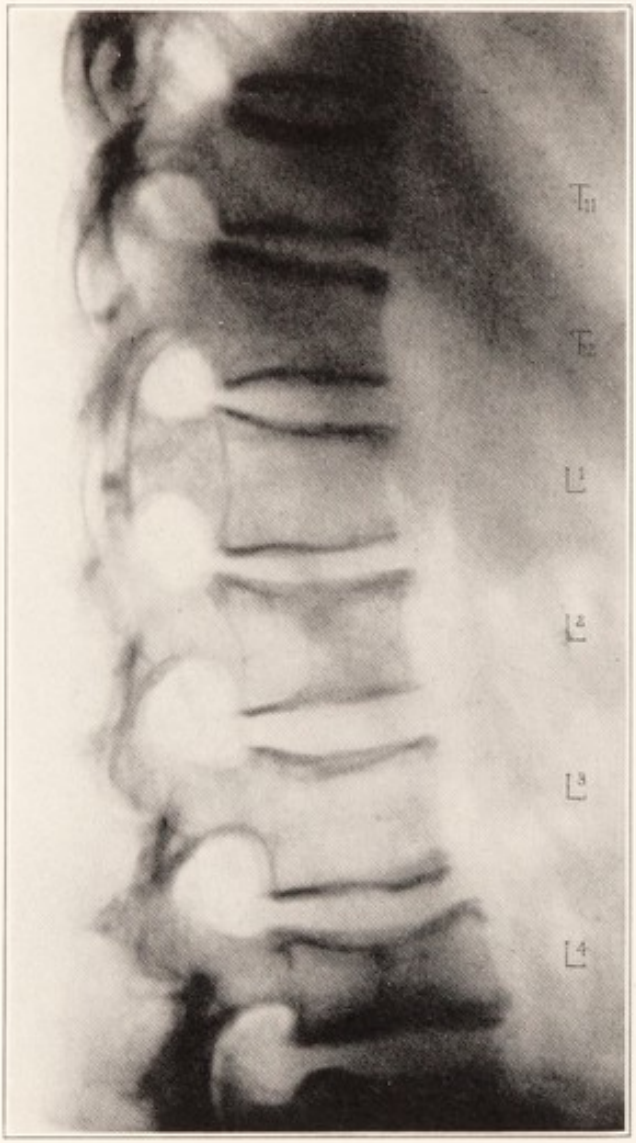


FIG. 79.—Case 15. Showing absorption of lumbar vertebral bodies with beginning collapse of LII, more advanced in LIV (Reduced ½).

She reported weekly to the hospital and though far better than she had been for a long time and anxious to return to school, so little change in the blood conditions and in degree of adiposity had taken place, she was given another series of treatments on *May 27*. The chief improvement at the present writing (*August, 1932*) has been in her subjective unaccustomed sense of well-being. There has been an apparent diminution of the hirsuties of the face and she is less plethoric in appearance; but she continues to gain weight and the abdominal striae are progressively increasing.

Another case of similar sort, likewise looked upon as probably of adrenal origin, has just been briefly reported for Dr. A. G. Maitland-Jones by Dr. R. W. B. Ellis of the London Hospital.*

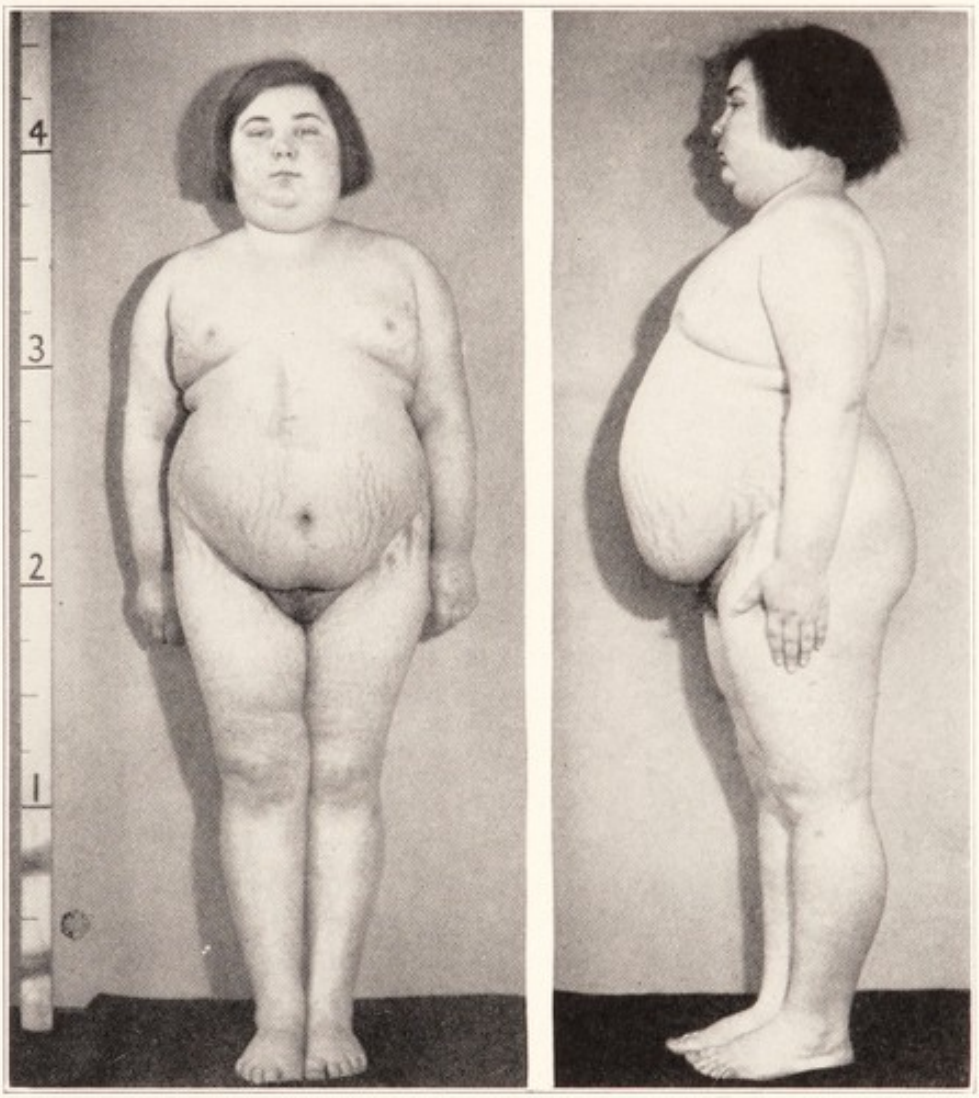
Case 16. [Dr. Ellis' patient]. **Preadolescent plethoric obesity. Precocious secondary characters of sex without menstruation. Abdominal striae. Diagnosis adrenal hyperplasia. Exploratory laparotomy.**

The patient, a girl 12 years of age, had first come under observation two years previously owing to marked gain in weight with early appearance of the secondary characters of sex. The obesity rapidly increased, being chiefly limited to face, neck, shoulders and abdomen. Striae appeared in the loins with pubic

* Ellis, R. W. B., "Obesity and Hirsuties of (?) Adrenal Origin," *Proc. Royal Soc. Med.*, March 1932, xxv, 722–724.

hair of male distribution. The pituitary fossa showed no abnormality; the visual fields and eye grounds were normal.

The patient was admitted to hospital because of pain in the left loin. Her weight was 104 pounds; height 4 ft. 4 in. (132 cm.); her face was "rubicund" (Figs. 80, 81). There was definite hirsuties over back of shoulders and arms. Blood-pressure registered from 130/95 to 150/80 with an accentuated aortic



FIGS. 80–81.—Dr. Ellis's patient aged 12; with premised adrenal syndrome. Striae in loins, thighs, and breasts. Scar of recent exploratory operation. Pubic hair of male distribution.

second sound. Blood urea was 21 mgm. per cent; blood phosphatase 0.435; inorganic phosphorus 2.75 mgm. per cent.

On the assumption that the syndrome indicated an adrenal hyperplasia, a laparotomy was performed but no tumor found, a satisfactory exposure owing to extreme obesity being difficult. Skiagrams showed a calculus at the lower end of the left ureter, which was passed spontaneously. Subsequently her weight increased to 134 pounds, and the striae atrophicae over loins, breasts, shoulders and thighs became more marked. Hirsuties also appeared on chin and lip and

around nipples and umbilicus. Differential blood count: erythrocytes 4,500,000; haemoglobin 80 per cent; leucocytes 11,600 with 75 per cent polymorphonuclears. Sugar tolerance essentially normal.

What this patient may ultimately show is uncertain. Dr. Ellis writes me that there is no roentgenological evidence of osteoporosis. It has been suggested that the effects of radiotherapy be tried.

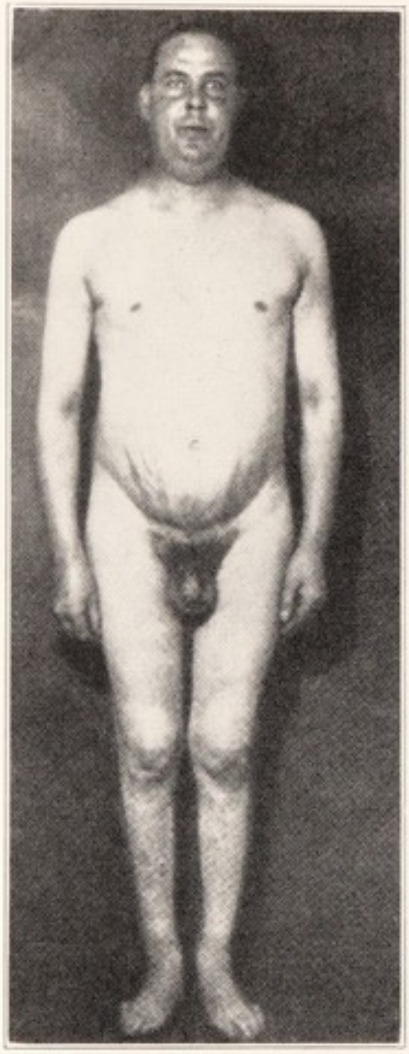


FIG. 82.—The Leyton-Turnbull-Bratton case, associated with carcinoma of the thymus (*cf.* Figs. 50 and 55).

These four additional cases, two of them with proven basophil adenomas, bring the number of verified examples in the series up to six (Cases 3, 6, 7, 10, 13, 14) out of the ten fatal cases with autopsy. In two instances (Cases 4, 12) the adenoma remains undifferentiated; in two others (Cases 2, 9,) the gland was said to be normal, and the possibility of verification unfortunately is now excluded.†

In view, therefore, of the presumed rarity of adenomas of basophil type, the finding of six examples in this short series would seem to represent too large a percentage for the relation of the lesion to the syndrome to be merely circumstantial.

So far as the presumable beneficial effects of radiotherapeusis is concerned, it must be confessed that Dr. Woodyatt is sceptical regarding the influence of the measure in his patient (Case 11), and I may have pressed this more than perhaps was justifiable. The same may be true of the presumably beneficial effects of radiation in Case 15, as can be freely admitted. However this may be, the establishment of a clinical syndrome and its cause must usually precede effective treatment, and if my belief that the disorder is an expression of pituitary basophilism should be substantiated by further studies elsewhere, the most effective treatment for the condition can be left for further experience.

† The writer's attention has been drawn to an important paper by Otto Leyton, H. M. Turnbull and A. B. Bratton of the London Hospital (*J. Path. & Bact.*, 1931, XXXIV, 635–660) which had escaped notice. The authors cite two examples of the same, or of a polyglandular syndrome closely allied to that under discussion, each of them associated with primary carcinoma of the thymus. One of the patients whose photograph is here reproduced (Fig. 82) bears so close a resemblance to Cases 10 and 11 (*cf.* Figs. 50 and 55) it could scarcely be other than the same malady. It may not be overventuresome to predict that serial sections of the pituitary body, which was described as essentially normal, will reveal a basophil adenoma as it did in the Bauer-Sternberg case.

IV. Peptic Ulcer and the Interbrain*

INTRODUCTION

THE generous founder of this lectureship, Dr. Donald Balfour, has recently reported the results of one thousand and more surgical procedures on the stomach and duodenum as conducted during the year 1930 in the famous Clinic to which he is attached. Sixty-five per cent of the operations were for acute, subacute or chronic, gastric, duodenal or gastrojejunal ulcers. Since it is reasonable to assume that only a small proportion of the patients with peptic ulcers of one sort or another

* Being the basis of the fourth Balfour Lecture, given April 8, 1931, at the University of Toronto.

that sought advice during this period were operated upon,* these figures indicate that the condition represents one of the most common maladies of the present day.

Until roentgenology and the opaque meal came to add a measure of precision to our clinical diagnoses, many ulcers naturally enough went unrecognized during life, but it is highly unlikely that they should have been similarly overlooked by pathological anatomists by whom forty years ago duodenal ulcer, at least, was looked upon as a rare disorder. What my colleague, Dr. Christian, has recently pointed out**—that the incidence of many maladies, commonly seen in his wards during the past fifteen years, has remained stationary or fallen off whereas gastric and duodenal ulcer have increased four-fold—can scarcely be ascribed wholly to improved methods of diagnosis.

Since the characteristic local lesion may be the only discernible evidence of disease to be disclosed after death, it has naturally enough been ascribed to purely local causes—vascular, traumatic, bacterial, biochemical or secretory. By various ingenious experimental devices, many have succeeded in producing acute peptic ulcers or erosions in the lower animals, and under certain circumstances the mucosal defects thus produced fail to heal. But it is only in man that ulcers occur spontaneously with any considerable frequency, and it is not at all improbable that the prevalence, particularly of duodenal ulcers, has something to do with the strain and stress of modern life; for people to-day rarely find it possible to lead the comparatively placid existence enjoyed by their forebears.

All clinicians are familiar with the facts: (1) that "highly strung" persons are particularly susceptible to "nervous indigestion" and associated ulcer; (2) that ulcers become symptomatically quiescent or even tend to heal when patients are put mentally and physically at rest; and (3) that symptoms are prone to recur so soon as the victim of the disorder resumes his former tasks and responsibilities. Though this emotional or psychic aspect of the ulcer problem, has been frequently emphasized in the past, the locus of the primitive emotions and their relation to parasympathetic discharges and vagotonia has only come to be partly understood in recent years. It is proper, therefore, at the outset to disclaim any pretense toward a novel explanation of the pathogenesis of ulcer. At the same time, the hope is expressed that what will be forthcoming may serve in a measure to reconcile the several conflicting hypotheses, many if not all of which doubtless contain certain elements of truth.

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* In a later issue of the weekly *Proceedings of the Mayo Clinic*, for October 7, 1931, Dr. H. R. Hartman states that in 1928 the diagnosis of gastric or duodenal ulcer was made in 2499 patients. In 2015 instances (90 per cent), the lesion was duodenal, in 224 instances (10 per cent) gastric, and in 27 cases (1 per cent), both gastric and duodenal ulcers were present. Of the duodenal ulcers, 797 (or 39 per cent), and of the gastric ulcers 155 (69 per cent), were operated upon.

** *Sixteenth Annual Report of the Peter Bent Brigham Hospital for the year 1929* pg. 139.

I. CASE REPORTS

What has incited my interest in the subject of ulcer has been the disturbing experience of having lost three patients from acute perforations of the upper alimentary canal soon after what appeared to be successful operations for the removal of intracranial tumors; and that each of these tumors happened to be situated in the cerebellum could not, it seemed to me, be other than of some significance. How to explain these occurrences was the difficult problem and in the attempt herein to do so, I may best proceed by first giving an account of the three distressing episodes.

A. ACUTE POSTOPERATIVE PERFORATIONS

These, as stated, in all three instances followed suboccipital operations for cerebellar tumors.

Case 1. (P.B.B.H. Surg. No. 3055).* **Cerebellar symptoms of six months' duration. Suboccipital exploration under ether anaesthesia. Enucleation of subcortical angioblastoma from right cerebellar hemisphere. Acute abdominal symptoms. Death in 24 hours from general peritonitis due to multiple perforations of the stomach.**

June 11, 1915. On the advice of Dr. C. C. Burpee, of Malden, Massachusetts, the patient, Alvar C., aged 34 years, a bank clerk, was admitted to the Brigham Hospital because of a choked disc and other evidences of brain tumor.

Past history.—He had had scarlet fever as a child complicated by an otitis media; also an attack of typhoid in his youth, but otherwise had always enjoyed good health until the onset of his present symptoms. He had been married nine years, had raised a family and was a man of exemplary habits.

Anamnesis.—In *December 1914*, six months before admission, he began having suboccipital headaches followed ere long by failing vision. In *March 1915*, his gait became unsteady and a month later he began to have attacks of morning vomiting accompanied by nausea. Diplopia, dizziness, and tremor of the hands had also been recently observed.

Physical examination.—Apart from the neurological signs, which were unequivocally those of a right cerebellar tumor with secondary hydrocephalus and choked disc, the examination was wholly negative. Regarding the abdomen, the record states that "no masses were seen or felt; no tenderness, muscle spasm or rigidity. Spleen and kidneys not palpable. Liver dullness extends to costal margin in midclavicular line. Percussion note everywhere tympanitic."

Operation.—June 17, 1915, 10 A.M. The patient was placed face-down in a comfortable position on the cerebellar table and anaesthetized by warm ether vapor, the Connell apparatus being used for its delivery through a nasal tube. The usual bilateral suboccipital exploration was made with exposure of both cerebellar hemispheres and removal of the bone comprizing the posterior half of the foramen magnum. To lower tension the left lateral ventricle was punctured before opening the somewhat tense dura. On reflecting the membrane a superficially placed, evidently benign tumor was disclosed in the centre of the right cerebellar field. The tumor, about the size of a golf ball, was readily enucleated intact owing to its smooth surface and definite capsule. The bleeding was trifling and easily controlled by a few clips. The wound was closed carefully in layers in the usual detail.

* This case has been briefly reported in another connection: Cushing and Bailey, "Blood-Vessel Tumors of the Brain," C. C. Thomas, 1928, Case XVII, pg. 124.

The anaesthetic had been given by Dr. W. M. Boothby with the Connell apparatus and was smoothly taken. The operation lasted just short of three hours and at its conclusion the patient was in good condition and there seemed to be no reason to expect anything other than an uneventful recovery.

Subsequent notes.—On first regaining consciousness (1:30 P.M.), while still in position on the operating table, the patient complained of feeling chilly and of abdominal discomfort. He vomited more than usual (a bile-stained fluid) and his bowels moved freely, the stool containing mucus streaked faintly with blood. After he was removed from the table at 3:30 P.M., he complained of increasing abdominal pain; the belly seemed somewhat stiff and tender to palpation but no especial significance was attached to the fact. During the rest of the afternoon, he continued occasionally to retch, vomit, belch and pass gas per rectum. He had also a peculiar grunting expiration which, however, was regular and without Cheyne-Stokes' rhythm.

He was finally taken to the ward at 6 P.M. His rectal temperature was then 102.4°. Owing to restlessness and further complaints of abdominal pain, he was given at 8:30 P.M. a sixth of a grain of morphia subcutaneously. Not long after this his pulse and respiration began to quicken and at 10:30 P.M. to quiet him he was given another one-sixth of morphia. From this time onward he became progressively worse; at 1:00 A.M. his rectal temperature was 104°. His appearance an hour later, when I was called to see him by my then assistant, Dr. E. B. Towne, reminded me of a state of "hyperthermic shock," whatever was meant by that.

