Studies in intracranial physiology & surgery : the third circulation, the hypophysis, the gliomas / by Harvey Cushing.

STUDIES IN INTRACRANIAL PHYSIOLOGY & SURGERY

HARVEY CUSHING

OXFORD MEDICAL PUBLICATIONS

THE CAMERON PRIZE LECTURES 1925

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The Third Circulation
The Hypophysis
The Gliomas

By
HARVEY CUSHING, M.D.

THE CAMERON PRIZE LECTURES
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DEDICATED

To My Successive Appointees in the 'Old Hunterian' at the Johns Hopkins Medical School

and to

The Arthur Tracy Cabot Fellows since 1912 *in charge of the Laboratory of Surgical Research at Harvard.*

Philip K. Gilman	1905–6	Samuel C. Harvey	1915–16
J. F. Ortschild	1906–7	William S. McCann	1916–17
Lewis L. Reford	1907–8	—	1917–19
Samuel J. Crowe	1908–9	George B. Wislocki	1919–20
Emil Goetsch	1909–10	Percival Bailey	1920–21
Walter E. Dandy	1910–11	Roger C. Graves	1921–22
Conrad Jacobson	1911–12	W. J. M. Scott	1922–23
Lewis H. Weed	1912–14	Claude S. Beck	1923–24
Gilbert Horrax	1914–15	Lester R. Whitaker	1924–25

And also to the succession of my Assistant Residents both in Baltimore and Boston, many of whom have since contributed so greatly to our knowledge of the nervous system and the progress of neurological surgery.

George J. Heuer	1908–9	Gilbert Horrax	1915–16
Samuel J. Crowe	1909–10	Samuel C. Harvey	1916–17
Emil Goetsch	1910–11	—	1917–19
William Sharpe	1911–11	Percival Bailey	1919–20
Walter E. Dandy	1911–12	C. E. Locke Jr.	1920–21
H. C. Naffziger	1911–12	Daniel W. Wheeler	1921–22
Charles Bagley Jr.	1912–13	Paul Martin	1921–22
Carl W. Rand	1913–14	Kenneth G. McKenzie	1922–23
Edward B. Towne	1914–15	Tracy J. Putnam	1923–24

Wm. P. Van Wagenen 1924–25

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INTRODUCTION

The conscience of our medical schools, at least of our American medical schools, has of late years been pricked by the well-justified criticism that the everyday symptomatic treatment of patients has been largely neglected in the curriculum. The medical sciences during the last few decades have rapidly expanded and, needing elbow-room, they have crowded the art of medicine to the back of the stage.

To the scientifically trained teacher the diagnosis, which must precede therapy, proves, of the two, to be by far the more engaging pursuit, for it brings into play an increasingly complicated series of modern laboratory tests which furnish all the intellectual enjoyment of a cross-word puzzle. But for many conditions which may thus be diagnosed, there is no specific treatment, and about all that is done for the patient, who hints that he has not seen much of his doctor at the bedside meanwhile, is to prescribe such psychotherapeutic comfort as time may permit, and such appropriate nursing as may be available. In short, far more emphasis is laid in our schools on the methods of finding out what is wrong, than on what should be done for it when it happens to be found.

With this modern tendency in mind, it is of especial interest that, as long ago as nearly half a century, a graduate of this, reputed to be a highly practical medical school, should have left to his Alma Mater a bequest the proceeds of which were to be awarded to a ' practitioner or member of the Medical Profession ' who should be adjudged to have made some addition to practical Therapeutics during the year preceding.*

* A provision subsequently altered by the Educational Endowments Commission to five years, and now apparently without limit.

Very little seems to be known of the founder, Andrew Robertson Cameron, beyond the fact that he was born in Torland, Aberdeenshire; that after two years at Marischal College he came to Edinburgh to complete his medical course, where he was fellow student with such as Crum Brown, Thomas Smith Clouston, and James Bell Pettigrew; that his graduation thesis from this School in 1861 was 'On the Corporeal Sympathies of Certain Mental Conditions'; that he went to Australia, settled in Richmond, New South Wales, and died there in 1878. We may imagine that, pitchforked into a new country where he could not, when in perplexity, fall back upon a metropolitan consultant for therapeutic suggestions, he piously determined that practical therapeutics should be emphasized at Edinburgh so far as an endowed lectureship could bring this about.

His experience, if this it was, is probably a still more common one to-day, when the only old-time practical course still retained in the curriculum of our American schools at least is that in obstetrics; and even this would probably go by the board were it not for legislative requirements. Our students, thoroughly versed in the complicated lore of modern medical science, are more at home in the laboratory than at the bedside; know more about calories and colloids, hydrogen ions and haemoglobin than they know about sick people.

This of itself is not entirely bad, but since the majority of these young men are destined for practice it would balance the ledger if before registration they should be obliged to serve for a few months as an apprentice or substitute for a rural practitioner, while he comes to town to brush up his science. Such an exchange would be beneficial to both parties, but particularly so to the student, who would learn more about the A.B.C.'s of medical practice than he has picked up in his entire course, and meanwhile would

be at his wits' ends to put to any practical use in these surroundings his painfully acquired knowledge of the preclinical sciences.

