Papers Relating to the

PITUITARY BODY, HYPOTHALAMUS

and

PARASYMPATHETIC NERVOUS SYSTEM

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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

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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

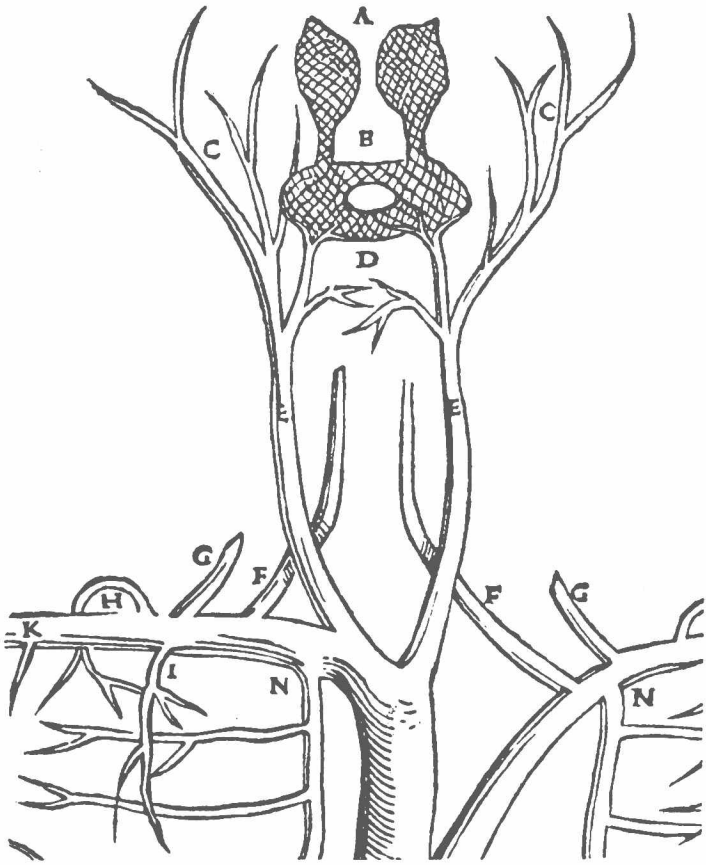

FIG. 1.—Vesal's original figure (1538). A, Plexus choreiformis; B, Plexus reticularis ad cerebri basim, rete mirabile.

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).

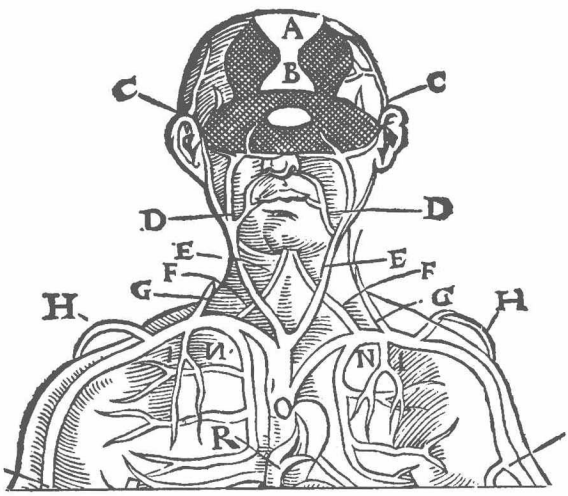

FIG. 2.—Ryff's adaptation (1541) of Vesal's diagram. A, Blut aderlin in beyden vordern holin des hirns. B, das wunderbarlich netzlin.

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:

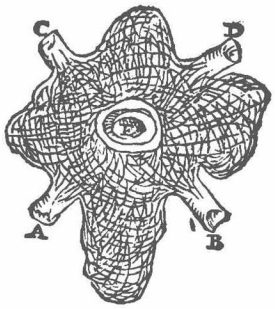

FIG. 3.—Vesal's 1543 diagram expressing his interpretation of Galen's conception of the *Rete*. A and B, entering vessels; C and D, corresponding veins; E, point of discharge for pituita from brain.

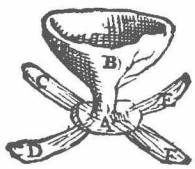

FIG. 4.—Vesal's representation of the infundibular funnel (B) by which the cerebral pituita is distilled into the gland (A) from which four ducts (C, B, E, and F) emerge to neighbouring foramina.

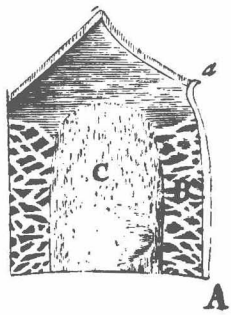

FIG. 5.—The diagram given by Willis (1664) of the *Rete*. (AA) arteria canalis directus. B, vasorum plexus restiformis. C, glandula pituitaria.

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