My personal notes state: "2 A.M. He is conscious, alert and subjectively comfortable but breathing rapidly with an expiratory grunt; no rhythmicity about respiratory act; pulse very irregular, often barely perceptible and uncountable at the wrist. Extremities cold and clammy though he says they feel hot."

And again at: "5 A.M. Has slept off and on the past three hours on his morphia. No change in general condition. Has voided. Difficult to tell what is wrong. He is mentally clear and cheerful. The abdomen is slightly distended and so sensitive it cannot be touched without making him wince. This superficial tenderness suggests some spinal cord (referred pain) complication. To exclude the possibility of a postoperative clot a lumbar puncture has been made. Fluid found clear and not under tension."

"6:30 a.m. Definitely failing though remains conscious and clear. Pulse barely perceptible. The condition now looks more like a *general peritonitis* as from a perforative ulcer, a mesenteric thrombosis, or acute obstruction (though no vomiting since morphia) than any intracranial condition with which I am familiar."

He grew increasingly worse, became cyanotic and nearly pulseless and the end came at 10:15 A.M., just twenty-four hours after the start of the operation.

[It was subsequently learned from the patient's wife that on the day before his operation he had eaten some cake, brought to him by a visitor and this had disagreed with him. Indeed, so long as she had known him, he had aways had a poor digestion and would frequently regurgitate food "like a baby with an overfilled stomach." In 1903, he had had an atack supposed to be appendicitis with "stoppage" from which he had recovered without operation after discharging some dark material by the bowel.]

Post-mortem examination (Dr. J. L. Stoddard).—The unrestricted autopsy was held at 1:15 P.M., three hours after death. Apart from the recent operative

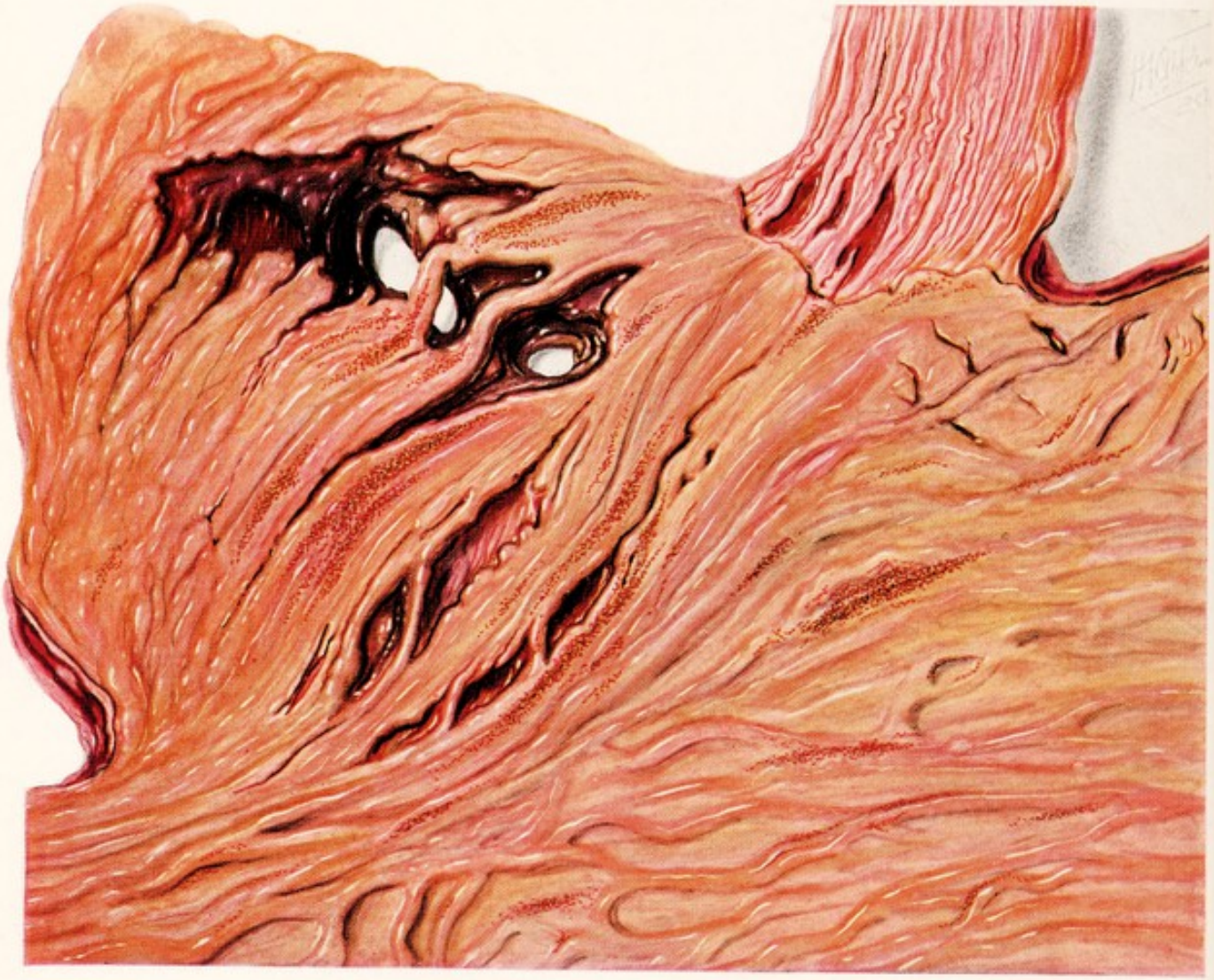

FIG. 83.—Case 1. To show gross appearance of mucosal surface of stomach and lower oesophagus. Note punctate haemorrhages, extensive haemorrhagic erosions, and three large perforations.

wound the intracranial conditions were normal. There was no evidence of clot or postoperative oedema.

The peritoneal cavity contained a large amount of turbid fluid with a generalized acute fibrinous peritonitis particularly marked in the upper abdomen. The stomach showed three circular perforations halfway between the cardia and pylorus on the lesser curvature (Fig. 83). About these perforations there were no indurations or indications of inflammatory reaction. On opening the stomach an acute process was disclosed resembling the acute gastritis of a corrosive poisoning. There were widespread submucosal haemorrhages and the mucous membrane in many places was so damaged the organ could readily have been torn by the fingers. The process was more marked in the cardiac half

FIG. 84.—Case 1. Typical punctate haemorrhagic erosion extending through submucosa (mag. ×15).

of the stomach and the lower portion of the oesophagus was likewise involved with longitudinal slits in the mucous membrane and submucosal haemorrhages. In certain areas, as at the site of the three perforations, the wall was actually necrotic throughout.

Microscopical examination (Prof. W. T. Councilman)—*Stomach*: Sections from the involved areas showed a normal mucosa with no degeneration of the glands though in places there was a slight infiltration with polynuclear cells. Sections from the margins of the mucosal rents showed evidence of haemorrhage into the coats as though torn by mechanical violence. The punctate areas in the fundus proved to be shallow, haemorrhagic erosions (Fig. 84) with marked oedema of the submucosa and a heavy infiltration of polymorphonuclear leucocytes involving all coats, even to the serosa, unmistakably an ante-mortem process.

In his further discussion of the case, Dr. Councilman expressed the belief that inflation of the stomach by ether vapor had produced the

rents in the mucosa. This view was regarded, however, as highly improbable for the Connell apparatus, which gives a measured percentage in tension of warmed ether vapor, had been utilized without accident of the sort in thousands of cases, many of them patients with cerebellar tumors. Several other possible explanations were considered: (1) for an acute corrosive poisoning there was no apparent source; (2) an agonal digestion of the stomach wall did not accord with the clinical evidences of peritonitis long before death; (3) the patient's face-down position on the operating table for many hours was considered as a possible cause only to be discarded.

At about this time, G. M. Smith[49] had shown that haemorrhagic ulcerations or erosions with necrosis could be easily produced when a combination of bile and 5 per cent hydrochloric acid were experimentally injected into the fasting stomach of animals. There had been no occasion to make a gastric analysis of the patient before the operation, but the history subsequently elicited suggesting that he had suffered from hyperacidity coupled with the fact that on recovery from the anaesthetic he had vomited an abundance of bile-stained fluid seemed therefore to offer the most plausible explanation of the lesions.

This harrowing experience, unsatisfactorily accounted for, was wellnigh forgotten when twelve years later it was vividly recalled by the series of events in the following case:

Case 2. (Surgical No. 30113). **Cerebellar-tumor symptoms of five years' duration. Suboccipital exploration under local anaesthesia temporarily supplemented by ether. Incomplete electrosurgical extirpation of large astrocytoma. Prolonged operation. Acute abdominal symptoms three days later with death on fourth postoperative day. Autopsy: multiple acute perforations of duodenum.***

George M., an engineer, 34 years of age, was admitted *November 16, 1927*, with the full-blown picture of a cerebellar tumor. Symptoms had occurred with the following chronology: For five years, dizziness on stooping with subsequent blurring of sight, also suboccipital stiffness and tenderness; for three years, occasional attacks of vomiting without nausea; for two years, increasing dysarthria and dysphagia, ascribed to the extraction of teeth; for eighteen months, loss of visual acuity; for ten months, staggering gait; for six months, increasing weakness of the right side; for three months, occasional "cerebellar fits" with retraction of neck, sweating, dizziness, and temporary unconsciousness; for two months, periodic diplopia.

Examination.—This showed: a bilateral choked disc of 5 diopters; marked ataxia and slight hypaesthesia of all extremities; sustained nystagmus to either side; left abducens palsy; marked static instability with tendency to deviate to the right; suboccipital tenderness; right astereognosis; dysphagia and dysarthria.

Operation. November 29, 1927.—The cerebellum was exposed by the usual bilateral crossbow incision with puncture of the dilated lateral ventricles. A median tumor was disclosed which grossly resembled an ependymoma but

* In a report on the cerebellar astrocytomas (*Surg., Gynec. & Obst.*, 1931, LII, 129–204), this is Case 53.

which proved to be a fibrillary astrocytoma. It had a long tongue projecting so far into the spinal canal that a laminectomy of the axis as well as of the atlas was necessary in order to expose its lower pole (Fig. 85). This forbidding growth was radically attacked but its extirpation was finally abandoned short of completion owing to respiratory difficulties set up by manipulations of the residual fragment which overlay the posterior floor of the ventricle.

The operation was started at 10:30 A.M. under novocain anaesthesia; at 12:50 P.M., because the handling of the tumor was causing the patient distress, inhalation narcosis was substituted. Owing to the tough, rubbery character of the growth it was removed piecemeal by electrosurgical methods, and the current was frequently in use during the three hours from 12:50 to 3:50 P.M. while the

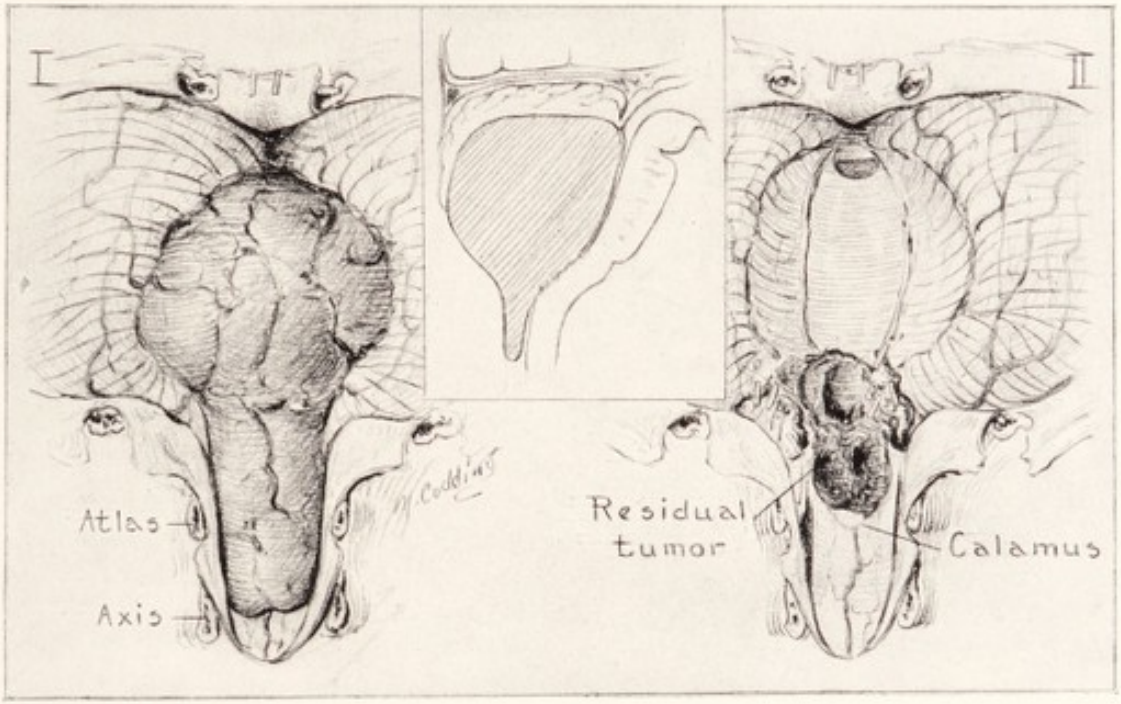

FIG. 85.—Case 2. Showing: I. Median astrocytoma with spinal tongue necessitating laminectomy of both atlas and axis for its exposure; II. the residual part of the tumor.

patient was under ether. The wound closure was not completed till 5:30 P.M. by which time consciousness had been wholly regained.

Postoperative course.—The patient was kept on the cerebellar table during the next several hours, for though his general condition was satisfactory, this position enabled the mucus and saliva, which he had difficulty in swallowing, to drain from his mouth. In two hours the rectal temperature had risen to 104.8 degrees. He was sponged and the temperature fell. At 11 P.M., he was removed from the table to bed. By 7:30 A.M., the next morning, he was thought to be out of danger and was returned to the ward: pulse 110, respirations 12, rectal temperature 101 degrees. He took liquid nourishment well though the pre-operative difficulty in deglutition was evidently increased. A lumbar puncture was performed, 35 c.c. of blood-tinged fluid not under tension being removed.

His condition appeared in every way to be satisfactory during the next two days until 4:15 P.M., *December 2*, when he had a sudden violent epigastric pain

which spread over the abdomen and into the shoulders. This was ascribed to a probable pleuritis and an attendant thought he heard a friction rub in the right anterior axillary line. Rectal temperature 102.4°. He soon became exceedingly restless and was given 10 mgm. morphia, which quieted him. The temperature continued to rise during the night and at 5:30 A.M., *December 3*, had reached 106.2°. There had been no vomiting and no suspicion of an acute abdominal complication was at any time aroused. The radial pulse became imperceptible and he died at 8:15 A.M. on this, the fourth postoperative day.

Post-mortem examination 4 hours after death (Dr. G. A. Bennett).—The brain showed a residual mass of non-adherent tumor deeply indenting and

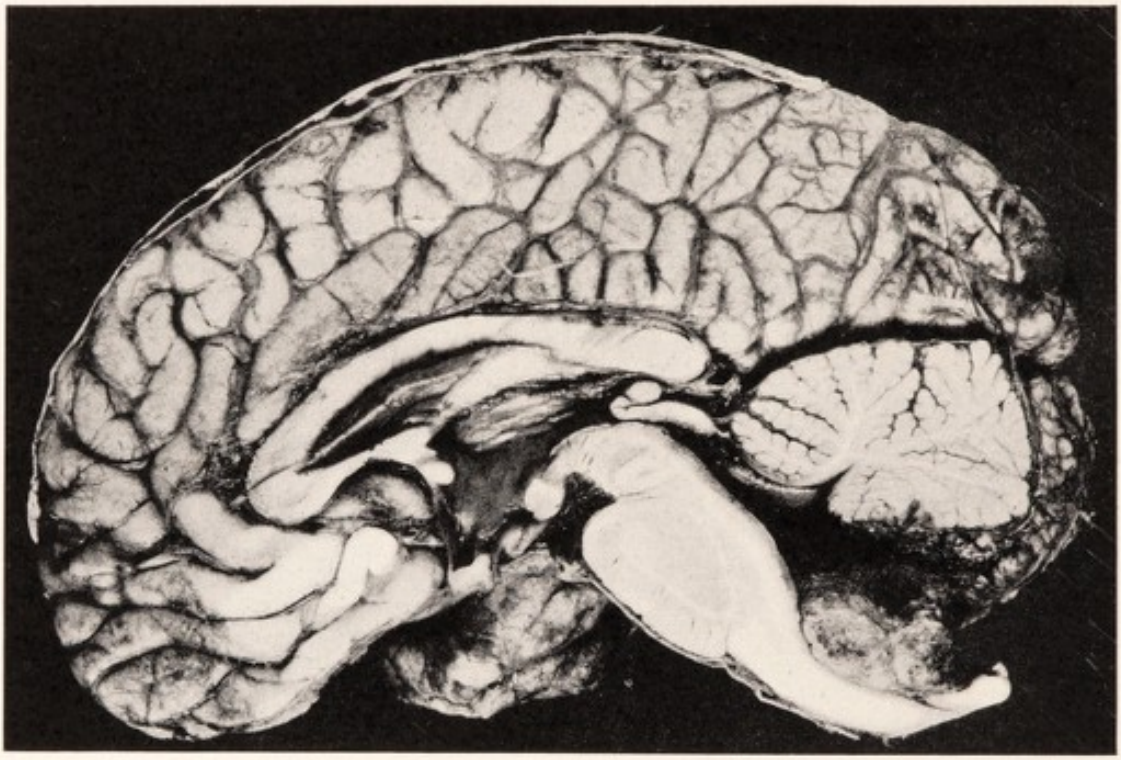

FIG. 86.—Case 2. Showing flattening and indentation of medulla by residual fragment of tumor.

flattening the medulla (Fig. 86). The lungs, apart from slight hypostatic congestion, were normal in appearance.

The *peritoneal cavity* was found to contain 1100 c.c. of a dark reddish-brown fluid. When this was removed a generalized diffuse fibrinoplastic peritonitis was disclosed. On separating the intestines, which were held together by the sticky fibrinous exudate, two perforations of irregular shape, through which the contents of the bowel were easily expressed, were found in the wall of the duodenum about 3 cm. distal to the pylorus (Fig. 5). The larger opening measured roughly 12 by 14 mm., the smaller 9 by 8 mm. Neither of them was indurated or showed evidence of a chronic inflammatory process. About 5 cm. farther down the duodenum were two shallow ulcerations or erosions in the mucous membrane, the larger of them measuring 8 by 4 mm. in diameter. The gastric mucosa, the ampulla of Vater, the pancreas and its ducts were all of normal appearance.

Microscopical examination.—Sections at the margins of the perforated areas showed merely a loss of structure with marked oedema and fibrin deposition.

Those taken through the erosions showed a completely destroyed mucosa which was replaced by an exudate of fibrin, inflammatory cells and blood; the submucosa and to some extent the muscularis were oedematous and heavily infiltrated with polymorphonuclear leucocytes, lymphocytes and fibroblasts. Homogeneous blue-staining thrombi, in which polymorphonuclear leucocytes were incorporated, were present in the capillaries, small arteries and veins, both of muscularis and submucosa. Occasional arteries of considerable size were surrounded by coarse-meshed fibrin. These features, in the opinion of the pathologists, were those constantly seen in duodenal ulcer and indicated that vascular thrombosis was the local cause of the lesions which were unmistakably antemortem in origin.