Even at the outset, the Senatus of the University must have felt that the terms of Dr. Cameron's foundation were elastic, for the first beneficiary was *neither* a practitioner *nor* a member of the medical profession, though Pasteur, had the Testator known of him, would certainly have been his first choice, and his second as certainly Syme's young house-surgeon who had been lured to Glasgow during Cameron's undergraduate days. Theirs, to be sure, were majestic and far-reaching contributions to what your benefactor had in mind, and we are not likely to see their kind again; but practical therapeutics may be helped in lesser and varied ways even by one who may never have seen the inside of a laboratory and yet who devises some novel method, or perfects an old one, of treating the sick and maimed.

Florence Nightingale might justly be regarded as one of the great contributors to practical therapeutics—even Mother Eddy, whose creed has forced upon us a better understanding of psychotherapeutics than we have had since the hey-day of Greek medicine. To be sure, their names do not appear among your Cameron lecturers, though the list comprises those whose contributions have been of many kinds, the product of researches and experiences in laboratories, in wards, in operating rooms; and I am heartened to see that two of them, Horsley and Macewen, have been men who were pioneers in the very practical sort of work in the surgery of the nervous system into which I have become drawn.

I am somewhat relieved, too, by the comforting admonition which says, 'You need not take too seriously the provision that the subjects of your discourses must have been worked upon in the last five years.' This is fortunate, for my spare time during this half decade has largely been

devoted to the study of a man who in his day was called a therapeutic nihilist. But then, there are occasions when a well-justified rebellion against an existing order may open the way for something better; and now that the smoke of battle has cleared and we no longer hear the barrage of the shot gun prescriptions of our predecessors, we may even salute the infinitesimal Hahnemann and look upon Osler's contempt for most drugs as indirectly a great benefaction to practical therapeutics.

On my own part, I feel that the Testator's intent in establishing this Prize has now been stretched as never before, for though some therapeutic contributions have come from my co-workers and pupils, I do not know that I personally am to be credited with anything more than the introduction of a few trifling technical procedures which in time are almost certain to be superseded. However, it was a dictum, I believe, of Huxley's that a teacher's influence, whatever else it amounts to, should be centrifugal, his own ideas being far less important than the ideas which radiate from his pupils and theirs in turn.

One of the greatest satisfactions of my professional life has come from the fact that since 1906 it has been my privilege to appoint annually some younger man who has been put in independent charge of a laboratory of experimental surgery; and as many of them have, first and last, interested themselves in problems which pertain to the subject of these lectures, it will be my privilege therein to call especial attention to the results of their studies, albeit at the risk of seeming to ignore the contributions of others which may have been of equal or greater importance.

I have chosen to dwell upon three topics: on the cerebrospinal fluid and the spaces through which it circulates; on some problems relating to the pituitary body and its disorders; and lastly on the subject of brain tumours in general and of the gliomas in particular.

LECTURE I

THE THIRD CIRCULATION AND ITS CHANNELS

'Cet enfant a de l'eau dans la tête, dit le vulgaire; cet enfant est hydrocéphale, dit gravement le médecin, répétant littéralement par un mot grec ce que dit l'ignorant dans sa propre langue. Mais quelle est cette eau? d'où vient-elle? Voilà ce dont les médecins auraient dû s'occuper.'

FRANÇOIS MAGENDIE, 1842.

As a tribute to the memory of François Magendie I propose to devote the first of these lectures to the subject of the cerebrospinal fluid, for just one hundred years have passed since the appearance of the earliest of his epoch-making publications in which attention was drawn to the physiological importance of the peculiar watery medium which bathes the central nervous system. And in paying this centenary tribute we need not forget that it is precisely fifty years since Key and Retzius published their monumental contribution to our knowledge of the intracranial spaces; and also that the actual discovery of the fluid is generally ascribed to Cotungo, who just 150 years ago gave it the name *Liquor Cotunnii*—with some neglect, be it said, of the observations of Willis (1695), of his contemporary Vieussens in Montpellier (1685) and, what is more, of the *spiritus animalis* of Galen.

Something of the state of our knowledge before Magendie's time may be gathered from a paper (1768) on 'Dropsy in the Brain', by the celebrated Robert Whytt, one-time Professor of Medicine in this university, wherein is given the first recognizable description of what must certainly have been tuberculous meningitis. 'The immediate cause of this disease [he says], and indeed of every kind of

dropsy, is always the same, viz., such a state of the parts as makes the exhalant arteries throw out a greater quantity of fluids than the absorbent veins can take up.' And he subsequently remarks that ' the symptoms of no distemper resemble those of water on the brain so much as those which arise from worms in the stomach '.

It is not for us to smile at this. Vomiting is one of the earliest and most persistent symptoms of the common midcerebellar tumour of childhood, with its complicating hydrocephalus for which even to-day a diagnosis of some gastro-intestinal disorder is usually made ; and whereas the vermifuge of Whytt's day might have given some relief by lessening the ventricular hydrops, the removal of the vermiform appendix, our modern tendency, would be far less likely to do so.