FIG. 87.—Case 2. Showing (slightly reduced) the perforations and erosions of the duodenum.

The operation in this case, as events proved, was ill judged, for the patient might have recovered had the tumor been left alone and the chance taken of providing symptomatic relief by decompressive measures. But this source of regret lies apart from the present discussion. What concerns us is the fact that here again was a fatality from a perforative peritonitis, wholly unsuspected during life. The attack of acute abdominal pain, which doubtless ushered in the process, was wrongly ascribed to a probable pulmonary complication brought about by the patient's deglutitory difficulties.

As in the first case, in an effort to explain the multiple perforations which here, to be sure, were duodenal rather than gastric, it was necessary again to consider: (1) the man's face-down position on the table; (2) the prolonged operative procedure; (3) the three-hour period of ether

anaesthesia with the Connell apparatus; and (4) the possibility of trauma in lifting the patient from the table. There was, moreover, the additional element of the powerful electrosurgical current that had been used with the negative electrode against the abdomen, the possible complications from which, in 1927, were unknown to us. Time, however, has shown from a multitude of other experiences that diathermy does not damage the nervous tissues, and though we have once seen a superficial burn due to imperfect contact of the large negative electrode against the skin, no other ill effects have ever been observed.

Here, then, was another distressing experience following a cerebellar operation with an early postoperative fatality due to multiple duodenal perforations for which there was no ready explanation. The account of a third episode of similar kind follows.

Case 3. (Surgical No. 30532). **Highly advanced cerebellar syndrome in a child. Suboccipital operation under ether with incomplete removal of large vascular medulloblastoma. Transfusion. Postoperative dysphagia with vomiting of brown fluid. Wound reopened with second transfusion. Autopsy: Perforation of oesophagus with digestion of mediastinal tissues.**

January 23, 1928. On the recommendation of Dr. John L. Eckel of Buffalo, Joseph C., 10 years of age, was admitted as an emergency with the unmistakable signs of a cerebellar tumor. The symptoms in their order of onset were as follows: For two or three years clumsiness, instability and ataxia; for six months, increasing dysarthria; for three months, suboccipital headaches and vomiting; for one month, tinnitus and internal squint.

Examination showed a bedridden child with an enlarged head, a secondary optic atrophy with near-blindness; a persistent wandering nystagmus; a left abducens palsy; paresis of left facial nerve; slurring of speech; marked ataxia, hypotonicity and hypermetria of all extremities with absent deep reflexes.

Operation. January 26. 10:40 A.M.—As the child was too ill and uncoöperative for local anaesthesia, gas-ether was employed. The suboccipital approach was exceedingly difficult and bloody. In spite of a preliminary ventricular puncture, so soon as the left cerebellar hemisphere was exposed a huge median tumor began to extrude through the thin overlying cortex. The growth was so vascular it was mistaken for an angioma cavernosum. It was impossible to do more than to scoop and suck out what appeared to be the chief mass of the growth and to control bleeding by electrosurgical methods and temporary packing. It was a desperate procedure and not until four hours had elapsed was it thought safe to close the wound. The child's radial blood-pressure during the last hour was too low to be registered but a transfusion of blood was given with prompt improvement. The extirpation was necessarily left incomplete but it was hoped that enough of the growth had been removed temporarily to relieve pressure symptoms so that radiotherapeusis could be employed.

On the following day, *January 27*, fearing from the child's symptoms that a clot might have formed, at 11 A.M. the entire wound was reopened under local anaesthesia. At this session great masses of highly infiltrating tumor which were extruding from the cavity were removed with further loss of blood necessitating a second transfusion which promptly restored the fallen pressures.

During the remainder of this second day and night, the child seemed much

improved and there was hope of recovery. Apart from the occasional vomiting of brownish "coffee ground" fluid, which caused us to apprehend a possible erosion of the gastric mucosa, conditions seemed favourable until 6 A.M. on *January 28* when there was a sudden rise of temperature to 104.4°. This was associated with laboured respiration, bronchial râles and considerable cyanosis. Two hours later the temperature had risen to 106°. There was copious vomiting of brownish-black fluid.

On the remote chance that the unfavourable turn was due to a clot or to a further dislodgement of infiltrated tumor, the wound at 9:15 A.M. was again

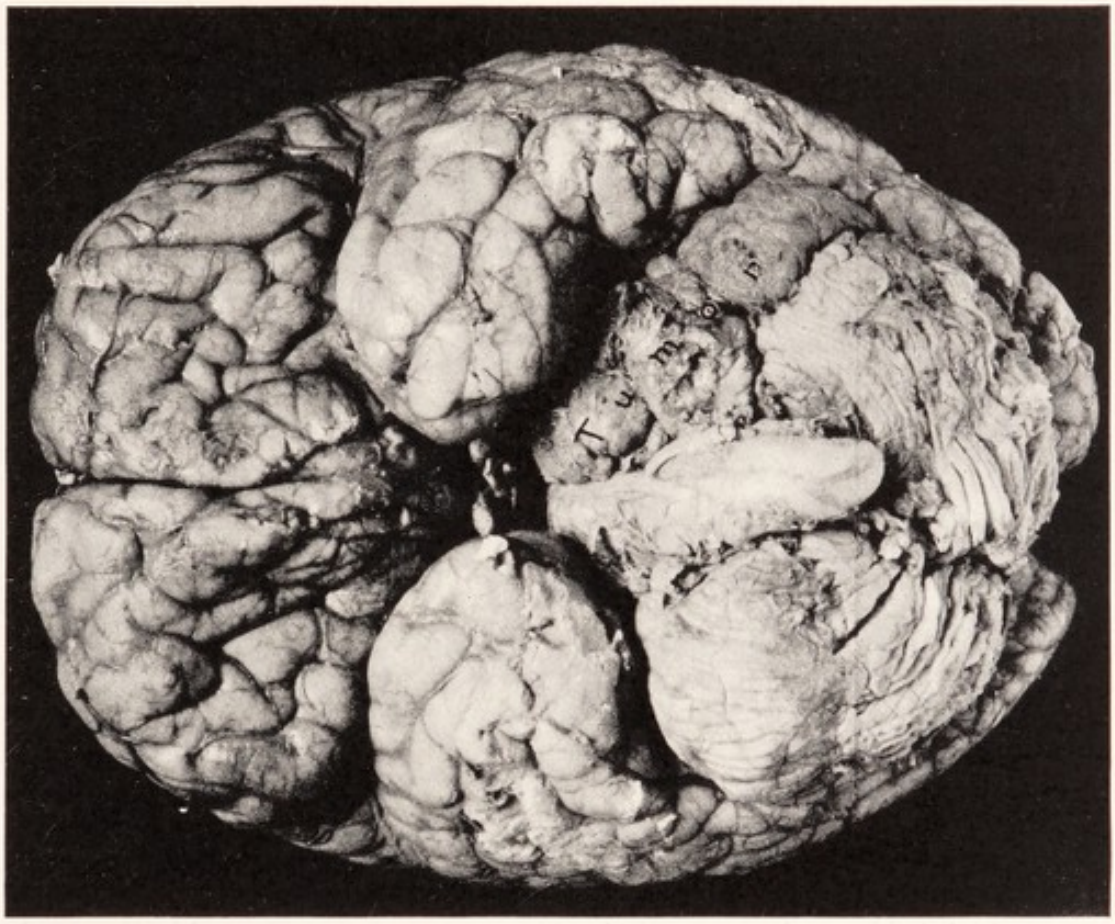

FIG. 88.—Case 3. Showing residual tumor mass (medulloblastoma) extending into left lateral recess.

quickly opened and closed without anything being found to account for the symptoms. A third transfusion was given with imagined improvement but this was temporary and the child died at 1:40 P.M., with a temperature of 106°, some fifty hours after the first operation.

Autopsy one hour after death; unrestricted (Dr. R. Z. Schulz).—The brain showed a large residual mass of the tumor which extended up into the lateral recess alongside the brain-stem and projected through the incisura tentorii flattening the side of the pons (Figs. 88, 89). There was a secondary hydrocephalus of high degree. The tumor proved to be a medulloblastoma.

In the further progress of the examination, the peritoneal cavity and the subdiaphragmatic organs were found to be normal in all respects; this was true also of the right chest. The left pleural cavity, however, was largely filled by dark

brownish fluid of precisely the same type that the patient had occasionally vomited; floating on its surface was a considerable amount of free fatty material and whitish débris. When, after removal of the fluid, the normal-appearing and crepitant lung was tilted forward, it could be seen that the pleura, over a large area including the side of the pericardium, the dome of the diaphragm, the bodies of the vertebrae and posterior thoracic wall, had been digested away together with the fat and areolar tissue of the mediastinal space. This left the aorta and its branches, the mediastinal nerves, the vertebrae and the oesophagus cleanly exposed as in a dissection (Fig. 90). In the side of the oesophagus was a ragged hole about 3 cm. in length from which, on compressing the stomach, the same brownish material found in the chest could be expelled.

Specimens of the free fluid after filtration showed a total acidity percentage

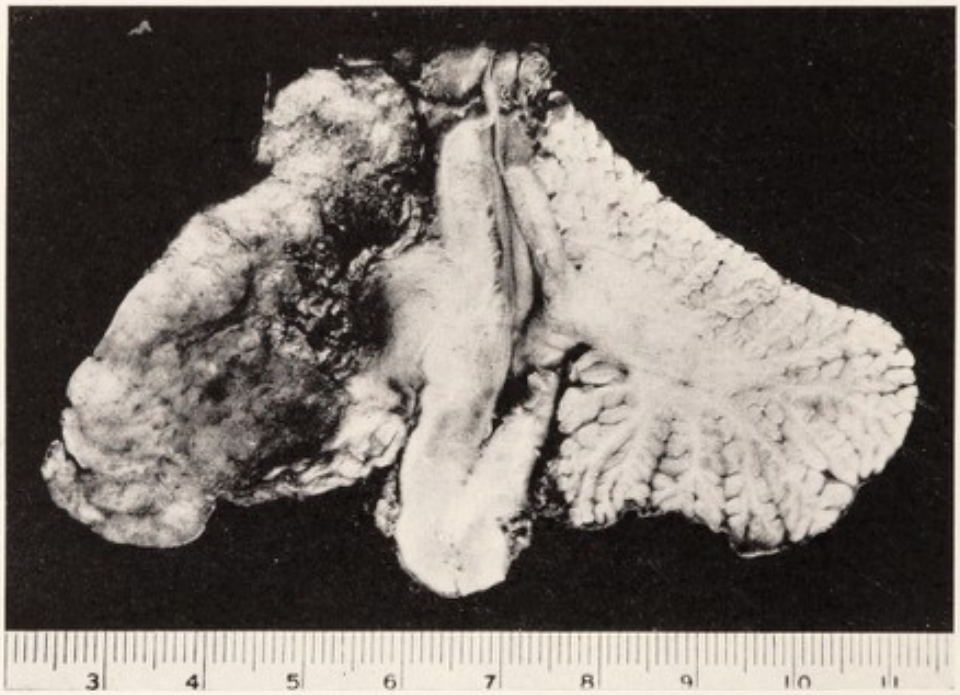

FIG. 89.—Case 3. To show (natural size) involvement of brain-stem by residual tumor.

of 52, which is about the upper limit of normal for free and combined acids in gastric contents. A piece of omental fat *circa* 5 cm. in diameter was incubated in 40 c.c. of the fluid and in forty-eight hours had disappeared, many fat globules remaining on the surface. A piece of muscle similarly treated was reduced to about a fifth of its original size in seventy-two hours.

Microscopical examination of the lower oesophageal wall showed a highly oedematous and partly autolyzed tissue containing occasional erythrocytes and an abundance of polymorphonuclear leucocytes.

Here, as in the two preceding cases, there were definite ante-mortem evidences of the lesion. The dark-coloured vomitus suggested an erosion somewhere in the upper alimentary canal, but the absence of all abdominal signs threw us wholly off the track, an oesophageal perforation being unsuspected.

This startling experience was reminiscent of that in the two foregoing

cases only for the reason that the antecedent operations had also been for a cerebellar tumor. Otherwise, there might have been no inclination to seek a common explanation for the three episodes particularly since the perforative lesion occurred in a different situation in each instance. This child at the time of operation was in a seriously enfeebled condition and in view of the subsequent hyperthermia might well enough have had an agonal digestion of the oesophagus; and this was the contemporary belief

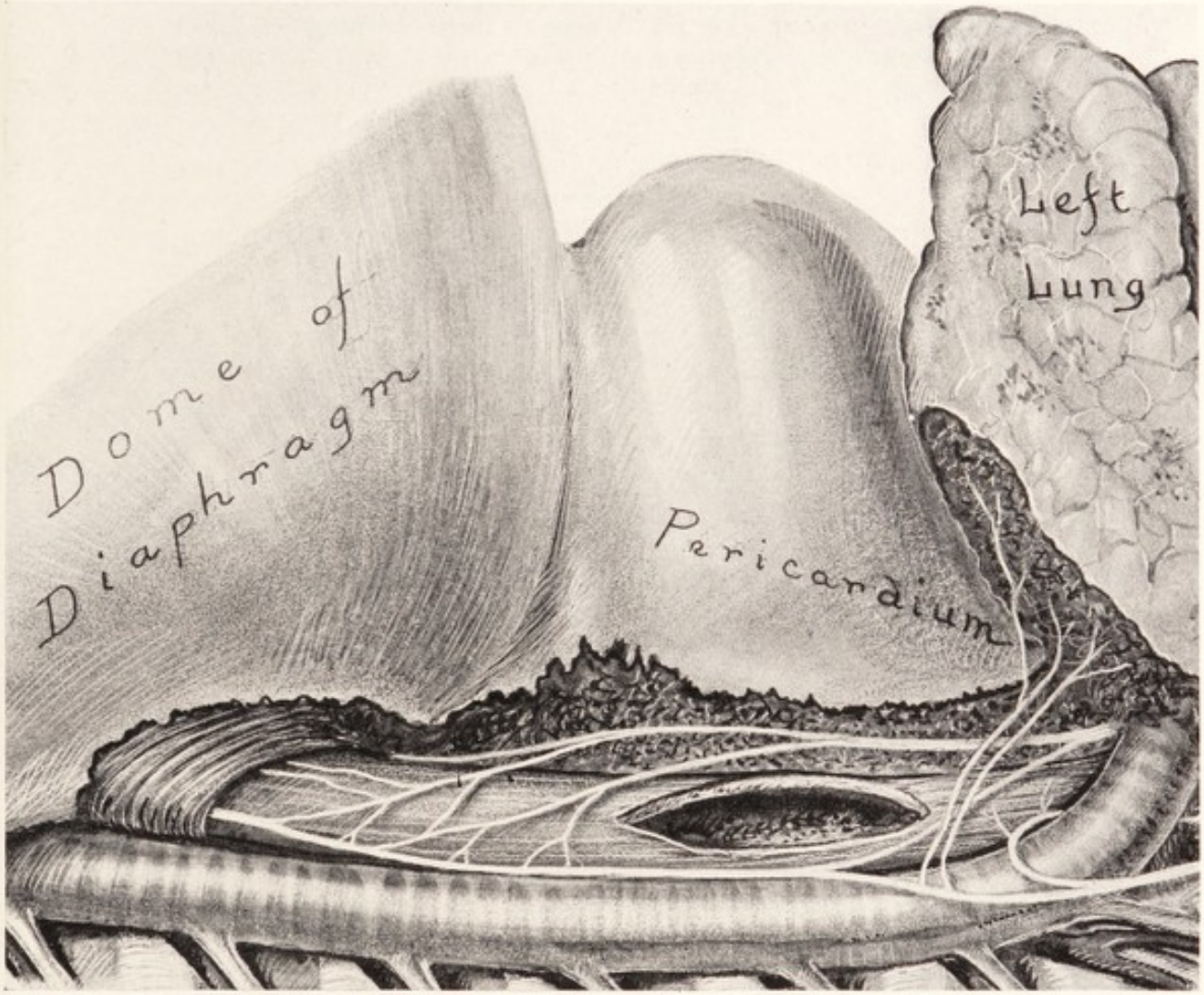

FIG. 90.—Case 3. Showing position of oesophageal perforation and upper visceral margin of mediastinal digestion leaving nerves and vessels wholly naked. (Nat. size).

expressed by the pathologists. Oesophageal perforations of like kind I recall having occasionally seen years ago at autopsies on typhoid-fever victims, it having been assumed that the perforation was due to regurgitation of gastric contents into the oesophagus; and to non-perforative ulcers of this same origin the once not uncommon post-typhoidal strictures of the oesophagus were formerly ascribed. It is, of course, known that true peptic ulcers may occur in aberrant islands of gastric mucosa in the lower oesophagus[28] just as they may occur in the patches of gastric mucosa in

Meckel's diverticulum,[35] but these anomalously situated lesions, though they may have some bearing on the subject, lie apart from the present discussion.

In each of these three cases, furthermore, there were ante-mortem symptoms: shown in Case 1 by acute abdominal pain, tenderness, and distention which preceded death by twenty hours; in Case 2 by sudden acute upper abdominal pain sixteen hours antecedent to death; and in Case 3 by the vomiting of fluid discoloured by changed blood and by respiratory disturbances for some twelve to fourteen hours before death. The operations in Cases 2 and 3 were highly critical procedures that must seriously have drawn upon the patient's resistance, but this was not true of the operation in Case 1. From these three observations, it is altogether natural to assume that erosions, which may not go on to actual perforation, are possibly of more frequent occurrence after operations for brain tumor than is commonly supposed. To this question we may now turn.

B. ANTE-MORTEM EROSIONS OF THE GASTRIC MUCOSA

Mucosal erosions whether haemorrhagic in type or the so-called stigmata of Beneke[7] are well known to pathologists. They were fully described by Carl Rokitansky, and Samuel Wilks in his celebrated *Lectures on Pathological Anatomy* stated[55]:

> We occasionally meet with small gastric ulcers, perhaps entirely unsuspected in the fatal illness, the symptoms having been overwhelmed by those of the main disease. These we have seen as single, reniform, or circular erosions, generally near the pylorus; sometimes they are quite shallow, and a little blood extravasated in the mucous membrane around would give rise to the suspicion that haemorrhage into the tissue, weakening it and leading to its solution, may be a cause of such ulcers.

The circumstances that permit one to demonstrate mucosal erosions after an intracranial operation are not often combined: namely, (1) an operation of the sort to produce them; (2) a postoperative fatality at the proper time to find them, for the multiple small erosions such as may be produced by a great variety of experimental methods are known to heal over quickly; (3) permission, after a fatal operation on the brain, for an unrestricted autopsy; and (4) a more careful scrutiny of the gastro-duodenal mucosa than is customary, particularly when the obvious cause of death lies elsewhere.

The absence of one or another of the four necessary factors mentioned may in part explain how it is that only two examples are here recorded. One of them happened to be picked up in an old autopsy protocol come upon while making a statistical study of the cerebellar astrocytomas a few years ago.

Case 4. (Surgical No. 664). **Recurrent cerebellar astrocytoma. Death after third operation due to streptococcal meningitis. Haemorrhagic erosions of stomach noted at autopsy.**

A child, six years of age, with an advanced cerebellar syndrome and blindness first came under observation at the Johns Hopkins Hospital; and on *May*

24, 1910, a large cerebellar cyst was opened and drained with freedom of symptoms for a year. On *August 3, 1911*, a large recurrent cystic tumor was partially removed by the late Dr. E. H. Nichols of Boston, again with a good temporary recovery. On *December 8, 1913*, she was admitted to the Brigham Hospital for recurrence of symptoms, among which occipital headaches, projectile vomiting, and constipation were prominent. At a third operation, a solid tumor mass was removed, the child dying six days later from a streptococcal meningitis with a temperature of 107°.

The protocol of the autopsy, held three and one-half hours after death, states that: "Near the cardia along the greater curvature are found several areas where the mucous membrane is lacking, the largest measuring 3 mm. in diameter. The bases of these ulcers [*sic*] are reddened as is also the fundus of the stomach." No sections were cut and the lesions were simply recorded by painstaking observers as incidental findings.

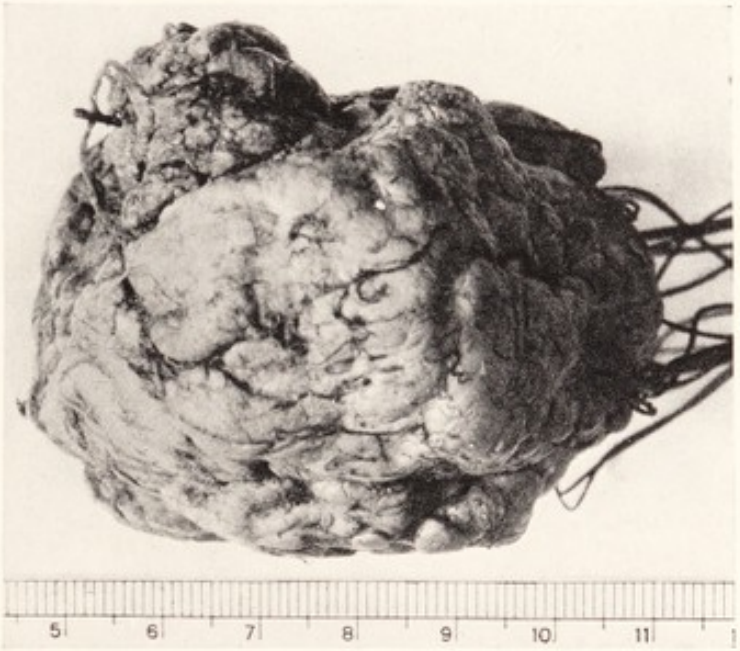

FIG. 91.—Case 5. Lateral view of the olfactory groove tumor (natural size) showing below the nodule that projected into the pituitary fossa between the anterior legs of the chiasm; also a branch of the torn anterior cerebral artery with clip.

How often similar small erosions of the gastric mucosa may occur after cranial operations is wholly conjectural, but their presence would explain why the vomitus not infrequently contains traces of blood which ordinarily is supposed to have been swallowed. The following is a recent example of erosions found at autopsy after a fatal operation for a lesion in the subfrontal rather than the cerebellar region.

Case 5. (Surgical No. 37259). **Extirpation of large olfactory groove meningioma. Injury to anterior cerebral arteries and fatality after 48 hours. Haemorrhagic erosions of stomach found post-mortem.**

A 53-year-old mill worker entered the hospital *September 11, 1930*, on the recommendation of Dr. I. A. Farrell of Pawtucket, Rhode Island. For six

months he had been working under a strain and his family learned accidentally that he had been vomiting every morning while at work and that he had shown some emotional instability. He was supposed to have a nervous breakdown. Three months later he began to have impairment of sight in the right eye with increasing weakness in the left side of the body.

Examination.—This revealed an apathetic, hemiparetic man with impaired memory and some disorientation. There was an apparent left homonymous hemianopsia to rough tests, a low grade of choked disc and loss of sense of smell in the right nostril. A diagnosis was made of a right frontal tumor, possibly an olfactory groove meningioma; this diagnosis was supported by ventriculography.

Operation.—On *September 23*, under novocaine anaesthesia, a large right frontal boneflap was turned down disclosing a tense dura. After reflecting this

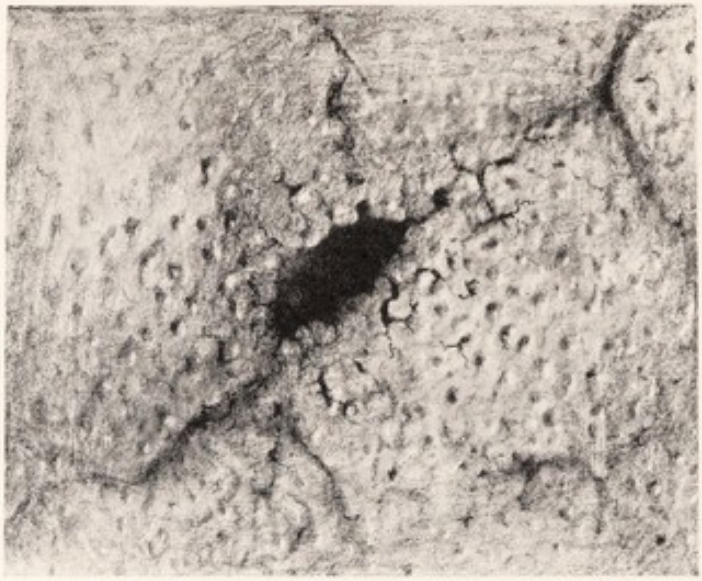

FIG. 92.—Case 5. Showing (mag. ×20) the appearance of one of the punctate haemorrhagic erosions.

membrane and uncapping the right frontal lobe, a typical nodular meningioma of considerable size (132 grams) was disclosed. The temptation to enucleate this tumor intact rather than by preliminary excavation and piecemeal removal was not resisted. At the final moment of dislodging the solid growth (Fig. 91) from its bed, there was a sudden profuse haemorrhage. Both anterior cerebral arteries firmly embedded in the tumor had been torn off. They were fortunately caught up in the sucker and occluded by clips before there was a serious loss of blood.

Following this operative accident the patient, as was anticipated, had a bilateral spastic paralysis of both lower extremities associated with spontaneous clonic movements. He exhibited the usual clutching and grasping reflexes in the right hand which alone retained spontaneous movements.

On the following day when the wound was dressed some slightly blood-tinged cerebrospinal fluid was removed from under the flap. Because he was taking nourishment poorly a nasal tube was introduced which withdrew about 50 c.c. of coffee-ground material in which erythrocytes were demonstrable by microscopical examination. On the second day his temperature suddenly rose

to 107° and he died in hyperthermia 48 hours after the conclusion of the operation. Shortly before his exitus he vomited a large amount of fluid which was grossly bloody.

Autopsy.—Permission was given for an unrestricted and immediate examination which was made twenty minutes after death (Dr. R. Z. Schulz). It was found that the tumor had been cleanly removed except for a small fragment incorporated with the stump of the right internal carotid artery. A clip had been placed apparently on the middle cerebral artery on the right side, probably

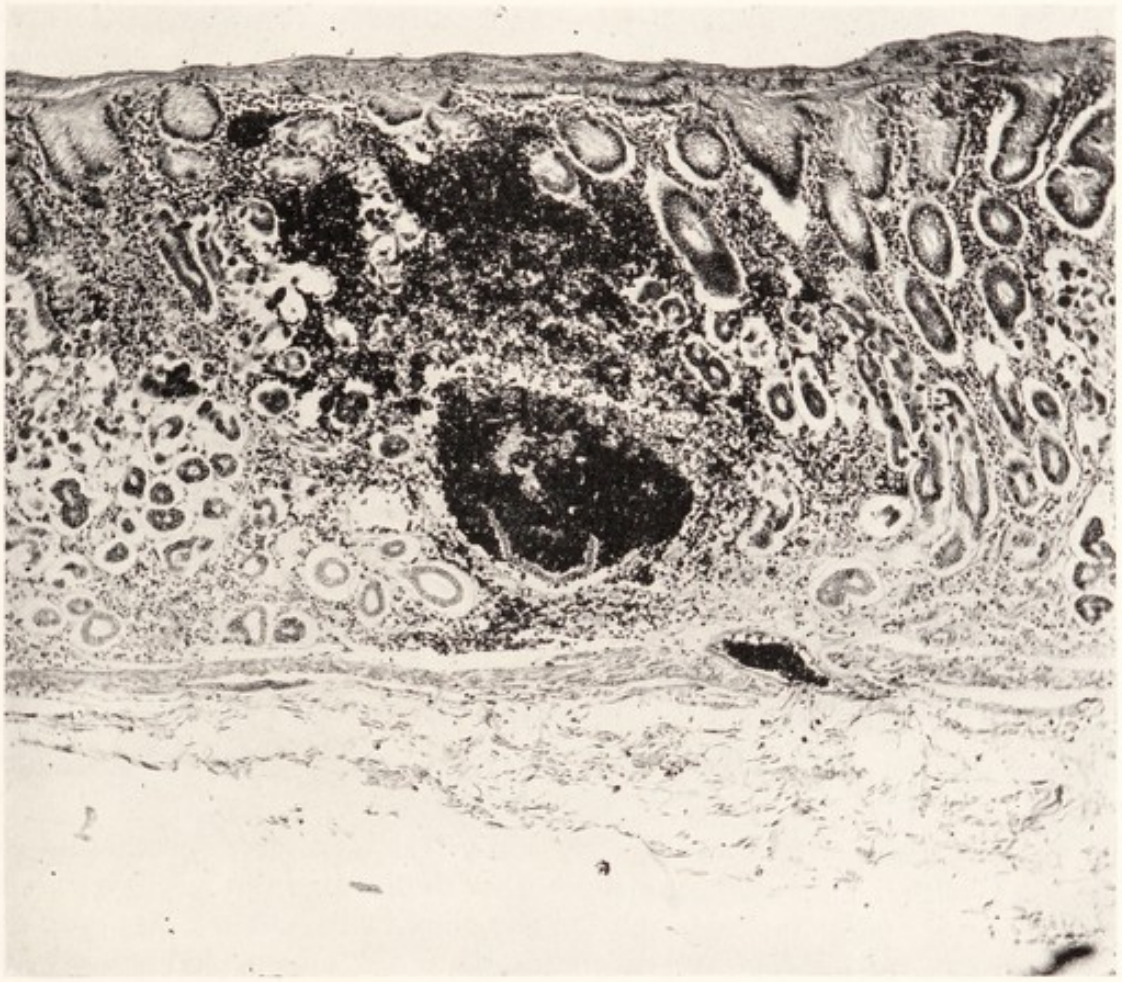

FIG. 93.—Case 5. Type of ante-mortem mucosal haemorrhage associated in other areas with erosions (mag. ×75).

also on the anterior cerebral on the left, though this could not be precisely determined.

On opening the stomach numerous flecks of coffee-ground material suggesting changed blood were found, also spots of recent haemorrhage with small clots attached to the surface of the mucosa which was studded with numerous small punctate ulcerations varying from 1 to 3 mm. in diameter. When looked at through a magnifying glass (Fig. 92), they proved to have slightly irregular margins. The erosions were very superficial and were found scattered everywhere, both in fundic and pyloric regions, with no site of predilection. The mucous membrane of the oesophagus and small intestine was normal in appearance.

Microscopical examination.—Sections of the stomach showed numerous small mucosal haemorrhages, some with overlying erosions and some with the mucosal surface still intact (Fig. 93). They were looked upon as essentially recent ante-mortem capillary haemorrhages. The red blood cells were well preserved and there was neither deposition nor phagocytosis of blood pigment. There was no evidence of arterial or capillary disease nor any noteworthy constriction or thrombosis of the vessels. Nowhere were haemorrhages observed in the submucosa, the architecture of which was well preserved.

Had we not been on the alert by this time (1930) for mucosal erosions after fatal operations for brain tumor wherever situated, it is safe to say that the minute lesions described might easily have escaped notice or have been regarded as of no significance. Their histological appearance, coupled with the finding of demonstrable blood in the gastric contents twenty-four hours before death, clearly indicates their ante-mortem character. Attention may be called to the fact that an olfactory groove tumor of the type described underlies the frontal lobe, and its posterior projection, overriding the optic chiasm, necessarily deforms the third ventricle. There consequently is always a risk of injuring important structures in the final dislodgment of the posterior fragments of such a growth even when it is removed piecemeal; and either from trauma or because of the vascular accident described in the operative note, the operation in this case was equivalent to a decortication of the frontal lobes. While the relation to the subject in hand of this particular fronto-diencephalic region will be fully considered later on, it may suffice at the moment to point out that the seat of the operative manipulations was far removed from that associated with the perforative lesions and erosions mentioned in the four preceding case reports.

C. GASTRIC EROSIONS AND PERFORATION ACCOMPANYING MALIGNANT HYPERTENSION

Lesions similar to those already described may of course occur in patients with intracranial conditions other than actual tumor. Two recent examples of malignant hypertension associated with choked disc may be briefly cited in illustration. In one of them the erosion led rapidly to perforation resembling the conical "punched ulcer" which in my student days was associated in the mind of the profession with some constitutional predisposition, more particularly with that once common disorder, chlorosis.

Case 6. (Medical No. 37972). **Malignant hypertension with choked discs. Moderate arteriosclerosis with cardiac hypertrophy. Hydrothorax. Death with hyperthermia. Autopsy: multiple recent gastric ulcers.**

On *November 14, 1930*, a poorly-nourished, high-strung divorcée 32 years of age, supporting herself and her children as a bookkeeper, entered the hospital with a history of five months of headache, dyspnoea, palpitation, insomnia, nycturia, and indigestion, with occasional attacks of nausea and vomiting. Examination showed an enlarged heart, moderate arteriosclerosis, choked discs, a blood pressure of 270/150, and slight traces of albumin in the urine.

She developed hydrothorax, which was relieved by punctures, and in course of the next six weeks went gradually down hill in spite of all efforts to alleviate her condition. On *January 7*, she became unconscious, developed fever, remained in coma for twenty-four hours and after a series of convulsive seizures died at 11 A.M. on *January 8*, with a terminal temperature of 104°.

Autopsy, 2½ hours after death (Dr. Hertig).—The examination revealed chronic myocarditis, mild vascular nephritis, moderate general arteriosclerosis, bilateral hydrothorax, and multiple recent gastric ulcers. The gastric mucosa was found to be intensely injected and to contain numerous, small stellate-shaped recent ulcerations, more marked on the lesser curvature, to many of which fairly recent blood clots were adherent. The mucosa of the duodenum was

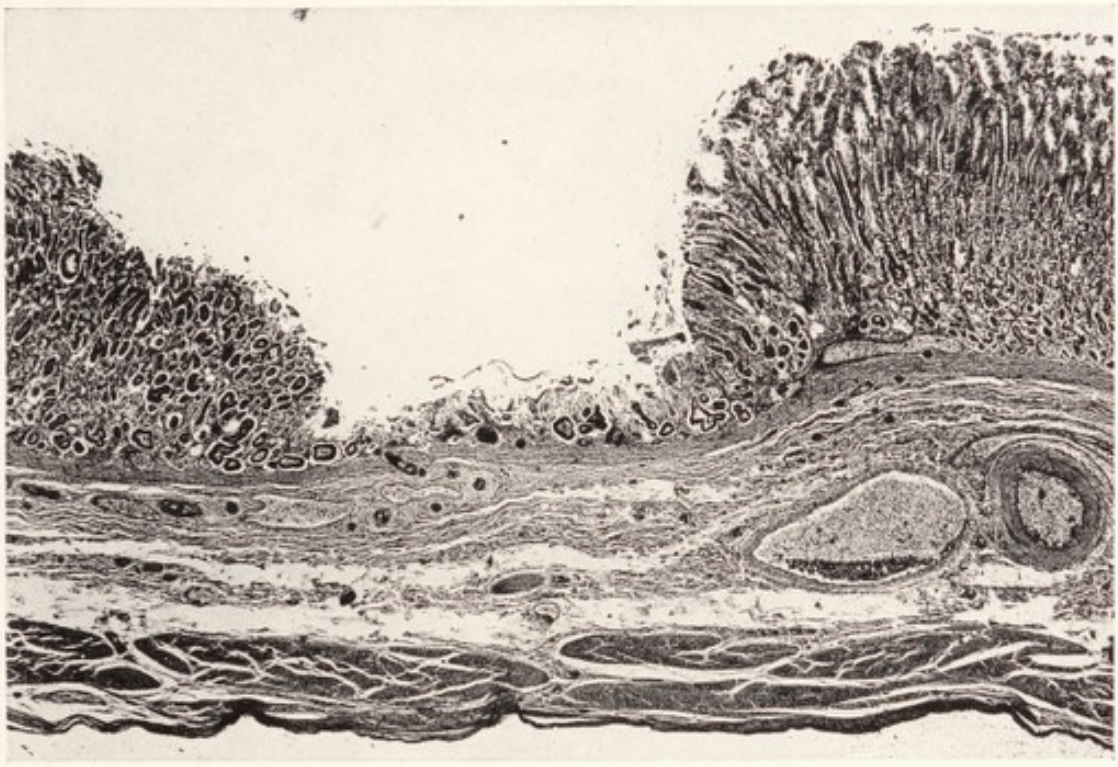

FIG. 94.—Case 6. Showing type of erosion associated with thrombosed vessels in submucosa (mag. ×22).

injected but without ulcerations. The gastro-intestinal tract elsewhere presented nothing of note.

Microscopical sections of the stomach showed, in addition to the recent acute erosions, a generalized congestion with thickening of the arterioles of the mucosa (Fig. 94). The base of the ulcerative defects contained a slight amount of necrotic débris, a few polymorphonuclear leucocytes, the surrounding struma being infiltrated by leucocytes, plasma cells, and lymphocytes. The mucosa was greatly congested and many small tightly contracted and thrombosed arteries were present both in mucosa and submucosa (Fig. 95). The larger vessels showed practically no intimal change.

In the following case—an example of the same clinical disorder—there had been an ante-mortem perforation of the stomach into the lesser peritoneal cavity.

Case 7. (Surgical No. 35716). **Malignant hypertension with choked discs. Moderate arteriosclerosis with cardiac hypertrophy. Haematemesis. Perforation of gastric ulcer. Operation. Death after five days. Delayed autopsy. Autodigestion of stomach.**

On *January 29, 1930*, Seth W., a somewhat obese man, aged 44, was transferred from the Deaconess Hospital as a brain-tumor suspect because of headaches and failing vision associated with vascular hypertension of a year's duration. He was not a "nervous" person and had never been troubled by gastric symptoms of any kind.