But Whytt, though a man ahead of his time, could have had no possible conception that the cerebrospinal fluid was a specialized fluid with a peculiar circulation of its own. And as my chosen title indicates, it is this particular feature of the fluid, namely its circulating character, that I wish to emphasize, and I shall have less to say about its biochemical and cytological characteristics in health and disease, so thoroughly studied by many,* than about the channels through which it percolates.

A. The Fluid and its Confines

On movement in a circle. It is quite evident that Magendie, who believed the fluid was secreted by the pia, much, for example, as pericardial fluid is secreted, had no idea

* An excellent text-book on the subject by Greenfield and Carmichael has just appeared (Macmillan & Co., 1925). The studies by Alpers,[67] and by Spurling and Maddock [69] on the alterations of the fluid in cases of tumour, and one with Ayer on Xanthochromia,[60] represent our only publications which deal with the composition of the fluid in disease.

of its movement as other than an ebb and flow. And this truly Galenic conception of a cerebrospinal fluid circulation still holds in most modern text-books of physiology, even though Key and Retzius gave a hint of the actual state of affairs by demonstrating the continuity of the fluid-holding leptomeninges as distinct from the subdural space, and by suggesting (without satisfactory proofs, to be sure) that the granulations of Pacchioni represent portals through which the fluid passes from the arachnoidea into the large meningeal sinuses.*

This is about as far as the modern text-books of physiology with which I am familiar go on the subject—if they actually go so far ; and though it is hinted in one of them that the fluid ' is believed to undergo a slow circulation ', it is said to ' pass from the foramen of Magendie into the subarachnoid spaces of the spinal cord, down which it travels on the posterior aspect and then ascends on the anterior aspect, where the greater part of its absorption occurs '. On the whole, it would appear that medical students get little information about the fluid as a circulating medium in their course in physiology, and what they get is mostly wrong.

This curious neglect of a vascular system which teems with bio-physical problems can only be explained on the grounds that the subject of intracranial dynamics is one of the few on which Carl Ludwig, the father of modern physiology, did not focus his fertile mind, and his pupils unto the third generation have followed suit.

Even here in Great Britain, where contemporary physiologists have devoted themselves with particular distinction

* It is interesting to note that Pacchioni himself held quite an opposite view in the matter, for to him these *glandulae conglobatae durae matris* secreted lymph from the dura, which he took to be a sensitive and muscular membrane; and this lymph passing inward served to bathe the brain. ' Dissertationes de Dura Meninge Humana.' 1721.

to a study of the nervous system, most of them, with the notable exception of Leonard Hill and more recently of Dixon and Halliburton, have concerned themselves less with the intracranial contents as a mass, which so interested the most famous of your Alexander Monros, than with localization of function and the course of impulses. However, the names of two Edinburgh men should not be overlooked in any mention of those who have contributed to our knowledge of the cerebrospinal fluid spaces. For, though James Middlemass and W. Ford Robertson of the Morningside Asylum were primarily interested in mental diseases, they were the first to make clear (1895) that the pia mater was merely the inner of the endothelial membranes enclosing the fluid, and so introduced the combined term of pia-arachnoid to designate the system as a unit.

That the arterial and venous blood has ' a motion as it were in a circle ', in contradistinction to the Galenic idea of an ebb and flow, was the conception, when put to proof, by which the immortal Harvey transformed medicine. For even though the idea, from the heart around and back to the heart, was not entirely new, at least so far as the lesser pulmonary circulation is concerned, it was a view against all authority, and in the case of Servetus was burned with its author at the stake.

But the existence of another fluid besides blood which ' circulated ' was soon suggested by Aselli's discovery of the lacteals and Picquet's of the thoracic duct ; and finally William Hunter—or was it again your Monro *secundus* who first postulated that the lymphatics represented a system of absorbent vessels which were supposed to conduct the watery constituents of the tissues ? To be sure, the movement of the chyle and lymph, under this conception, is not actually in a circle in a strictly Harveian sense, but rather what one might describe as across a sector of the

blood circle. And the same is true of the cerebrospinal fluid, which proves to be in continual movement, in a definite

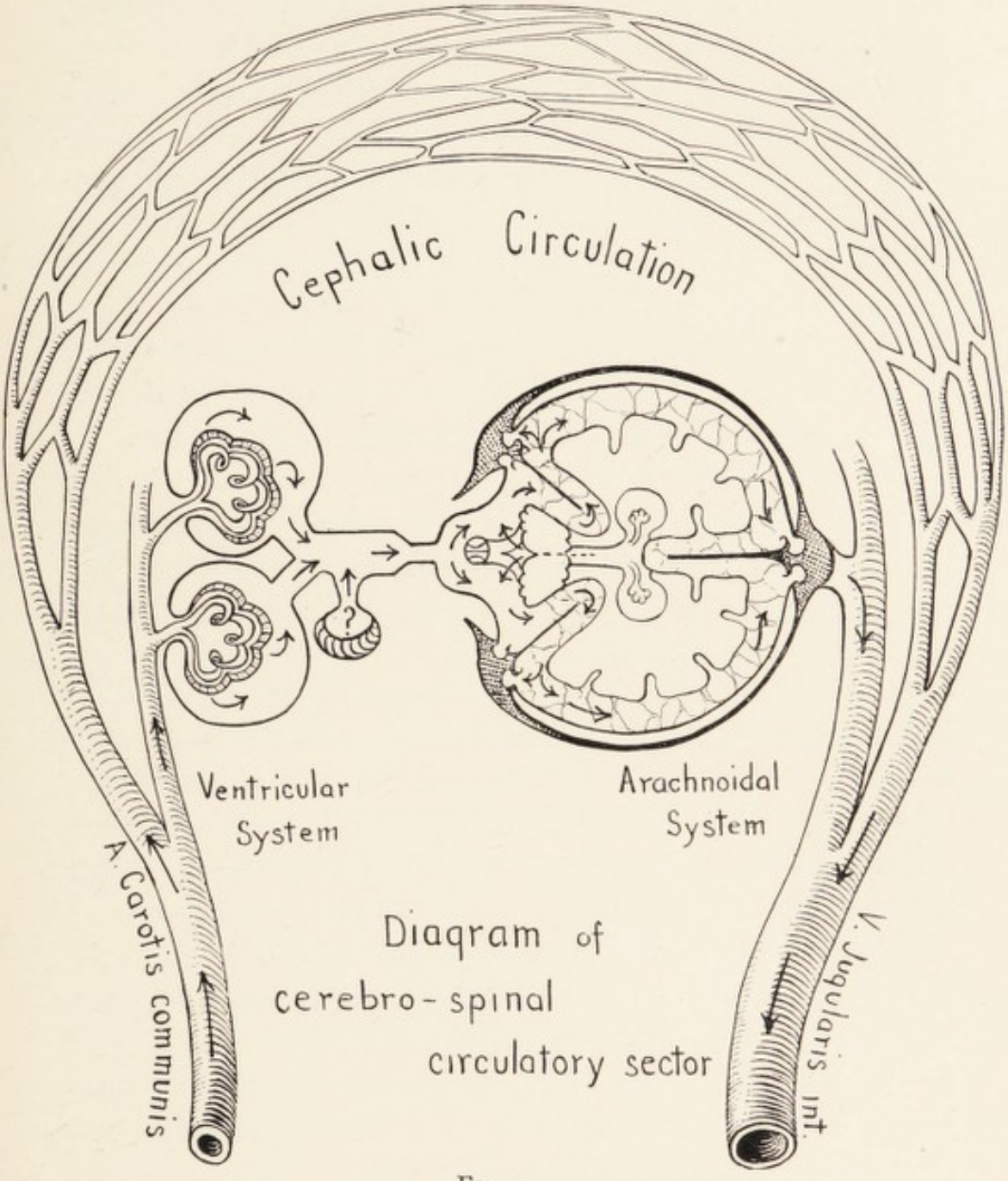

Fig. 1.

direction, through a highly specialized pathway, that cuts across the blood circle to envelop an organ in which a lymphatic apparatus of the usual type does not exist (Fig. 1).

In explanation of hydrocephalus. Though these matters which concern the brain *en masse* may have failed to engage the attention of physiologists, they have been, if anything, of even greater interest and concern to the neurosurgeon than the localization of function, since the success or failure of many of his undertakings depends more upon his familiarity with the fluid circulation and its possibilities as a complicating factor in his procedures, than upon any other one thing. For the fluid, indeed, may prove his most stubborn enemy or his most valued ally.

Probably none of the younger generation of neurosurgeons can appreciate the trepidation felt when, for the first time in the course of an operation for cerebellar tumour, a needle was inserted into the occipital horn of the lateral ventricle to reduce tension and diminish bleeding. Corning must have had a similar sensation when he first pricked the spinal meninges for the purpose of introducing drugs (1855); Keen when he first deliberately tapped the ventricles (1889); Quincke at the time of his first lumbar puncture (1891); von Bramann on his first callosal puncture (1909); Ayer when he first tapped the cisterna magna in man (1920). Contempt of these procedures has come only with familiarity, and we soon forget that they were once so novel that their performance took courage.

My own interest in the dynamics of the intracranial chamber was first aroused while engaged twenty-five years ago in the Hallerianum in Berne on a problem suggested by the late Theodor Kocher, who was preparing a monograph on cerebral compression for Nothnagel's *Specialle Pathologie* (1901), wherein he laid far more stress on the results of my researches during that happy year than they perhaps deserved.

On my return to Baltimore, with the intention of specializing in the surgery of the nervous system, among

the first of my patients—as will probably have been true of most young men entering this particular field—were infants with what is known as essential hydrocephalus, for which a greater number of treatments have as yet been advocated (I have been guilty of proposing one or two myself) than successes recorded—if indeed there are any clear-cut successes recorded. I had only the vaguest possible ideas of the cerebrospinal pathways ; and if Leonard Hill's statement, made in the course of his admirable Hunterian Lectures in 1896, were true—' That no pathological increase of cerebral tension can be transmitted to the cerebrospinal fluid, because the fluid can never be retained in the meningeal spaces at a tension higher than the cerebral veins '—I could not understand how it was that a fluid which acted chiefly as a water-bed for the brain could give surgeons so much trouble, and so determined to find out something more about it if that were possible.