Examination.—This disclosed choked discs of six diopters with secondary

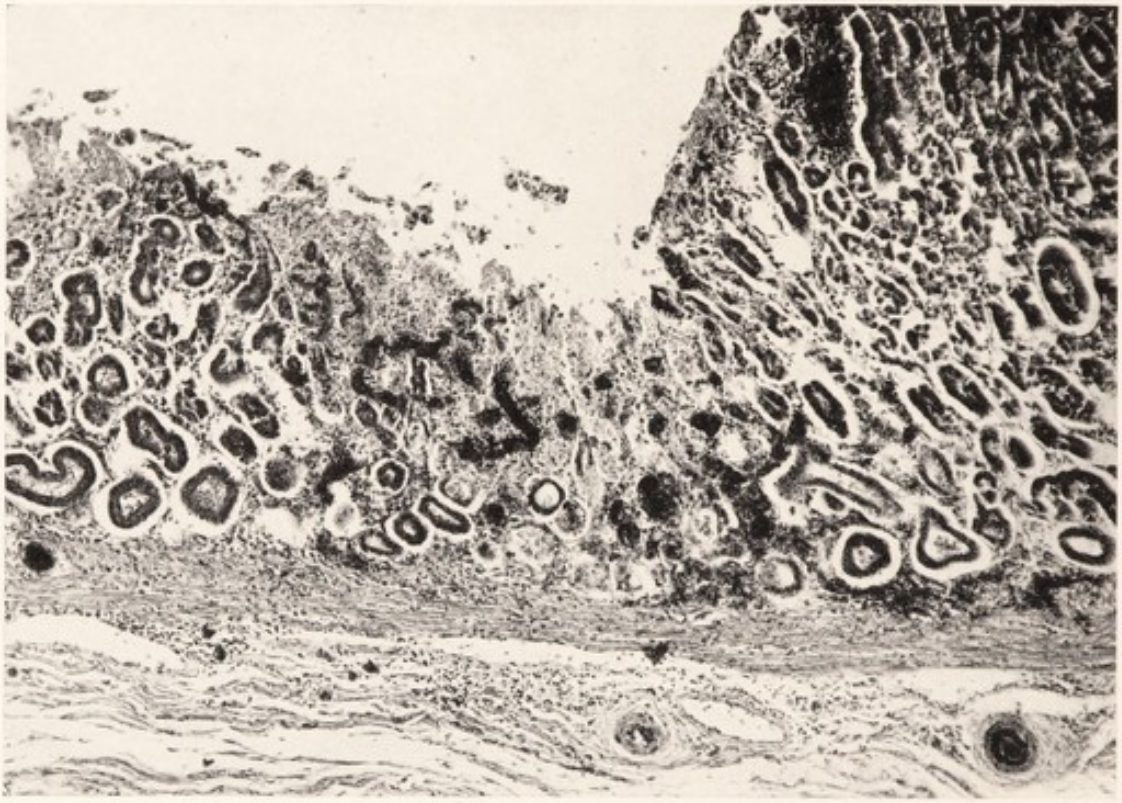

FIG. 95.—Case 6. Showing congestion and thrombosis of mucosal veins with beginning erosion. Note constricted and thrombosed artery in lower right-hand corner of field (mag. ×80).

atrophy and visual acuity reduced to 20/200. The blood-pressure was 210/145 and the heart was slightly enlarged. Occasional hyaline casts were found in the urine and on two occasions the slightest possible trace of albumin. The examination was otherwise negative.

On *February 5*, to exclude tumor, ventriculograms were made and the ventricular cavities found to be normal in position and outline. On *February 10*, a sudden haematemesis occurred with vomiting of 500 c.c. of blood. This was repeated on the following day with the loss of another 800 c.c. of blood. For the resultant secondary anaemia (haemoglobin 50 per cent, erythrocytes 1,920,000), the patient was treated medically and seemed to be doing well when suddenly at 5 P.M. on *February 17* he was seized with severe epigastric pain, and an exploratory operation by Dr. John Powers disclosed a perforation in the posterior wall of the stomach 1 cm. in diameter and 8 cm. proximal to the

pylorus. This ulcer was closed, inverted, and plicated, and the patient transfused. He did reasonably well for the next five days when he became comatose and died *February 22* at 7:30 P.M. with a rectal temperature of 104°.

Autopsy (*February 23*, 8:15 A.M.) revealed a peritonitis restricted to the lesser peritoneal cavity with terminal septicaemia from a gas-producing bacillus. The sutures closing the perforation had been dissolved away and the stomach was in shreds from autodigestion. The pancreas had become involved and there was extensive fat necrosis. Post-mortem changes in the brain, which was riddled with gas bubbles, made its microscopical study unprofitable. Apart from considerable sclerosis of the cerebral vessels, there was no tumor or other observable organic lesion.

In striking contrast were the simple gastric erosions observed at the early autopsy on Case 6 and the extreme autolysis of the stomach found in this last case in which the examination had been delayed for twelve hours. The lesions in both might well enough have been regarded as having been due to post-mortem digestion had it not been for the haemorrhagic nature of the erosions in the first case and the history, in the other, of a perforation which occurred five days before death.

The possible dependence of what is known as gastromalacia upon some neurosecretory disturbance in the gastric wall prior to death may next be considered.

D. GASTROMALACIA

In his first communication to the Royal Society, May 18, 1772,[27] made somewhat reluctantly at Sir John Pringle's solicitation, John Hunter stated that after death, a "dissolution of the stomach at its great extremity" is occasionally found; and as this condition had been most frequently seen in the bodies of those who had died violent deaths, it was naturally ascribed to a post-mortem continuance of digestion.* Why the stomach does not digest itself during life Hunter answered much as the question might be answered to-day, by saying it can only do so when deprived of the "living principle." Even this was doubted by Claude Bernard and his English pupil, Pavy, of Guy's Hospital, who showed that the solvent power of the gastric secretion could act on living tissue. It was assumed that the layer of mucus was what protected the secreting membrane from the action of its own juices, until Pavy in 1868 offered an explanation so simple it met with almost universal approval at the time and in various guises is periodically revived—in effect, that the normally

* Years later, another Scot, Robert Carswell (*Cf. Edinb. M. & S. J.*, 1830, XXXIV, 282–311), putting this to the test of experiment showed: (1) that the dependent portion of the stomach of rabbits killed after feeding was always found digested; (2) that the gastric juice from such an animal transferred to the empty stomach of a dead rabbit would digest its wall; and (3) that autodigestion did not occur in the stomach of an animal killed while starving, or in one whose gastric contents were immediately washed out after death. In short post-mortem autodigestion occurs only when the stomach is secreting. It remained for Pavlov and others to make clear that the presence of food in the stomach was not the only factor in exciting the flow of gastric juice.

alkaline blood circulating in the stomach walls counteracts the acid of the mucosal secretion.

Death does not commonly occur among hospital patients with chronic maladies while their stomachs are digesting food and this may account for the fact that what is known as gastromalacia, once the subject of ardent discussion, is nowadays infrequently seen and rarely mentioned. While something more will be said of this matter later on, two examples of the process may here be cited as an extreme contrast to the minute erosions described in Cases 4, 5, and 6 and the acute perforative lesions in the first three cases recorded.

Case 8. (Surgical No. 25562). **Symptoms suggesting a right cerebellopontile tumor. Negative exploration. Fatality on fourth day. Autopsy: Large aneurysm of basilar artery; extreme oesophago-gastromalacia.**

Archibald McL., a mining engineer aged 47, referred from the Battle Creek Sanitarium, was admitted *January 11, 1926*, for a presumptive cerebellar tumor.

Anamnesis.—There had been: (1) for seven years, suboccipital headaches produced by any sudden jar and progressively increasing in severity; (2) for four years, a continuous bilateral tinnitus, deglutitory difficulties, a sensation of tightness in the right face, and diplopia on looking to the left; (3) for one year, ataxia of hands and a drunken instability of gait; (4) for two or three months, a right facial palsy, constipation and difficulty of emptying the bladder.

Examination.—This disclosed a low grade of papilloedema, nystagmus, a right trigeminal hypaesthesia, paresis of the right face, a moderate bilateral deafness, ataxia of cerebellar type, and an absent gag reflex with some dysphagia and dysarthria. The blood Wassermann was negative; the blood pressure 140/80. A tumor of the right lateral recess was predicted.

Operation. January 26.—A suboccipital exploration under local anaesthesia failed to reveal the expected tumor. The manipulations, while in search of it, produced a marked fall in blood-pressure and provoked spells of vomiting which continued off and on during the remainder of the procedure. There was no herniation of the cerebellar tonsils; in fact, the upper spinal cord appeared to "ride" higher in the foramen than usual, the ninth, tenth, and eleventh nerves being well exposed to view. The wound was closed.

During the remainder of the day he vomited frequently and for some unaccountable reason his dysphagia and dysarthria were more marked than before. On the following day, *January 27*, though still nauseated, his condition was good and no anxiety was felt regarding his recovery. On the morning of *January 29*, the third day, he seemed to be doing well but he was found at noon to have a temperature of 104°. A lumbar puncture was performed disclosing faintly blood-tinged fluid under no increase of tension. During the afternoon, the lungs began to fill with secretion, he became increasingly cyanotic, and passed into a deep stupor followed by death at 1:30 A.M. on *January 30*, the morning of the fourth day. Because of deglutitory impairment no nourishment had been taken by mouth for over twelve hours.

Autopsy, 7:30 A.M., six hours after death (Dr. H. Pinkerton).—This disclosed: (1) a large aneurysm of the basilar artery greatly distorting the brain stem (Fig. 96); (2) generalized arteriosclerosis; (3) a terminal bronchopneumonia; and (4) gastromalacia. The peritoneal cavity in the region of the spleen contained 500 c.c. of brownish dirty fluid containing small masses of mucus.

The fundus of the stomach and lower oesophagus were found to be completely disrupted and in shreds. A perforation measuring 15 cm. in diameter was present with dissolution of the adjacent stomach wall. The rupture extended up to the cardia and into the oesophagus for a distance of about 10 cm. The pyloric region showed considerable autodigestion which involved the superficial layers only.

FIG. 96.—Case 8. Aneurysm of the basilar artery (natural size) mistaken for tumor of right lateral recess (*cf.* projection of sac to left) and causing marked deformation of brain stem.

Here was a typical example of post-mortem autolysis of the stomach and oesophagus in which the presence of changed blood in the gastric contents was not observed during life. But inasmuch as no nourishment had been taken, the presence of half a litre of brownish fluid found free

in the abdomen can scarcely be accounted for unless the gastric mucosa had been actively secreting long before the cessation of circulation.

In the following example of gastromalacia, evidences that erosions were present before death are somewhat more definite.

Case 9. (Surgical No. 34711). **Extirpation of right parietal metastatic hypernephroma. Death after 36 hours. Ante-mortem regurgitation of blood-containing fluid. Autopsy: Gastromalacia and eosophageal perforations.**

John G., a carpenter, 58 years of age, was admitted *August 28, 1929*, in a stuporous condition with the history of headaches for the preceding six months. The eyegrounds were normal; there was no evidence of nephritis or arteriosclerosis. In the process of making a ventriculogram for diagnostic purposes the needle entered a xanthochromic cyst in the right parietal lobe.

On *September 10* (9 A.M.), an exploratory operation under novocaine was made by Dr. Horrax and a partly cystic tumor which proved to be a metastatic hypernephroma was enucleated. On the following day at 10:30 A.M. because of continued stupor and a rising temperature (104°) the flap was reëlevated under the mistaken belief that a postoperative clot had formed.

The patient remained unconscious and unresponsive with stertorous respirations and an evident hemiplegia. At 6:30 P.M. he was given a nasal feeding which was promptly regurgitated with a large amount of dark brownish material evidently containing changed blood. Death occurred at 9:45 P.M., eleven hours after the second operation, with a rectal temperature of 103.4°.

Autopsy, three hours after death (Dr. Connor).—The brain showed oedema of the right cerebral hemisphere but contained no additional metastases. There was a primary hypernephroma of the left kidney and bronchopneumonia. A bilateral perforation of the oesophageal wall communicated with the right and left pleural cavities, each of which contained about 400 c.c. of brownish mucoid fluid containing fat droplets. The oesophageal openings measured from 4 to 5 cm. in length, and the adjacent oesophageal tube was necrotic, only a few strands of fibrous tissue, nerves and blood-vessels remaining. The margin of the digested area in the thorax showed a border of reddening suggesting that the circulation must have been in action at least in the early stages of the process. The fundus of the stomach was highly necrotic, with only a few blood-vessels, nerves and strings of reddish mucoid material remaining. The pyloric end of the stomach was comparatively unaffected and the remainder of the gastro-intestinal tract showed no change.

The important features of this example of oesophago-gastromalacia from the point of view of the present discussion are: (1) the presence of dark-brown fluid (probably blood-containing) regurgitated three hours before death; (2) the note in the pathologist's protocol that the appearance suggested an ante-mortem even if an agonal process. As in Case 3, also with oesophageal perforation, it is difficult to understand how the pleural cavity should have contained such a large amount of blood-containing gastric fluid had the stomach not been actively secreting and have retained its motility after the perforations occurred even were they agonal events. As this is the only tenable explanation for the conditions found, it presupposes some disturbance of control on the part of the vegetative nervous system which served in some way to set aside Hunt-

er's "living principle" and at the same time to provide an abundant gastric secretion. For in the absence of active gastric juice the process could hardly have taken place.

E. CHRONIC ULCER

Up to this point, only those lesions have been discussed which might well enough have been ascribed to post-mortem or agonal changes had it not been for symptomatic evidences of peritonitis or of pain or of blood in the gastric contents several hours before death. Even so, the process in all instances has been an acute one whereas the cardinal clinical feature of a gastric ulcer is its peculiar chronicity. This, first clearly pointed out by Cruveilhier, must have been known to John Hunter, to judge from Clift's drawings of some of his specimens published in Matthew Baillie's *Morbid Anatomy* (1799); but just what Hunter thought about them unfortunately went up in smoke when his manuscripts were burned.

What it is that favours chronicity in a gastric or duodenal ulcer is a much-debated subject. All will agree, however, that an erosion of the mucosa must be the primary stage in its formation; and since there is every reason to believe that acute erosions (of the type described in Case 5,) are of common occurrence, any one of them may well enough be the precursor of a chronic lesion, should the original insult be sufficiently great or should a minor insult be continuous or frequently repeated at the same spot. As a matter of fact, a duodenal ulcer, at least shows every inclination to heal, as indicated by the frequency with which shallow scars are found after death, and its tendency to recur, rather than any pathological evidence of chronicity, is its peculiar characteristic.

Only one pathologically verified chronic ulcer which, with reasonable assurance, can be ascribed to an encephalic lesion, has been observed in our tumor series. The history of the case follows:

Case 10. (Surgical No. 29708). **Radical removal from a child of a median cerebellar medulloblastoma with wide opening of fourth ventricle. Repeated subsequent radiotherapeutic sessions. Death after two years. Massive intraventricular recurrence. Duodenal ulcer with evidences of cicatrization.**

The patient, Ruth F.,* aged 9, was admitted *September 23, 1927*, with an advanced cerebellar tumor syndrome of seven months' duration: *viz.*, headaches, projectile vomiting, loss of weight, anorexia, cerebellar ataxia and choked discs.

At operation on *October 6, 1927*, a typical midline cerebellar medulloblastoma was cleanly extirpated, chiefly by suction, leaving the floor of the fourth ventricle fully exposed. The patient made a good recovery from this operation and was subsequently given x-ray treatments over the entire cerebrospinal axis at intervals of from two to four months. For the first year she remained wholly free from symptoms.

She was readmitted to hospital *July 29, 1929*, because of the abrupt accession of symptoms of a week's duration. A series of six x-ray treatments were then

* Case 50 of medulloblastoma series as reported: *Acta Path. et Microbiol. Scand.*, 1930, VII, 1–86.

given and she was again discharged. For the first time, no improvement followed the radiotherapeutic sessions and on *September 21, 1929*, she was again admitted to hospital. She had become apathetic, incontinent and emaciated. There were daily attacks of vomiting; feeding was a difficult problem; there was a constant slight pyrexia.

In spite of her desperately poor condition, a reëxploration of the cerebellar region was made on *October 10*. This was disappointing in that it failed to disclose the expected local recurrence, the fragment of tissue that was removed after redividing the vermis proving, under supravital preparation, to be wholly degenerated tumor. In the course of the operation clear fluid had been obtained

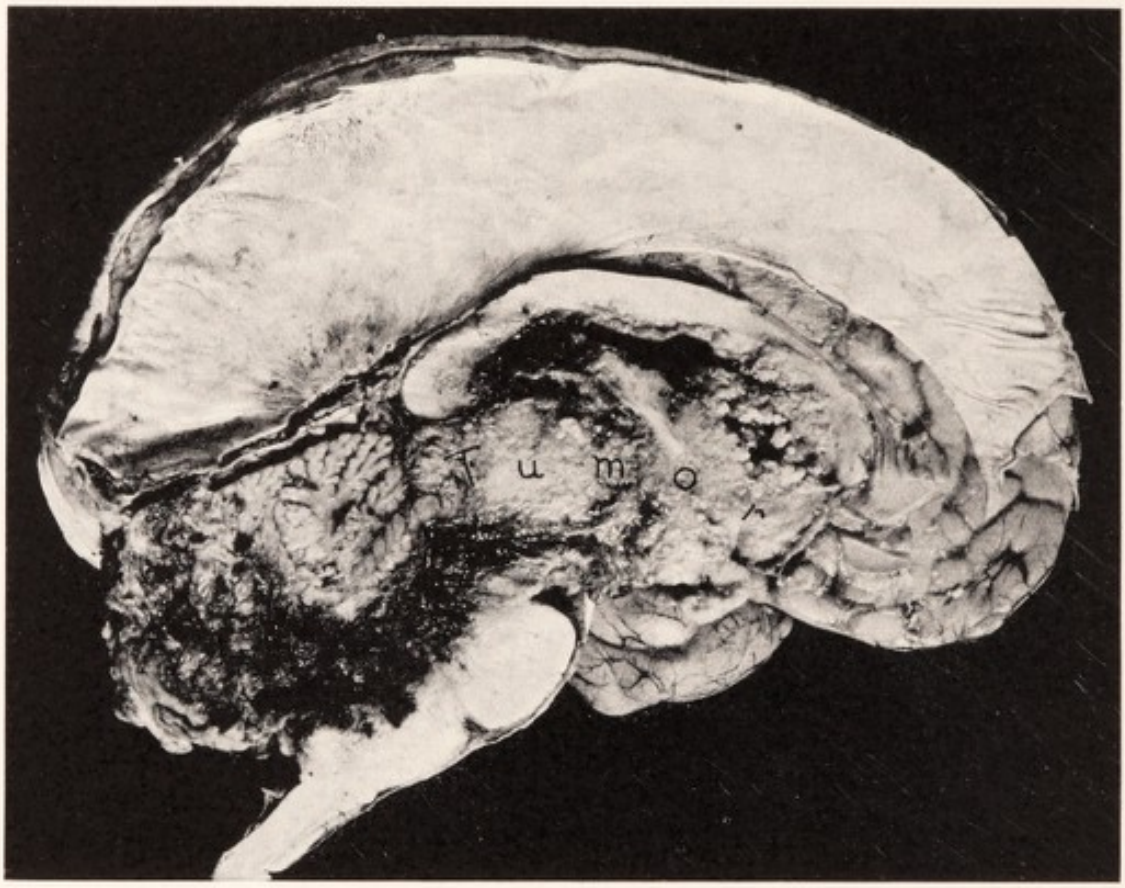

FIG. 97.—Case 10. Note invasion of medulla and massive obliteration of cerebral ventricular system by recurrent medulloblastoma.

by a puncture of the cerebral ventricles, and this, on examination, failed to show any tumor cells.

Following this futile procedure, the child's critical condition remained unchanged. In the subsequent bedside notes, attention was called to her abundant perspiration which was limited almost wholly to the right side of the face. She gradually passed into coma and died on *October 27* at 2:42 P.M., with a terminal hyperthermia (106.5°). An unrestricted post-mortem examination was held one hour later.