One of my early co-workers in the Hunterian Laboratory in Baltimore, Dr. Lewis L. Reford, undertook to study the development of the leptomeninges by injecting India ink under light pressure into the spinal canal and into the spinal subarachnoid spaces of living pig embryos of various ages.[2] After the tissues had been ' cleared ' so that the course of the injection-mass could be observed, it was found : that in the younger embryos fluid introduced into the canal passed headwards into the ventricles from which there was no escape ; that later on, whether injected into the canal or into the subarachnoid space, the mass would spread from the region of the IVth ventricle around the base of the brain ; and finally that in older pigs it would extend up over the hemispheres in what appeared to be developing meningeal spaces which had no connexion with the extracranial lymphatics.*

* Dr. Reford's preparations, at Professor Mall's request, were shown at

With this small beginning, and without any definite sequence, a variety of studies were undertaken during the next few years: with Dr. James Bordley, jun., on the relation of the fluid to the experimental production of choked disc [5] (these were days when choked disc was generally regarded as a toxic neuritis); with Dr. S. J. Crowe on the passage into the fluid of hexamethylenamin [6] which remains one of the few known substances capable of overcoming the barrier of the plexus; with Dr. John Sundwall,[11] who made studies of the comparative histology of the plexus and first showed me the large cells with an affinity for vital dyes, referred to later as meningocytes, which lie below the epithelial layer; with Dr. Emil Goetsch in an effort to determine whether the active principle of the pars nervosa could be detected in the fluid; [8] with Dr. W. E. Dandy, who devised an ingenious method of producing experimental hydrocephalus by occlusion of the aqueduct of Sylvius [9] and of determining the place of block by the injection of phenol-sulphonephthalein just introduced by Abel and Rowntree; with Dr. Conrad Jacobson, who made a comparative study of the sugar content of the fluid and of the blood under various experimental conditions of hyper- and hypoglycaemia, and found them to be in practical correspondence, though the fluid sugar showed delay in its appearance after intravenous injection.*

a meeting of the Association of Anatomists, but no report of them was completed for publication. Cf. *Anat. Record*, 1907, vol. i, p. 69.

* These studies [10] were never published, for Dr. Jacobson's attention became diverted by an investigation of the splitting of cane-sugar and the comparative effect in the elimination of laevulose and dextrose before and after shunting the liver by an Eck fistula. His original topic has of late, since the introduction of insulin, come to occupy the attention of many (cf. F. G. Dietel, *Ztschr. f. d. ges. Neurol. u. Psychiat.*, 1925, xcxxv, 563; also F. Fremont-Smith and M. E. Dailey, *Arch. of Neurol. and Psych.*, 1925, xiv, 390).

These studies were merely along bypaths to the actual goal we continued to bear in mind, namely, furtherance of our knowledge of the mechanism of hydrocephalus, of which there probably were many kinds. Many examples of this most distressing condition in infants had meanwhile come under observation in the clinic, and it was found that in most of them the fluid could be withdrawn from the ventricles by lumbar puncture. Moreover, when a needle attached to a manometer was inserted through the bulging fontanelle into the ventricle and another in the lumbar sac, the pressure level of the fluids in both usually remained the same and fluctuated equally with crying, straining, or jugular pressure, as well as on the withdrawal of fluid from either end of the system. At the same time we observed, as many others doubtless have done, that even though large amounts of fluid might be withdrawn—as much as a completely collapsed fontanelle would permit, and amounting at times to over 300 c.cm.—within twenty-four hours the fluid would have re-accumulated, albeit with slightly altered chemical and cellular characteristics, and perhaps with slightly increased tension.

From these simple clinical tests I became convinced that some fault of development in the portals of outflow for the fluid from the meningeal spaces, or their occlusion by disease, was more likely to be the cause of hydrocephalus in infants than either an acquired obstruction to the passage of fluid from ventricles to the subarachnoid spaces, or a 'block' somewhere in the course of these mesh-like though abundant channels. Obstructions of the latter kind, nevertheless, were occasionally encountered, and I well remember my amazement when carrying out one of these combined procedures in a hydrocephalic child, at finding only a small amount of normal fluid under low pressure in the lumbar subarachnoid space, whereas a

highly turbid fluid under tension was secured from the dilated ventricles.

These were days when cerebrospinal fever was epidemic in the United States, and though in this infant there had been no history of the malady, a pure culture of Weichselbaum's organism was secured from the ventricular fluid, whereas the lumbar fluid proved to be sterile. Flexner at this time had just introduced his antimeningococcus serum, and the case, observed with F. J. Sladen, was the first so far as I know to be treated by the intraventricular injection of serum.[3] Here we were obviously dealing with a block of the aqueduct or foramen of Magendie, in other words with what Dandy came to call a 'non-communicating' form of hydrocephalus; but, leaving the hydrocephalus due to cerebellar tumours out of consideration, I was impressed by the fact that the ventricles could be emptied by lumbar puncture in most cases of hydrocephalus in childhood, and concluded that the block must occur elsewhere than at the IVth ventricle, and would probably be found at the portals of exit from the meninges, whatever they might prove to be.