Autopsy, 3:45 P.M. (Dr. Schulz).—Two striking things were disclosed: (1) a massive intraventricular involvement by tumor (Fig. 97) in the absence of macroscopical evidence of tumor implantation in the spinal or cerebral meninges; and (2) a chronic duodenal ulcer. The oesophagus and stomach were wholly

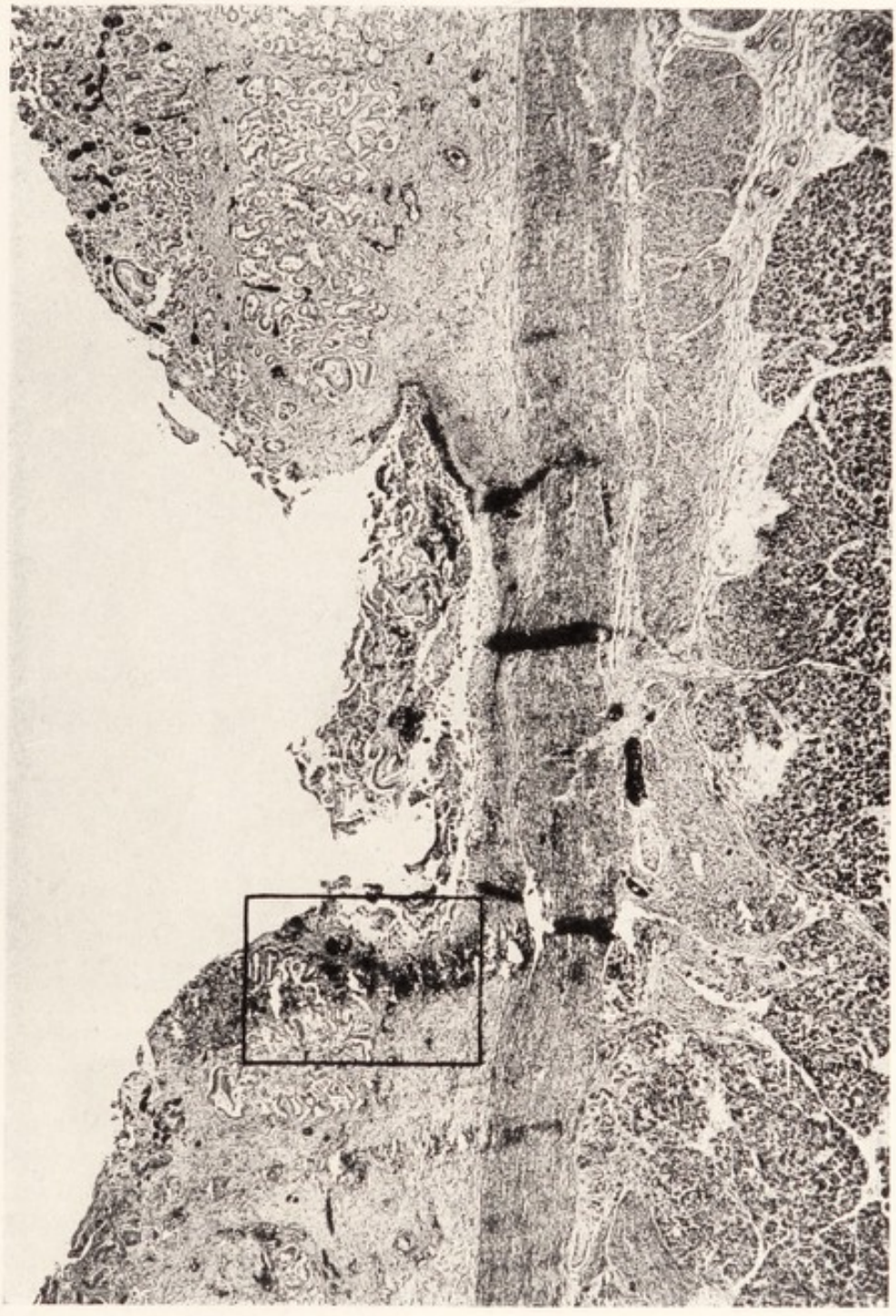

Fig. 98.—Case 10. Showing duodenal ulcer (mag. ×20) in child associated with tumor metastasis involving third ventricle (*cf.* Fig. 15).

normal in appearance, the mucosa being well preserved, but in the first portion of the duodenum, 3 cm. below the pyloric sphincter, was a small ulcer measuring 3 by 4 mm. It had a firm, elevated margin and depressed centre forming a crater. The distal bowel elsewhere was apparently normal.

Microscopical examination of the ulcer shows that it extends down to the muscularis, that its margins are steep and slightly undermined (Fig. 98). On its floor there is a narrow zone of dense hyalinized connective tissue, and in one region some fibrin and blood cells. Within the excavated crater lie desquamated epithelium and blood elements. The scar tissue at the rim of the ulcer shows chronic inflammatory cell infiltration. In the adjacent tissue are small thrombosed blood vessels filled with fibrin and a few polymorphonuclear leucocytes (Fig. 99).

FIG. 99.—Case 10. Showing, from squared area in Fig. 16, thrombosed vessels and cicatrization of mucosa in lower right part of field (mag. ×100).

In this case a large recurrent, thoroughly radiated medulloblastoma filled the cerebral intraventricular system. The child had been subject to frequent attacks of sudden vomiting, but as this is characteristic of most cerebellar tumors, its possible association with a peptic ulcer was not suspected, nor were any studies made in this direction. During the course of cerebellar operations on patients under local anaesthesia, it is well known that vomiting may be easily provoked, and this is commonly ascribed to stimulation of the vagal nuclei in the floor of the fourth ventricle. What is more, all neurosurgeons are familiar with the fact that after major intracranial operations the vomitus for the first few days may show evidences of changed blood. While this is usually attributed to the

swallowing of blood from some source during the progress of the operation, it is highly probable that it may be due, more often than is commonly supposed, to acute neurogenic erosions of the gastric mucosa.

Though I am not aware of any other examples in my tumor series of the post-mortem finding of a chronic ulcer, we not infrequently see in the hospital wards patients recovering from serious intracranial operations in whom during convalescence digestive disturbances are in evidence which strongly suggest incipient ulcer symptoms. But this perhaps is true no less of operations of other sorts. Somewhat more definite is the fact that a goodly number of patients with symptomatic evidences of an organic lesion in the region of the third ventricle have had a roentgenologically demonstrable gastric or duodenal ulcer. The following example will serve in illustration.

Case 11. (Surgical No. 34129). **Tumor of third ventricle (demonstrated by ventriculography) causing pressure symptoms associated with gastro-intestinal disturbances. Subsequent periodic radiation of lesion with marked improvement. Recurrent duodenal ulcer.**

Edward C., an electrician, aged 25, was admitted *June 5, 1929*. Apart from periodic indigestion, to which scant attention was paid, he had enjoyed uniformly good health. Suddenly, on *May 12, 1929*, fatigued by a 200-mile motor-car drive, he had a sudden severe occipital headache with vomiting. A succession of these occurrences followed and he was soon obliged to give up work. The seizures, which came in paroxysms, were characterized by retraction of the neck, dizziness, sweating, protrusion of the eyes, and painful flexure of the arms; they would terminate with a cough or a yawn when sudden relief would be experienced. He was taken to a hospital on *May 31* and treated for "gastric symptoms." While under observation, he acquired a diplopia with choked discs and was transferred to the Brigham Hospital as a brain-tumor suspect.

Examination.—This showed a man with a rigid neck, a bilateral abducens palsy more marked on the right, and choked discs of 4 diopters. The reflexes were hyperactive, with a bilateral Babinski. Ventriculograms disclosed a symmetrically disposed hydrocephalus with a filling defect of the third ventricle and a block of the foramina of Monro. He was given a series of four x-ray treatments, began promptly to improve, and the choked discs rapidly subsided. He was discharged *June 23* practically symptom-free and two weeks later resumed his occupation.

He remained well for over a year when he once more began to have "nervous indigestion" associated with nausea and hunger pains for which he finally reported to the ambulatory clinic. Suspecting that these symptoms might be due to a recurrence of the intracranial lesion, and as the patient was unwilling to reënter the hospital for study, the attendant recommended further radiation of the third ventricle and on *February 18, 19, and 21, 1931*, three additional treatments were given. After an interval of two weeks, the symptoms again disappeared and he was lost sight of. No dietary restrictions had at any time been imposed.

Eleven months elapsed when on *January 18, 1932*, he again reported to the clinic stating that his gastric symptoms had recurred and he wished to have more x-ray treatments. Because the symptoms were so suggestive of ulcer, barium studies were made and a typical active duodenal ulcer was disclosed.

As he was unwilling to enter the hospital to have his ventriculograms repeated, he was given another series of radiotherapeutic treatments on *January 18, 19, 20 and 21*, directed to the third ventricle. Within three days after the last session, the symptoms of indigestion had wholly disappeared and he returned to work. He reported on request, *March 3*, for barium studies which showed the trace of a healed ulcer unassociated with local tenderness. He was symptom-free and could eat the most indigestible articles (*e.g.* cabbage) without discomfort.

Here, then, was a symptomatic and roentgenologically demonstrable duodenal ulcer associated with a symptomatic and roentgenologically demonstrated tumor of the third ventricle. The growth fortunately proved to be susceptible to the effects of roentgen therapy, and when pressure symptoms were thereby relieved the gastric symptoms promptly subsided. Indeed, in the absence of any actual return of intracranial symptoms, therapeutic radiations of the third ventricle have on two subsequent occasions had a prompt and long-enduring effect in checking the recurrent symptoms of the ulcer.

Other examples of symptomatic and roentgenologically demonstrable ulcer have been encountered in association with diabetes insipidus and with tumors of the nervus acusticus; but it is needless further to pile up the evidence drawn from a single clinic, particularly since the relation of organic intracranial disease to peptic erosions or ulcers will come up for later discussion.

II. PATHOGENESIS OF PEPTIC ULCERATIONS

A satisfactory, all-embracing explanation of acute or chronic ulcerations of stomach and duodenum is yet to be found. From the first it has been a highly controversial subject regarding which there are many divergent views. Until an acceptable explanation is reached, we cannot look forward to the prevention of ulcer, and physicians and surgeons will continue to differ widely in their views regarding the proper therapeutic régime to follow in its active stage and how to forestall its tendency to recur when once healed. What is more, even those surgeons who believe that most ulcers should be operated upon differ in the procedures which they advocate for its cure or alleviation. Indeed, it is doubted in some quarters whether haemorrhagic erosions (*cf.* Cases 4 and 5) or acute perforative lesions (*cf.* Cases 1, 2, 3, and 7) or gastromalacia (*cf.* Cases 8 and 9) are in any way related to chronic ulcer, it being the fashion just now in some foreign clinics to ascribe ulcer, as Cruveilhier did long ago, to an antecedent gastritis.

The literature of ulcer pathogenesis is enormous. In his review of the subject[40] in 1911, Möller cited 325 references, and this number in the intervening two decades has probably been quadrupled. Based on experiment or on experience at bedside and operating table, pathologists, physiologists, pharmacologists and clinicians have offered innumerable explanations. Old hypotheses long forgotten are from time to time revived with some slight modification, and the fact that in defence of each one of them a strong brief could be written means that in all probability

more than one causative element must be concerned. It indeed is quite possible that the several hypotheses—vascular, traumatic, secretory, toxic, bacterial, biochemical and so on—are capable of being harmonized.

Most of the attempts experimentally to produce in the lower animals peptic ulcers have been made on the stomach itself under the assumption that the disorder is essentially a local one. Erosions and occasionally chronic ulcers have thus been produced by a great variety of procedures which in most instances are remote from the circumstances in which ulcer so commonly occurs in man. Attention, indeed, has been so largely confined to the local search for an explanation of the lesions that their ease of production by injuries of the central nervous system has been largely forgotten, though it is an old story. In his discussion of ulcer pathogenesis in 1885, Professor Welch stated[53] that "the neurotic theory of the origin of gastric ulcer is altogether speculative and has never gained wide acceptance." While this view is generally held at the present day, the evidence in favour of the theory is nevertheless accumulating and I shall endeavour to draw it together as briefly as circumstances permit.

A. NEUROGENIC VERSUS LOCAL EXPLANATIONS

In a section of his celebrated *Handbuch der pathologischen Anatomie* (1841–1846)* dealing with "the ulcerative processes of the stomach," Carl Rokitansky described with unsurpassed clearness, brevity and detail all the processes that have been illustrated in the eleven cases given above—acute perforating ulcers, haemorrhagic erosions and the simple chronic ulcer. He also described two forms of acute softening which he sharply distinguished from cadaveric softening or self-digestion of the stomach. The first of them, a gelatinous softening, occurs in the newborn and is frequently associated with a demonstrable intracranial lesion; hence, "the proximate cause may be looked for in diseased innervation of the stomach, owing to a morbid condition of the vagus, and to extreme acidification of the gastric juice." Of the second form of softening he distinguishes two types: one of them "occurs, both in children and adults, as the sequel of acute affections of the brain or its membranes, and is probably brought about by a reflex action of the oesophageal and gastric branches of the vagus"; in the other type associated with cachectic states, the stomach contains large quantities of "coffee-ground" fluid which is often vomited during life. Softening of this latter type often attacks the lower third of the oesophagus (*cf.* Case 3) leading to perforation and effusion into the left thorax. He admits that a conscientious pathologist may find difficulty in distinguishing between cadaveric softening and morbid softening unless he take the clinical history and mode of death into consideration.

This, so far as I can gather, is the first definite suggestion that any of the ulcerative processes under discussion may have a neurogenic origin. So far as chronic ulcer is concerned, Rokitansky does not go further than

* The third volume, in which the pathology of the organs of nutrition is considered, was the first to be published (1841).

to state that it probably commences as an acute circumscribed haemorrhagic erosion which increases by sloughing and exfoliation layer by layer, and is invariably accompanied by a chronic catarrh of the mucous membrane.

Though his works are no longer read and his reputation as a pathologist was soon to be eclipsed by the greater fame of Virchow, Rokitansky's teaching based on a vast experience gained at the autopsy table made a deep impression on his contemporaries which still endures. Thus, for example, there survives in Vienna, whence it has spread into many pathological laboratories throughout the world, a tradition of the dead-house, in effect, that autolytic destruction of the stomach is most often found in the bodies of persons who while digesting have died from an intracranial disorder, particularly when it was associated with a terminal fever of high degree. Beyond this the general subject of gastric erosions or of gastromalacia arouses no present-day interest and is scarcely mentioned in contemporary textbooks on pathology. That it has any possible bearing upon or any possible relation to chronic peptic ulcer is no longer even suggested.

Traceable to Virchow is the concept that ulcer is essentially a local process; and out of this has come the highly unprofitable search for its primary cause in the walls of the stomach itself—a search beset by pitfalls and contradictions. The discredited view of Rokitansky, on the other hand, that the disorder has a neurogenic source has slowly but surely gained ground* as our knowledge of the vegetative nervous system and its cerebral connections has increased. His influence may be traced in four more or less independent directions which deserve separate consideration. The *first* of them leads to the association of brain tumor and ulcer in regard to which, so far as I can observe, he made no allusion; the *second* concerns the gastro-duodenal ulcers and erosions of infancy; the *third* leads to the experimental production of ulcer by lesions of the nervous system; and the *fourth*, to concepts concerning ulcer production which have been looked upon as somewhat fantastic though based securely on pharmacological grounds. The last of these four currents of thought is the most important; but to the others some reference, however brief, may in turn first be made.

B. ULCERS AND INTRACRANIAL DISORDERS

In most of the eleven cases assembled to illustrate this report, the surgical procedure and not the tumor was looked upon as the provocative

* In his brief discussion of ulcer in the article usually quoted (Virchow's *Arch.*, 1853, v, p. 363), Virchow makes no reference to Rokitansky and merely refers to a recent article by Günsburg (*Arch. f. physiol. Heilk.*, 1852, xi, 516–527) who on the basis of a single clinical case showing hyperacidity advanced views regarding the possible vagal influence on ulcer similar to those which Rokitansky had propounded eleven years before. It is probably because of this that Günsburg's paper is so frequently referred to, as, for example, by Ewald in his *Lectures on Diseases of the Digestive Organs* (New Sydenham Society, London, 1892, ii, 425 *et seq.*) who quotes Günsburg as saying that "the [ulcerative] destruction of the mucous membrane of the stomach proceeds from a quantitative anomaly of the secretion of free acids."

cause of the lesions in the proper alimentary canal. The exceptions were the two cases of hypertension with choked disc (Cases 6 and 7), the man (Case 11) with an unverified tumor of the third ventricle, and the child (Case 10) with intraventricular metastasis. As a matter of fact, in the absence of operative intervention, acute or chronic ulcers are known to accompany intracranial tumors, when properly situated to produce them, more often than can be explained by mere coincidence. The remarkable thing is that the combination of the two lesions should occur at all and be found post-mortem, for an acute perforative gastric lesion is so obviously the immediate cause of death the brain may not be examined; or should an obvious intracranial tumor lead to a fatal issue, permission for a post-mortem examination is likely to be restricted to an examination of the brain alone.

Not only, therefore, are the combined lesions—brain-tumor, and ulcer—unlikely to be observed, one masking the other, but, what is more, when observed and reported they are not easily located. Nevertheless, a few examples, old and recent, may be given. In 1868, Professor Carl Hoffmann, of Basel,[25] one of the early upholders of the view that softening (oesophagomalacia or gastromalacia) was a process which began before death, described two cases of oesophageal perforation in adults with ante-mortem signs of peritonitis. The second case had definite intracranial symptoms and was found at autopsy, three and a half hours after death, to have a gummatous, interpeduncular tumor with softening of the right half of pons and medulla.

In 1874, Rudolf Arndt, the Greifswald psychiatrist, in illustration of the fact that functional disturbances may produce symptoms remote from the seat of organic disease, reported the case[1] of a 26-year-old woman with nutritional disturbances, somnolence, amenorrhoea, and vomiting, who died from the effects of a walnut-sized sarcoma of the meninges occupying the interpeduncular space at the base of the brain. There was also disclosed, during the examination, a hyperaemic softening of the stomach with numerous ecchymoses of the fundus, a condition which was ascribed to a reflex disturbance of vagal innervation. Aware that this was not a very convincing case, some years later Arndt reported another example[2]—that of a man of 55 with cerebellar symptoms and Cheyne-Stokes respiration who was found after death to have a median cerebellar tumor compressing the corpora quadrigemina and medulla together with a markedly hyperaemic and ecchymotic lower oesophagus and duodenum in association with ecchymoses, extravasations, and haemorrhagic erosions of stomach. On the basis of these findings, and of the experiments of Schiff and of Ebstein to be referred to later on, the author suggests that round ulcer is an angioneurosis or trophoneurosis, the acute erosions being regarded, in agreement with Rokitansky, as an early stage of the chronic form of ulcer.

Scattered through medical literature under various titles may be found other examples. In a study of the source of postoperative haematemesis observed in von Eiselsberg's clinic after surgical operations, von Wini-

warter[56] stated (1911) that in two unaccountable instances fatal bleeding from the stomach had followed intracranial operations; and in view of my own experiences it is curious that both of them were suboccipital operations for supposed cerebellar tumors.