But why under these circumstances, it may well be asked, should the hydrocephalus not be external rather than internal? In other words, would not the backing up of fluid be more marked where the dam was interposed than at the source? Clinical experience had apparently answered this question in the negative, for it had long been known that it was almost impossible to convert an internal into an external hydrocephalus even when a large hole was made in the thin cortex separating the two fluid spaces, intraventricular and meningeal, in an advanced example of the disorder. It is true that in these observations the communications were made between a dilated ventricle and the subdural space not then known to be an extra-systemic and merely potential space. It is true also that an external hydrocephalus can

occasionally thus be produced, but under ordinary circumstances the thin cortex will become floated up against the dura in its former position—a fact which would have been enough to convince any one who gave it a moment's thought that the source of fluid must be in the ventricles as the observations of Faivre and Luschka had long since suggested, rather than that it was a product of the meninges themselves, formed as the pleural fluid, for example, is formed.

As we knew nothing at this time about the portals of drainage other than that Key and Retzius had associated them in some way with the Pacchionian bodies, structures not demonstrable in infants, and being then under the impression that some of the fluid, as maintained by many, normally escapes into the extracranial and extraspinal lymphatics, which might therefore be utilized as pathways for absorption, the attempt was made to drain the subarachnoid lumbar fluid directly into the retroperitoneal tissues through a trephine opening in the body of the Vth lumbar vertebra.[4] It was thought that this loose tissue in direct proximity to the thoracic duct would be a medium more favourable for permanent drainage than the subaponeurotic layer of the scalp which had been previously utilized for the purpose with disappointing results.

But the procedure came to be discarded because of a most unexpected complication. Two or three of the hydrocephalic infants thus operated upon, after doing well for ten days or two weeks, died of an intestinal intussusception which we assumed had been provoked by the presence of some substance in the fluid which stimulated abnormal peristalsis. Since it had recently been made clear that posterior lobe extract possessed this property we naturally came to suspect that this might be the cause ; and on this experience our subsequent efforts to detect it in the fluid were primarily based.

Baffled in this, which proved to be a futile procedure, and believing that somehow or other in curing hydrocephalus the fluid must be allowed to get directly into the venous circulation, attempts were made to accomplish this: by Dr. R. D. McClure who, as an improvement on the method of Payr, essayed to transplant a vein between the subdural space and a vessel in the neck;[7] and by myself, with the placement of a specially devised silver tube which led from the dilated IIIrd ventricle through the corpus callosum directly into the longitudinal sinus. As in most other surgical experiences with essential hydrocephalus, the results were inconclusive, but the observations at least taught us that no blood subsequently passed from the sinus into the ventricle, which was regarded as an indication that the tension of the fluid must at all times be greater than that in the veins.

Filling gaps in our knowledge. These early endeavours, now of little more than slight historical interest, all tended to show how imperfect was our knowledge of the source or sources of fluid supply and of the method whereby it was absorbed. In other words, too much attention had been paid to the bath itself and too little attention to the tap, to the construction of the tub as a container of the bath, and to the place and mechanism of its outlet. Accordingly, on my transfer to Boston in 1912, Dr. Lewis H. Weed and I set ourselves to these problems, and the following questions for which we needed answers were gradually formulated:[13]

> Granting that the choroid plexuses are the chief source of the cerebrospinal fluid—and this has not been conclusively proved—is the process, as some believe, a transudation, or a secretion, or as Mestrezat regards it, a mere dialysation from the blood? What conditions activate and what conditions inhibit these choroidal glands? Have they an internal as well as an external secretion?

To what primary diseases are they subject? How early in embryonal life do they secrete? Why does the fluid which they elaborate differ so greatly from that secreted by most other glands? Why are the cells so impermeable to the passage from the blood stream of drugs and of substances such as the bile pigments, which in conditions of jaundice quickly stain all other body tissues and fluids?

Granting that the fluid thus secreted by the choroid plexuses leaves the ventricles and spreads over the brain and down the cord in the subarachnoid spaces, does it receive accessions from elsewhere, from the ependyma or from pituitary or pineal glands? Are there lymph channels in the brain, and if not, how does the central nervous system dispose of its products of tissue waste? If there are [anything comparable to] cerebral lymphatics do they discharge into the subarachnoid spaces and is the subarachnoid fluid therefore of the same character chemically, physically and cytologically as the ventricular fluid? Why normally is the fluid practically limited to the subarachnoid spaces, and under what conditions does it become subdural?

Granting that fluid may escape by way of the Pacchionian granulations, is this the chief or only manner of escape? If an important avenue, why are these structures lacking in the lower animals and in the human infant? Are these granulations, therefore, pathological processes, and if so, what are their precursors? Are there other means of fluid absorption along the nerves by way of the lymphatics, and if so, how important are they? How do the spaces in the pia-arachnoid develop and do the choroidal glands mature and secrete before or after their formation? Are there faults of development at these meningeal outlets for fluid which can account for congenital hydrocephalus and for malformations such as spina bifida and cephalocele? Are there analogies in the fluid circulation of the eye to which we may attribute the disturbances of circulation of the intra-ocular fluids?

It so happened that we came to attack these questions in reverse order, 'upstream' as it were; and instead of beginning with the plexus, though this was not wholly neglected, attention was first paid to the portals of exit. Dr. Weed soon hit upon a satisfactory method of identifying

these structures,[14] which was free from the objections raised against those employed by his predecessors. This consisted of a long-continued subarachnoid injection in the living animal, of potassium ferrocyanide and iron-ammonium citrate in isotonic solution, under a pressure but slightly above the normal, with the subsequent immediate fixation of the tissues in an acid medium. This procedure, which served to precipitate Prussian-blue granules out of the foreign salts introduced in solution, made it possible to utilize histological methods to identify the situation of the granules in the tissues and tissue spaces.

It was found that the granules were precipitated in and passed through the mesothelial cells which cap the arachnoid villi that project in large numbers through the dura into its many venous sinuses, large and small, cortical and basilar. This, broadly speaking, was confirmatory of the view of Key and Retzius, but it substituted these innumerable and widely disposed microscopic structures for the Pacchionian granulations to which they had ascribed the function of absorption, and which merely represent pathological enlargements of some few of the villi.[15]

The same methods were utilized by the late Dr. Paul Wegefarth in showing that the absorption of fluid from the anterior chamber of the eye takes place into the scleral sinuses through the intermediation of similar anatomical structures which lie at the so-called filtration angle[17]. At the same time, Drs. Wegefarth and Weed became interested in the question of the fluid pressures and, in agreement with Dixon and Halliburton, who happened coincidentally to be engaged in similar studies, concluded that the cerebrospinal fluid under normal circumstances is under a higher tension than the blood in the venous sinuses.[19] * Wegefarth mean-

* To this question Weed and Hughson[47] returned some years later and arrived at the conclusion that the pressure of the cerebrospinal fluid under

while had found that an artificial communication between the sinus and subarachnoid space, even under normal conditions, was not followed by intracranial bleeding unless the intracranial pressure was lowered below that of the sinus; and he suggested that hydrocephalus might be treated by multiple punctures, made along the mid-line of the fontanelle, directly through the sinus into the lepto-

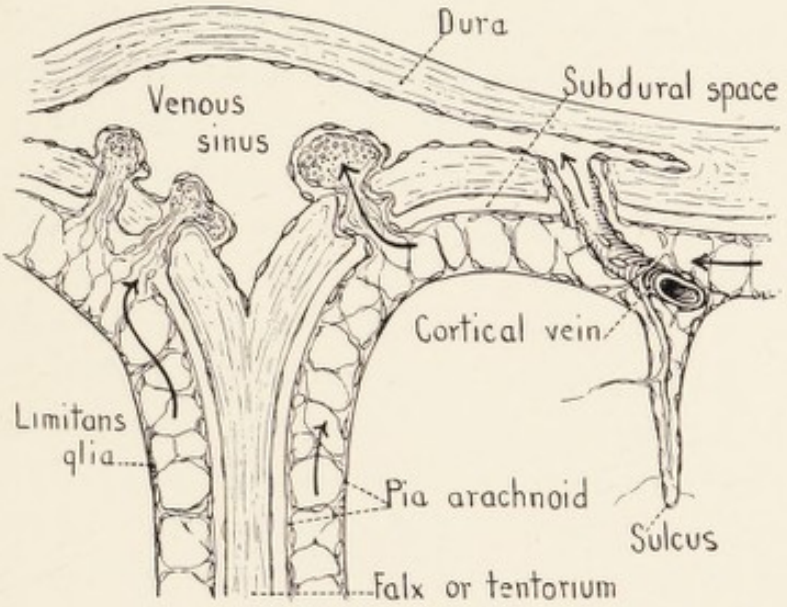

FIG. 2. Diagram to show relations of pia-arachnoid, the arachnoidal villi, and cortical veins to the dural sinuses (modified from Weed).

meninges with the expectation that the opening would become immediately plugged by arachnoid, and that in this way artificial functioning villi might be produced.[18]

With this substitution of countless microscopic arachnoidal villi (Fig. 2) for the occasional Pacchionian granulation as the essential portals of escape for the fluid, our conception of the process of absorption was greatly clarified, albeit the view which Dandy and Blackfan had just advanced,[12]

normal circumstances is from 5–50 mm. of water above the venous pressure in the sagittal sinus.

that the fluid was absorbed by the pial vessels, was not in accord. Moreover it fitted in with my preconceived idea that the cause of 'idiopathic' hydrocephalus would be disclosed when the portals of absorption were found.