Subsequently, pathologists in various university centres began to show a renewed interest in these matters. Thus, in 1908[7] Professor Beneke of Marburg, in a study of the causes of "black vomit," furnished statistics concerning gastric erosions and ecchymoses observed in 293 autopsies on medical cases; and though the statistics are somewhat difficult to appraise, the two largest single groups accompanied by erosions were represented (1) by diseases involving organs adjacent to the stomach, and (2) by a group of sixty intracranial disorders, to which ten others classified as "shock in the newly born" might well be added. In 1910 Professor Rössle of Jena made the interesting suggestion[44] that ulcer was commonly a secondary disease (*zweite Krankheit*), reflexly produced through irritation of the vagus by a primary disease elsewhere. Acting upon this idea, in 1918 Professor Carl Hart, of Berlin,[23] attempted to determine the relation, if any, between peptic ulcer and remote disorders; and he found to his surprise that 17 per cent of the ulcers disclosed post mortem during a period of four years were associated with affections of the brain—a percentage exceeding that in which cardiovascular disorders, tuberculosis, or cholelithiasis represented the *erste Krankheit*.

Still more important have been certain studies emanating from the University of Moscow, where, under the leadership of the pathologist, Mogilnitzky, particular attention has been paid to the relation of ulcers to intracranial lesions definitely affecting the interbrain, more particularly the corpus Luysii. In 1925[39] he briefly mentioned four examples of fatal intracranial disorders associated with gastric ulcer; and three years later his pupil, Korst,[32] after mentioning that Mogilnitzky had observed eight cases of tumor of the midbrain or interbrain with gastric or duodenal ulcer proceeds to give three other highly interesting examples. One of them was a frontal lobe tumor involving the basal ganglia in which degenerative processes were observed in the right hypothalamic nucleus on the corresponding side; the second case, a three-year-old child, had an ependymal tumor of the fourth ventricle which had compressed the vagal nucleus and caused a marked hydrocephalus, all the vegetative nuclei of the third ventricle being found degenerated; the third case was one of hydrocephalus associated with sclerosis of the brainstem and a complicating meningitis. In all three instances haemorrhagic erosions of the gastric mucous membrane were found after death.

C. ULCERATIVE PROCESSES IN INFANCY

Five years after Rokitansky's observations were published, there appeared a monograph[15] by Elsässer on autodigestion of the stomach as it occurs in the newborn; and this much-quoted article served to revive the polemics between representatives of the Berlin and Vienna schools as to whether the process was purely cadaveric or whether it started *intra*

vitam. Elsässer's report was based on the study of thirty-eight examples which he had observed, many of them having been associated with intracranial disorders; but he emphasizes that erosions and softening occur only when the stomach is actively digesting at the time of death. Though the post-mortem examinations in all instances were delayed for twenty-four hours or longer, autodigestion was never observed except under the conditions mentioned.

The bearing of all this upon the erosions, perforations, and ulcers of the newly born, often associated with melaena neonatorum, appears to be very largely overlooked or forgotten, owing possibly to the fact that immediately after parturition the mother gets more attention than the child. There nevertheless has been a later-day revival of interest in the subject. In 1911 it was pointed out by Rudolf Pott[42] from Beneke's laboratory in Halle that intracranial birth haemorrhages are usually caused by lacerations of the dura near the junction of tentorium and falx resulting in extravasations of blood into the posterior fossa. In several of the many reported cases, haemorrhagic mucosal erosions and occasionally haemorrhages into the adrenal glands were described in the autopsy protocols without any comment on their significance. In 1892, however, the attention of Professor von Preuschen of Greifswald was drawn to the matter by the example of an infant with melaena who died on the second day after birth, the autopsy showing (1) a subtentorial haemorrhage with extravasation into the fourth ventricle, and (2) haemorrhagic erosions of the gastric mucosa.[43] He was led to believe that an intracranial lesion might be a common cause of melaena in infants, and in collaboration with Pomorski, then an assistant in Grawitz' laboratory,[41] experimental injuries of the hindbrain were made in animals demonstrating the fact that erosions of the gastric mucosa were common sequels of such lesions.

Though the examples of gastromalacia described by Elsässer and the erosions of von Preuschen mentioned above have been acute lesions, ulcerations of more chronic type which occur in the duodenum of infants and which are roentgenologically demonstrable, have more recently been the object of attention. Emmett Holt, in 1913, made a careful study of the subject[26] and two years later Gerdine and Helmholz[20] recorded a series of eleven infants who before death had shown blood in vomitus or stools, duodenal ulcerations occasionally with perforations having been found at autopsy in all instances. Whereas von Preuschen after due consideration discarded as improbable the bacterial origin of ulcer in the newly born, Gerdine and Helmholz warmly supported their colleague Rosenow's well-known views in this regard, all of the lesions which were histologically examined having shown diplococci or streptococci. Attention, however, may be drawn to the fact that in the only three instances in which the brain was examined meningitis was the cause of death; and it may also be noted that streptococci and staphylococci are organisms normally found in the upper part of the alimentary canal.

In the series of cases that I have reported, only three were children, one of whom was found to have had a perforation of the oesophagus.

When this was called to the attention of my colleague, Professor K. D. Blackfan, he kindly looked into the matter and somewhat to his surprise, I believe, found in the autopsy series for 1931 at the Children's Hospital in Boston four examples of death from oesophageal perforation all of them associated with an intracranial lesion (occlusion of the aqueduct of Sylvius with hydrocephalus 1, meningitis 3). In all instances vomiting had characterized the malady and in one at least it contained large amounts of changed blood.

In his *Textbook of Diseases of the New Born* (page 448), Von Reuss states that melaena occurs more frequently after prolonged and difficult labours and suggests that cerebral birth injuries may predispose to erosions; and it is, of course, well known, as Helmholz and others have pointed out, that the roentgenologically demonstrable duodenal ulcers in infants and children are prone to heal and probably therefore are often overlooked.*

D. EXPERIMENTAL NEUROGENIC ULCERATIONS

So far, the argument favouring the neurogenic production of erosions and ulcers may appear somewhat lame, based as it has been: (1) on the lesions which have been seen to occur as a sequel to certain intracranial operations; (2) on the occasional accompaniment of intracranial tumors by ulcers; and (3) on the occurrence of ulcerative processes in the newborn in association with cerebral birth injuries or intracranial disorders of other kinds. The issue has been largely a difference of opinion over the question, on the one hand, whether the erosions and softenings were in any way related to chronic ulcer, and, on the other, whether they were wholly cadaveric lesions or were attributable to processes which were already under way at the time of death. We now come to something more definite; namely, the consequence of experimental lesions; and it may be best to consider separately: (1) *the effect of lesions of the peripheral nerves to the stomach*, and (2) *the effect of lesions of the brain.*

1. Peripheral Lesions of Vegetative Nerves.—Rokitansky, as has been told, assumed that the intracranial disorders to which he attributed ulcer acted in some way through the mediation of the vagus and this naturally led at many hands to a vast amount of experimental work with highly contradictory results. What is more, reports were made from time to time of gastric ulcers in association with an involvement of the vagus by some pathological process such as a tuberculous lymph-node or mediastinal tumor. It has been found in laboratory animals that erosions, at least,

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* Another condition deserving of mention in this connection as a possible or probable secondary disorder rather than primary anomaly is the so-called hypertrophic stenosis of the pylorus in infants. That this may be an expression of hypervagotonus resulting in muscular hypertrophy from spasm rather than a congenital anomaly has been suggested but never given full credence. Professor Lehmann of Frankfort a.M. (*Ztschr. f. Kinderh.*, 1931, L, 691–704) has pointed out that it occurs not infrequently in association with megalocolon, cardiospasm, congenital dilatation of the bladder and so on—conditions which may likewise be looked upon as a consequence of hypertonicity in the cranio-sacral autonomic.

may be produced in rabbits or dogs either by stimulating or dividing one or both vagi, whether above or below the diaphragm; and not only this but the same effects appear to follow stimulation or resection of the splanchnic nerves or coeliac plexus whence pass the sympathetic nerves to the stomach.

On wading through the literature of the subject, no possible order would seem to come from this chaos. But if the elementary fact is borne in mind that the thoraco-lumbar (sympathico-adrenal) system of Gaskell and the cranio-sacral (autonomic) system of Langley represent, as Hans Meyer has shown, a nicely balanced dual mechanism, the visceral effects of the two systems being antagonistic one to the other, it becomes apparent, in spite of the many contradictions, that the peripheral lesions which have led with the greatest constancy in the laboratory to ulcerative lesions have either been paralytic on the part of sympathetic nerves or stimulatory on the part of the vagus.

Most of the experimental procedures, naturally enough, because of their greater ease of production, have been paralytic in nature; and though vagal section whether above or below the diaphragm has led to erosions and acute ulcerations at many hands, it is possible that, in the process of paralyzing the nerves, a primary stimulatory effect may actually have been produced. But however this may be, more consistently successful results have followed severance of the splanchnic nerves or extirpation of the coeliac plexus (*e.g.*, della Vedova, 1900,[52] Durante, 1916,[13] and Gundelfinger, 1918[22]), or from bilateral adrenalectomy (*e.g.*, Finzi, 1913,[17] Gibelli, 1909,[21] and Mann, 1916[37]).

The effects of long-continued peripheral nerve excitation are far less easily investigated. Nevertheless, successful attempts have been made in this direction. Thus, Keppich (1921)[30] produced gastric ulcers showing definite tendency to chronicity in ten out of eleven rabbits by placing electrodes on the vagi near the cardia and leading them out over the animal's back so that the nerves could be intermittently stimulated over periods from five to twenty-five days; and more recently Stahnke (1924),[51] avoiding the complicating effects of a primary operation, stimulated the vagi in dogs near the cardia by placing his electrodes in the lumen of the lower oesophagus with resultant hypermotility, hypersecretion, pylorospasm, chronic gastritis and ultimate erosions.

So far as the stomach is concerned, on this working basis of imbalance between sympathetic and parasympathetic systems, it is known that vagal stimulation causes increased motility and secretion, whereas sympathetic stimulation gives reverse effects; and as a natural corollary, vagal paralysis diminishes secretion and motility, whereas sympathetic paralysis increases them presumably by releasing the vagus from the check normally exercized by the sympathico-adrenal apparatus against its overaction. On these general principles is based the surgical division of the left branch of the vagus as it passes to the stomach wall—a procedure advocated for ulcer patients showing high preoperative free acidity with hypermotility, and routinely practised by some surgeons both in

this country[31] and abroad with results said to be, at least temporarily, excellent.*

2. Lesions of Vegetative Nerve-tracts in the Brain.—In 1845, three years after Rokitansky's views became known, Moritz (Maurice) Schiff, a brilliant and highly original pupil of Magendie's, made the interesting observation[45] that a unilateral cerebral lesion in dogs and rabbits involving optic thalamus and adjacent cerebral peduncle would often lead, after a few days, to softening of the stomach and occasionally to actual perforation. Schiff ascribed this to a patchy (*en plaque*) neuroparalytic hyperaemia of the gastric mucous membrane brought about by injury of the central pathway for vasomotor nerves to the stomach. He subsequently observed also[46] that a unilateral division of the pons or of the medulla as far back as the calamus scriptorius, and even that hemisection of the two upper segments of the spinal cord, would cause the same effect. Whether unilateral division of the cord lower down or injuries of the sympathetic nervous system would produce lesions of the same kind he was unable to determine as the animals failed to survive. Nevertheless, by this ingenious series of experiments, he was able to trace the course of the vasomotor nerves of the stomach [*sic*] from the thalamus to the commencement of the cervical cord. He also observed: (1) that stimulation of the corpora quadrigemina, the cerebral peduncles, the pons and cerebellar peduncle caused gastric movements comparable to those elicited by vagus stimulation; (2) that these movements were blocked by division of the vagi; and (3) that stimulation of the splanchnics, and more particularly of the coeliac plexus, caused contraction of the vessels of the stomach.

Schiff's final views regarding these matters were published in 1867 in his celebrated *Lectures on the Physiology of Digestion.*[47] In general terms, he recognized that there were vaso-constrictor and vaso-dilator fibres to the stomach; that the former passed by way of the coeliac plexus, whereas flushing effects were produced by stimulation of fibres in the pneumogastric. It requires little imagination, reading between the lines of his discussion, to foresee the present-day distinction between counterbalancing sympathetic and parasympathetic systems, both of them under the control of higher centres which Claude Bernard located in the medulla but which modern views, as will be seen, tend to place in the hypothalamic nuclei of the interbrain.

Schiff's experimental observations were soon repeated and essentially confirmed by others. In November 1875, Brown-Séquard,[10] before the *Société Anatomique*, exhibited the stomach of an animal which had died from the effects of a chronic perforative gastric ulcer produced by an injury (cauterization) of the cerebral cortex. While upholding Schiff's

* It however has been observed that gastric acidity may return in course of months or years after experimental double vagotomy even when associated with a subtotal gastrectomy, indicating a highly efficient compensatory mechanism (*cf.* Shapiro, P. F., and Berg, B. N.: *Proc. Soc. Exper. Biol. & Med.*, 1932, XXIX, 743–745).

views in general, he distinguishes between softening and haemorrhagic lesions which latter he found to be a uniform consequence of experimental injuries at the junction of the middle cerebellar peduncle and the pons.

More fully reported were the series of contemporary experiments carried out by Wilhelm Ebstein,[14] then director of the Medical Polyclinic in Breslau. By injecting chromic acid he made small unilateral punctate lesions alongside the anterior corpora quadrigemina without injury to the adjacent peduncle, and in nine of twenty-three animals succeeded in producing ulcerative erosions. He also got similar though more delayed effects by unilateral lesions of the thalamus, medulla and of the upper cervical cord, but found complete transection of the cord to be without effect on the stomach. He attributed this negative result to the consequent lowering of blood-pressure whereas the intracranial lesions, presumably from stimulation of a vasomotor centre, elevated the blood-pressure leading to submucosal extravasations of blood which permitted the corrosive action of the gastric juice locally to take effect.

Similar experiments were conducted some twenty years later by von Preuschen and Pomorski[43,41] as an outcome of their interest in melaena neonatorum. Pulmonary and gastric haemorrhages were produced by punctate lesions of the crura cerebelli, corpora quadrigemina, pons and floor of the fourth ventricle in rabbits. Their most constant results, however, occurred when chromic acid was injected into the right anterior colliculus, only two failures to get ulcerations after ten hours having been observed in eleven animals with lesions made in this situation.

More recently (1925–1926) the matter has been taken up anew by Professor Mogilnitzki and his surgical colleague Burdenko of the University of Moscow.[11] With the object of stimulating or paralyzing vegetative nervous centres in the diencephalon, more particularly the corpus Luysii, which they assumed to be the pathway for vaso-dilatation, they made lateral punctures into the hypothalamic region and observed in stomach and duodenum not only haemorrhagic erosions and perforations but also in some instances chronic cicatricial ulcerations. Thus, from the time of Schiff, unilateral lesions, which in some way have affected not only the presumptive source of vegetative (vagal) impulses in the hypothalamus but the supposed pathway of the fibres from this region backward as far as the medulla and upper cord, have in the hands of several investigators led to ulcerative processes in the stomach or duodenum with fairly consistent regularity.

Most of these experiments, as will have been noted, have been made in rabbits, an animal particularly prone to show gastric erosions under a great variety of circumstances; and what is more, the lesions in most instances have been without evidence of chronicity. A far more telling series of experiments has recently been carried out by Professor Allen D. Keller, of the University of Alabama, who has kindly permitted me to give the following brief reference to his unpublished observations.

In a study primarily undertaken to throw light on the heat-regulating mechanisms of the brain stem in cats, bilateral lesions were made in the expectation

of freeing the hypothalamus from its connections with the brain stem. From these operations the animals recovered perfectly, showed no appreciable effects of the lesions, and appeared to be entirely normal in all respects. After the expiration of a few days, however, they refused food, had spontaneous vomiting, and died in from four to ten days. Post-mortem examinations invariably showed gastric lesions ranging from simple hyperaemic areas to erosions extending through all the layers of the gut, and to punched-out perforating ulcers. The definitely delimited hyperaemic areas were always found at the terminal end of a small artery. The preliminary event, in other words, was a characteristic patch of hyperaemia resulting in a submucosal extravasation visible from both mucosal and peritoneal surfaces, and which was definitely the precursor of the mucosal erosion.

Many of these observations, therefore, which are in line with the original concept of Rokitansky, tend to conciliate his views with those of Virchow in explaining how the local vascular lesion on which the gastric secretion acts comes to be brought about through neurogenic influences. None of the recorded cerebral lesions that have served experimentally to produce ulcer, except those of Burdenko and Mogilnitzki, have been made higher than the midbrain, nor have they been sufficiently circumscribed, in want of knowledge concerning the precise pathway for the vegetative impulses, to permit us to determine whether the effects have been due to stimulation or to paralysis of efferent sympathetic or of parasympathetic fibre tracts.

That there are important nerve centres in the walls of the third ventricle was first emphasized by Edinger, and the recent painstaking studies, particularly by Rioch (1930), have served to locate them in minute detail. From a physiological standpoint, three principle nuclear accumulations (Beattie) may be distinguished: (1) the supra-optic cluster, (2) the tuberal cluster, and (3) the more posteriorly situated hypothalamic cluster from which pupillary responses, sympathetic in character, can be electrically elicited. Stimulation of the tuberal nuclei, on the other hand, appears to give parasympathetic (vagal) responses; and there is considerable evidence from anatomical as well as physiological studies that the active principle of the neurohypophysis exerts a direct influence on the tuberal as well as on the supra-optic cell clusters.

Though the course of the fibres from these hypothalamic nuclei backward toward the medulla and cord to emerge in the cranio-sacral autonomic periphery, on the one hand, and in the thoraco-lumbar sympathetic field, on the other, is still obscure, the matter has been attacked in various ways: (1) by tracing the early embryonic development of the finely myelinated fibres coming from these nuclei* which are among the first identifiable fibres to be laid down (Cajal, Kölliker and van Gehuchten); (2) by the study of fibre degenerations after experimental lesions

* One might well expect that anatomical evidences of the "oro-anal" autonomic (parasympathetic) apparatus would be the first to appear in view of the greater need in the newly born of a buccal and cloacal vegetative mechanism for sucking, digestion, and evacuation, than for an apparatus like the thoraco-lumbar sympathetic, useful in the emergency of escape or combat.

(Beattie, Brow and Long); and (3) by stimulatory experiments on serially decerebrated animals (Langworthy and Richter). While much remains to be learned, the general course of the fibres* is now sufficiently clear (*cf.* Spiegel[50] and Beattie[6]) to make it apparent that the experimental injuries of Schiff, Ebstein, Keller, and others have served to stimulate or injure the principal descending fibre tracts, but whether the secondary peptic lesions which are under discussion have been due to parasympathetic (vagal) stimulation or to sympathetic paralysis must remain conjectural until more precise information is at hand.

III. PHARMACOLOGICALLY GAINED INFORMATION

A. CLINICAL INTERPRETATION

Through the effect of drugs much of our knowledge of sympathetic and autonomic systems has been acquired. It began with Schmiedeberg's observation, made in Ludwig's laboratory in 1871, that after the injection of nicotine stimulation of the vagus quickened rather than slowed the frog's heart; and subsequently Langley and Dickenson demonstrated (1889–90) that painting the paravertebral ganglion with nicotine or a nicotine-like substance (pituri) served effectually to block sympathetic impulses passing from the cord. That nicotine has a powerful vagotonic effect can be appreciated by all of those who remember the consequences of their first cigar; and that on the part of habitués excessive smoking among other things is highly disturbing to digestive processes is well known to clinicians and fully recognized if not always admitted by the victims of ulcer themselves.**

To Gaskell's pathfinding studies (1886) we owe our present conception of the thoraco-lumbar sympathetic (the sympathico-adrenal system of Cannon), but it was left for Langley to prove the existence of a separate "cranial outflow" and a "sacral outflow" (his "oro-anal" autonomic or parasympathetic system), the two systems being essentially different in their phylogenetic development and physiological activity.[33] But the conception that there exists in constant operation a physiological antagonism or balance between these two systems appears to have reached its

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* The sagittal bundle of fine fibres, which through their entire course run near the ependyma (*fasciculus periependymalis* of Ramón y Cajal or the *dorsal longitudinal bundle* of Schütz) and which apparently connects with the nucleus paraventricularis of the hypothalamus, in all probability represents the principal pathway for the discharge of vegetative impulses. The subject has recently been ably discussed by Otto Marburg (*Arb. a. d. neurol. Inst. a. d. Wien. Univ.*, 1931, XXXIII, 135–164). According to W. F. Windle, several ill-defined tracts which form relatively early in the tuber, hypothalamus, striatum, and olfactory lobe, pass into the reticular formation of the midbrain and are among the first to reach the ill-defined trigeminal and vagal centres. The connection between olfactory, visual, gustatory and tactual (pharyngeal) impulses and the phenomenon of vomiting is of course well known; and however these stimuli may be received, their vagal effects are apparently discharged along these descending pathways.

** *Cf.* Moynihan, B. *Two lectures on gastric and duodenal ulcer.* Bristol: John Wright & Sons Ltd., pg. 43.

development not in Cambridge but elsewhere. First clearly pointed out by Hans Meyer's pupils, Fröhlich and Loewi,[18] and subsequently elaborated by Hans Meyer himself,[38] this concept became popularized by others who, first and last, have been attached to the Vienna School.

So far as concerns the stomach, the action of adrenalin in checking motility and diminishing secretion is equivalent to a stimulation of the sympathetic apparatus. On the other hand, the action of other drugs, notable among which are pilocarpine and physostigmine, is equivalent to stimulation of the cranial autonomic (parasympathetic) system of which the vagi are the more important branches, and the effects are counteracted by atropine. The several drugs which serve as vagal stimulants are somewhat selective in their action on the divisions of the parasympathetic apparatus, whereas adrenalin, as Cannon has emphasized, acts explosively on the entire thoraco-lumbar system at one and the same time.

Since there is no known paralysant for the sympathetic system (unless ergotoxine may be such) counteractive to adrenalin as atropine counteracts pilocarpine, in studying the effects of lowered sympathetic activity recourse must be had to the experimental extirpation of the prevertebral chain, splanchnic nerves, coeliac plexus or of the adrenal glands themselves. Sympathetic paralysis thus produced is equivalent in its effects to autonomic (parasympathetic) stimulation due to a release phenomenon; and on the other hand, parasympathetic paralysis theoretically is equivalent to sympathetic stimulation though the effects may be not so evident.

A clinical application of this concept of counterbalance between sympathetic and parasympathetic systems, particularly in relation to the vegetative functions of the pneumogastric, was brilliantly presented[16] by Eppinger and Hess (1910), then colleagues of Hans Meyer in Vienna, in their monograph on *Vagotonia*—a treatise which gave a wholly new interpretation of certain kinds of "nervous invalidism." Vagotonic persons according to their thesis react with sweating and salivation to small doses of pilocarpine; they are apt to be asthenic, to have cardiac arrhythmias, and to show gastric hyperacidity, these symptoms being invariably aggravated by pilocarpine. What is more, the "nervous dyspepsia," gastrosuccorrhoea, pylorospasm, cardiospasm and hunger pains to which vagotonic persons are prone are beneficially affected by atropine. Though Eppinger and Hess briefly discuss the relation of vagotonia to gastric ulcer, they do not expressly state that it predisposes to ulcer, but on the contrary seem to imply merely that persons afflicted by ulcer in the absence of hyperacidity, hypermotility and so on merely happen to be exempt from constitutional vagotonicity.

The old idea, nevertheless, that a disordered action of the vagus had something to do with ulcer formation had from time to time been revived, and with the increase of knowledge concerning the relation of the nerve to the digestive functions, the belief was held by some that chronic ulcer was the expression of a neurotrophic disturbance—a sort of *mal perforans* of the stomach. Thus in his discussion of Pavy's theory, that ulcer was due to a chemical imbalance brought about by lowered alka-

linity of the blood, Wilks had stated that a neurogenic influence could no more be overlooked than it could in an obviously neurotrophic ulcer of the cornea; and similar ideas have been newly restated in view of the frequency with which ulcer has been observed in tabetics.

But the general ideas formulated by Eppinger and Hess were first definitely focused on spasmodic peptic ulcer in 1913[8] by Professor von Bergmann who emphasized: (1) that the parasympathetic nervous system is discovered in ulcer; (2) that patients with ulcer respond to pilocarpine more markedly than do normal persons; and (3) that the long continued use of atropine will cure or ameliorate the familiar symptoms which accompany the disease.

This ingenious explanation of ulcer has found favour not only with many clinicians but also with roentgenologists, notable among whom may be mentioned Martin Haudek, of Vienna.[24] In subsequent papers[9] on the subject, von Bergmann, while disclaiming that hypervagotonicity is the cause of *all* ulcers, asserts that they are more common in persons with a neuropathic constitution who show irritability of the secretory and motor functions of the stomach—in other words, in persons with an overactive parasympathetic nervous system. Thus, through a dysharmony or imbalance of the two divisions of the vegetative apparatus the local spasm leading to impaired vascularity of the mucosa that precedes erosions and ulcers is prone to occur.

This novel conception of ulcer pathogenesis, like all other explanations, has found its prompt opponents. Loeper and Marchal,[36] for example, in discussing the matter (1926) express the belief that the irritative disturbances on the part of the cranial autonomic system are the consequence rather than the cause of chronic ulcer, which they ascribe to the outpouring of leucocytes (*leucopédèse*) in the submucosa. Simnitzky[48] also (1926), in calling attention to von Bergmann's admission that stimulation of the vagus is more active in an acid milieu, and of the sympathetic more active in an alkaline milieu, agrees with Bálint[3] (1926) in ascribing ulcer to primary acidosis of the tissues rather than to dystonia of the vegetative nervous system, which is reminiscent of the early conception held by Pavy and others of ulcer pathogenesis.

1. Substantiation by peripheral action of drugs.—Meanwhile, von Bergmann's assistant, Karl Westphal,[54] undertook to see if ulcer might not be produced in the lower animals by drugs known to stimulate the parasympathetic system. For this purpose pilocarpine and physostigmine were selected and given subcutaneously to rabbits in toxic doses (cats, dogs and guinea pigs were less susceptible), localized areas of ischaemic cyanosis being produced leading to erosions from subsequent action of the gastric juice on these vulnerable points. The lesions occurred, however, only when the animal was actively digesting and when the contents of the stomach were acid.*

* Another drug, histamine, which some look upon as a parasympathetic stimulant in that it causes pronounced flushing with increase of gastric secretion, is more selective in character than pilocarpine; it supposedly acts (Dale *et al.*) on the glands

These observations on pharmacologically produced ulcerations, important and suggestive though they are, lie open to the same criticism that applies to other locally produced experimental ulcers in that they emphasize the effects of the drug on the neurosecretory end-organs. That vagal stimulants like pilocarpine may appear to act with especial vigour on a parasympathetic centre will now be considered.

2. Substantiation by central action of drugs.—Following the discovery by Karplus and Kreidl of the Vienna School in 1909[29] that electrical stimulation of the hypothalamus [doubtless the posterior hypothalamus] caused pupillary dilatation, sweating, and other phenomena indicating the existence of a diencephalic centre for the sympathetic nervous system, increasing attention has been paid to the functions of the hitherto much neglected interbrain. In 1925, the interesting observation was made by Cannon and Britton[12] that cerebral decortication in the cat led to an emotional state which they designated "sham rage" from its close resemblance to the behaviour of the infuriated normal animal. A prominent feature of these emotional explosions was a mass discharge of the sympathetic nervous system with liberation of adrenalin. Bard[4] subsequently made it clear (1928) that this pseudaffective state in decorticated animals depended upon an intact posterior interbrain; and Fulton and Ingraham in turn (1929) showed[19] that a chronic state suggesting "sham rage" was present in cats whose cortico-frontal pathways to the interbrain had been surgically divided. Whereas Gaskell had looked upon the thoraco-lumbar sympathetic as largely a spinal involuntary mechanism, and Langley had carried the cerebral stations of the cranial autonomic apparatus no further headward than the midbrain, these later-day disclosures, indicating that cortically uninhibited affective states emanating from the diencephalon can discharge the sympathico-adrenal apparatus, shed an entirely new light on the subject.

At another time [pg. 67 et seq.], certain observations were reported on the effects of injecting posterior pituitary extract (pituitrin) and pilocarpine into the cerebral ventricles. When either the extract or the drug is thus introduced in susceptible (vagotonic?) subjects, it leads to stimulatory effects among which sweating, flushing, lachrymation and excessive, sometimes blood-tinged vomiting were notable features. These effects were interpreted as being essentially parasympathetic in nature and it was assumed, therefore, that the parasympathetic as well as the sympathetic nervous system most probably had a primary nuclear representation in the interbrain.

Whereas pilocarpine supposedly acts exclusively on the nerve terminals,

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themselves rather than through their nerve supply, and fails to increase gastric motility. Nevertheless Büchner, Siebert and Malloy, of Aschoff's Institute in Freiburg (*Beitr. z. path. Anat.*, 1928, LXXXI, 391–425) have produced gastric ulcers in starved rats by the injection of histamine. They interpret the observations as favourable to a purely biochemical cause of ulcer—a "correlation disturbance" due wholly to increased gastric acidity. This is a form of hair splitting and the authors in their interesting paper (p. 394) admit that the "correlation disturbance" may be brought about by impulses in the vegetative nervous system.

the human tests indicated a far more vigorous central and presumably diencephalic action. It accordingly was suggested to my co-worker, Dr. Richard Light, that he try to determine on rabbits whether pilocarpine, introduced intraventricularly, would produce Westphalian erosions in smaller amounts than when given subcutaneously. In collaboration with C. C. Bishop and L. G. Kendall, this matter was put to the test,[34] and it was found that even small doses of from 3 to 6 mgm. injected into the rabbits' ventricles produced erosions and that injections of 10 mgm. would cause them in 94 per cent of the animals, whereas 75 mgm. or more were needed to produce corresponding lesions with equal frequency when the drug was given subcutaneously.

The importance of these observations, in my estimation, lies not so much in the fact that a small dose (2 mgm.) of pilocarpine injected into the human ventricles has a prompt and widespread parasympathetic effect, as in the disclosure that pituitrin, when similarly administered, has a corresponding effect. What is more, the response to intraventricular pituitrin, surprizingly enough, is entirely different from the response which follows its intravenous or intramuscular injection. When introduced into the ventricles of susceptible persons, it causes flushing, sweating, salivation, and prolonged vomiting which, like the effect of intraventricular pilocarpine, can be checked by atropine or prevented either by preliminary atropine or by the narcotic drugs (*e.g.* tribromethanol and the barbiturates) which are known to inhibit the hypothalamic centres. When, on the other hand, pituitrin is injected subcutaneously, it causes pallor without sweating and promptly checks gastric peristalsis and secretion, its action in other words being entirely comparable to the effect of adrenalin.*

The following roentgenological observations of gastric motility made in collaboration with my colleague, Dr. M. C. Sosman, (*cf.* pg. 106 et seq.), have thrown further light on the subject. After a barium meal, the gastric waves as they progress from cardia to pylorus have first been timed, and toxic drugs or extracts have been then administered with results, briefly stated, as follows:

A. Intramuscular injection

1. Adrenalin (1 c.c. of a 1:1000 solution) causes an almost immediate cessation of all visible movement for 20 minutes or longer.

2. Pituitrin (1 c.c. "surgical") has precisely the same effect on the stomach as adrenalin, with cutaneous pallor.

3. Pilocarpine (12 mgm.) also causes a definite diminution of motility associated with moderate sweating.

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* So far as I am aware, there is no other instance of a drug or extract which has contrary effects when administered in different regions of the body; but next to nothing is known of the effects of drugs directly applied to the diencephalic nerve centres. In view of the sensitivity of the vagus nuclei in the fourth ventricle to exceedingly dilute solutions of emetine or apomorphine, it is reasonable to assume that painting the walls of the tuber cinereum with one of these drugs will produce the same or an even more vigorous effect on the stomach.

4. Histamine (1 mgm.) causes a cutaneous flush without sweating and no striking change in gastric motility.

B. Intraventricular injections

1. Adrenalin (not tried).
2. Pituitrin (1 c.c. "surgical") promptly accelerates motility and soon causes retrograde peristalsis with retching and vomiting which can be checked by atropin. Other effects are sweating and flushing.
3. Pilocarpine (2 mgm.) causes prompt activation of motility, spasm of pylorus, retrograde peristalsis, prolonged retching, and vomiting. These effects which are associated with a drenching sweat, a cutaneous flush and fall in temperature can be checked by atropine. Vomitus shows increased gastric acidity and positive guiac test for blood.
4. Histamine (2 mgm.: two observations). No visible effect on peristalsis. Sense of fullness in head, dry mouth, no flush, no vomiting.

The assumption that these striking consequences of intraventricular pilocarpine and pituitrin were produced by local stimulation of a centre for parasympathetic discharges, has received support from recent observations by Beattie[5] (1932). He has shown on animals that direct electrical stimulation of the region of the tuberal centres in the infundibulum causes not only increased gastric peristalsis and secretion, but, if long continued, leads to small haemorrhagic ulcers of the mucous membrane near the lesser curvature. After section of the vagi these gastric effects were not obtained.

Thus, the reaction of the stomach to the intraventricular injection of either pilocarpine or pituitrin in man and to direct stimulation of the tuber in animals is hypermotility, hypertonicity, and hyperchlorhydria, these three factors being those that commonly persist in cases of chronic gastric ulcer.

Eppinger and Hess, taking their cue from Langley, did not venture in 1910 to place the autonomic control of the vagus higher than the midbrain and felt obliged to postulate the existence of a substance or hormone termed "autonomin" whose continuous activity preserves the normal tonus in the smooth muscles of the vegetative organs—a substance bearing the same relation to the autonomic (parasympathetic) system that adrenalin bears to the thoraco-lumbar sympathetic. That the secretory hormone of the neurohypophysis (pituitrin), in view of the observations mentioned above, may represent their hypothetical autonomin is not improbable, and the idea at least provides a working basis for further study.

IV. SUMMARY AND CONCLUSIONS

The attempt to find a reasonable explanation for the acute perforative lesions affecting oesophagus, stomach, and duodenum, which in three instances caused early fatality after operations for cerebellar tumor, has led, not only to a review of the extensive literature on the neurogenic aspects of ulcer pathogenesis, but also to certain experimental observations that strongly suggest the presence in the diencephalon of a parasympathetic centre. From this centre, apparently tuberal in situation

fibre tracts pass backward to relay with the cranial-autonomic stations of midbrain and medulla of which the vagal nucleus is by far the most important because of its influence upon the activity of the lungs, heart, and upper alimentary canal.

Experimental lesions anywhere in the intracranial course of these fibre tracts from anterior hypothalamus to vagal centre, presumably from parasympathetic stimulation (or possibly from vagal release due to sympathetic paralysis) are prone to cause gastric erosions, perforations or ulcers (Schiff; Ebstein; and others). Intracranial injuries and diseases affecting these same basilar regions of the brain are known to be accompanied by ulcerative lesions of the upper alimentary canal. It is reasonable to believe, therefore, that the perforations following the cerebellar operations forming the basis of this study were produced in like fashion by an irritative disturbance either of fibre tracts or vagal centres in the brain stem.

Stimulation of the postulated parasympathetic centre by intraventricular injections of pilocarpine or pituitrin cause, in man, an increase in gastric motility, hypertonus and hypersecretion leading to retching and vomiting which ultimately contains occult blood. The same effects, associated with observable patches of hyperaemia of the gastric mucous membrane have been shown (Beattie) to follow direct electrical excitation of the tuber cinereum in animals.

The active principle of the neurohypophysis (pituitrin) demonstrable in the tissues in the form of hyaline bodies, is known to find its way through the infundibular stalk to the region of the nuclear cell masses of the tuber either by direct migration (Edinger, Collin) or by the intermediation of blood sinuses (Popa and Fielding); and the secretory product may possibly pass between the ependymal cells to enter the cavity of the third ventricle (Herring, Cushing and Goetsch, Karplus and Peczenik). What is more, the secretion appears to be under the control of autonomic fibres that pass from the supra-optic nucleus into the posterior lobe. Hence, there is an anatomical basis for the presumption that posterior lobe extract (pituitrin) should have a stimulatory influence on the local vegetative nerve centres. That intraventricular pituitrin would cause a parasympathetic discharge with vagotonic effects, whereas given subcutaneously its action resembles that of adrenalin, could not have been foretold.

The interbrain has been shown (Cannon, Bard) to be the seat of primitive emotions which are normally under cortical control; but in experimentally decorticated animals, probably from release of the sympathetic nucleus in the posterior hypothalamus, there occur explosions of "sham rage" accompanied by a mass-discharge of the sympathico-adrenal system.

The parasympathetic apparatus, in all probability, under normal conditions is likewise strongly affected by cortical or psychic (Pavlov) influences. However this may be, direct stimulation of the tuber or of its descending fibre tracts, or what thoeretically amounts to the same thing,

a functional release of the vagus from paralysis of the antagonistic sympathetic fibres, leads to hypersecretion, hyperchlorhydria, hypermotility and hypertonicity especially marked in the pyloric segment. By the spasmodic contractions of the musculature, possibly supplemented by accompanying local spasms of the terminal blood-vessels, small areas of ischaemia or haemorrhagic infarction are produced, leaving the overlying mucosa exposed to the digestive effects of its own hyperacid juices.

Thus it is possible to reconcile the neurogenic theory of ulcerations sponsored by Rokitansky with Virchow's variously modified theory of a primary local cause, whether the lesions are considered in terms of simple erosions, of acute perforations, of autodigestive softening, or of chronic ulcers, and whether they chiefly involve oesophagus, stomach, or duodenum.

Those favourably disposed toward the neurogenic conception of ulcer have in process of time gradually shifted the burden of responsibility from the peripheral vagus to its centre in the medulla, then to the midbrain, and now to the interbrain, newly recognized as a highly important, long overlooked station for vegetative impulses easily affected by psychic influences. So it may easily be that highly strung persons, who incline to the form of nervous instability classified as parasympathetic (vagotonic), through emotion or repressed emotion, incidental to continued worry and anxiety and heavy responsibility, combined with other factors such as irregular meals and excessive use of tobacco, are particularly prone to have chronic digestive disturbances with hyperacidity often leading to ulcer—effects wholly comparable to those acutely produced by irritative lesions experimentally made anywhere in the course of the parasympathetic system from tuberal centre to its vagal terminals.

While this conception of the aetiology of ulcers does not account for all ulcerative processes under all conditions, it offers a reasonable explanation of the majority of them and is in accord with the personal experience of most victims of chronic recurring ulcer. This, briefly, is as near as one can come, with the data at hand, to an interpretation of the neurogenic origin of peptic ulcer and an explanation of its existing prevalence.

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THIS BOOK

Papers Relating to the

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and

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