I therefore may be prejudiced in feeling that those who have subsequently written on the surgical aspects of hydrocephalus [Dandy[43] (1921), Fraser and Dott (1922)] have not sufficiently borne in mind in their classifications of hydrocephalus the ease with which these microscopic villi may be occluded by the products of inflammation or by blood in the meningeal spaces, with the consequent reduction, either as an acute or chronic process, in the absorptive powers of these tiny but important structures through which the fluid normally escapes. Weed's later demonstration[36] of the ease and certainty with which a chronic hydrocephalus of high grade may be experimentally produced by the simple injection into the subarachnoid channels of lamp-black, which serves to occlude the arachnoid villi, would seem to make it most probable that damage or imperfect development of these structures is the most common cause of otherwise unexplained cases of early or congenital hydrocephalus.

The perivascular channels. But to return to the views of others in regard to the process of absorption or drainage. In a study of the brains of animals subjected to experimental anaemia, Frederick W. Mott had observed that the perivascular 'lymphatics' of Robin (better known to pathologists as the Virchow–Robin spaces) which represent prolongations of the leptomeninges around the vessels that dip into the brain substance, were particularly well shown. These observations led him to conclude that absorption of the fluid from the subarachnoid spaces normally took place by way of these 'lymph' channels, with the natural corollary that the cerebral capillaries represented the chief absorbent

vessels. This same view, if I read him aright, came to be held by E. E. Goldmann and is set forth in his classical monograph (1913) on vital staining of the central nervous system.*

It may be assumed that both pathologist and anatomist are talking of the same thing when the one mentions the perivascular spaces of Virchow † and of Robin,‡ and the other the space of His. § However all three of these distinguished investigators originally gave such casual descriptions of the spaces in question that it is surprising that they should have become eponymic. Certainly the space which His disclosed by his injections must now be regarded as an artifact; and the view still maintained by many pathologists that the space of Robin is an adventitial lymph space within the wall of the blood vessel itself is surely erroneous even though it has crept into our anatomies.‖

* It may be said in passing that an admirable (for the time) account and diagram of the cerebrospinal pathway, including a description of the perivascular spaces, was given by J. Batty Tuke in one of his Morison 'Lectures on Insanity' (*Edinburgh Medical Journal*, 1894, vol. xxxix, pp. 680–3), at a time when the possible physical causes of mental disease were being emphasized. But I know of no better description of them in English than that given in the first of Mott's Oliver Sharpey Lectures (*Lancet*, July 2, 1910, pp. 5–6) in which even the periganglionic extension of these spaces (Bevan Lewis) was clearly pictured.

† R. Virchow: Ueber die Erweiterung kleinerer Gefässe. *Archiv f. pathologische Anatomie u. Physiologie*, 1851, vol. 3, pp. 425–62.

‡ Ch. Robin: Recherches sur quelques particularités de la structure des capillaires de l'encéphale. *Journal de Physiologie*, 1859, vol. 2, p. 537.

§ Wm. His: Ueber ein perivasculäres Canalsystem in den nervösen Centralorganen und über dessen Beziehungen zum Lymphsystem. *Zeitschrift f. wissenschaftliche Zoologie*, 1865, vol. 15, pp. 127–41.

‖ Thus: 'The lymph finds its way out of the brain and spinal cord by means of *perivascular spaces in the tunica adventitia* of the blood vessels. These perivascular spaces communicate with the subarachnoid space.' (Quain, 11th ed., vol. 3, pt. 1, p. 339.) In his admirable *Histopathologie des Nervensystems* (1922, vol. 1, p. 196), Spielmeyer says: 'The meshwork of

One might naturally suppose, since the superficial vessels of the brain and cord lie within the subarachnoid space, that they would carry down with them only a sleeve of pia, but as a matter of fact the so-called pial vessels of the surface, like the trabeculae within the subarachnoid spaces are, as Weed has clearly shown,[56] covered by an endothelial lining. Hence, the perivascular sleeve is necessarily a double one (Fig. 3) and there can be no question but that the space enclosed, whatever its function, lies in direct communication with the subarachnoid spaces ; nor can there be any doubt as to its having a ' visceral ' (vascular) lining of arachnoid and a ' parietal ' (nervous) lining of pia rather than that, as generally conceived, it is formed by a sleeve of the pia alone which lies adjacent to the limitans glia.

But to return to our personal story. Under the condition of Weed's earliest experiments, no deposit of Prussian-blue granules was found in these perivascular spaces unless the animal were bled during the course of the injection. However, our interpretation of these facts was contrary to Mott's, for to us it seemed more probable that the normal flow in these channels should be from the brain towards the subarachnoid spaces[16] rather than the reverse as he had assumed ; and it was even then beginning to be known that these perivascular spaces become packed with cells in many disorders affecting the brain, which accounts for the early pleocytosis in the fluid (Figs. 4, 5).

this reticular adventitial structure represents a lymph space, and this is the only certainly demonstrable lymph pathway in the central nervous system. It is named after Virchow and Robin. Moreover the space is not, as it was believed before, *between the adventitia and media but it concerns a real adventitial space which Held therefore designated as an " intra-adventitial " lymph space. The external boundary of this space is the intima pia.*' The contradictions in these statements, here italicized, are more apparent than real, and are based apparently on an inadequate appreciation of the histogenesis of the spaces.

Light on the Monro-Kellie doctrine. In further explanation of the direction of flow in these perivascular spaces, we must revert to the doctrine first formulated by your Monro

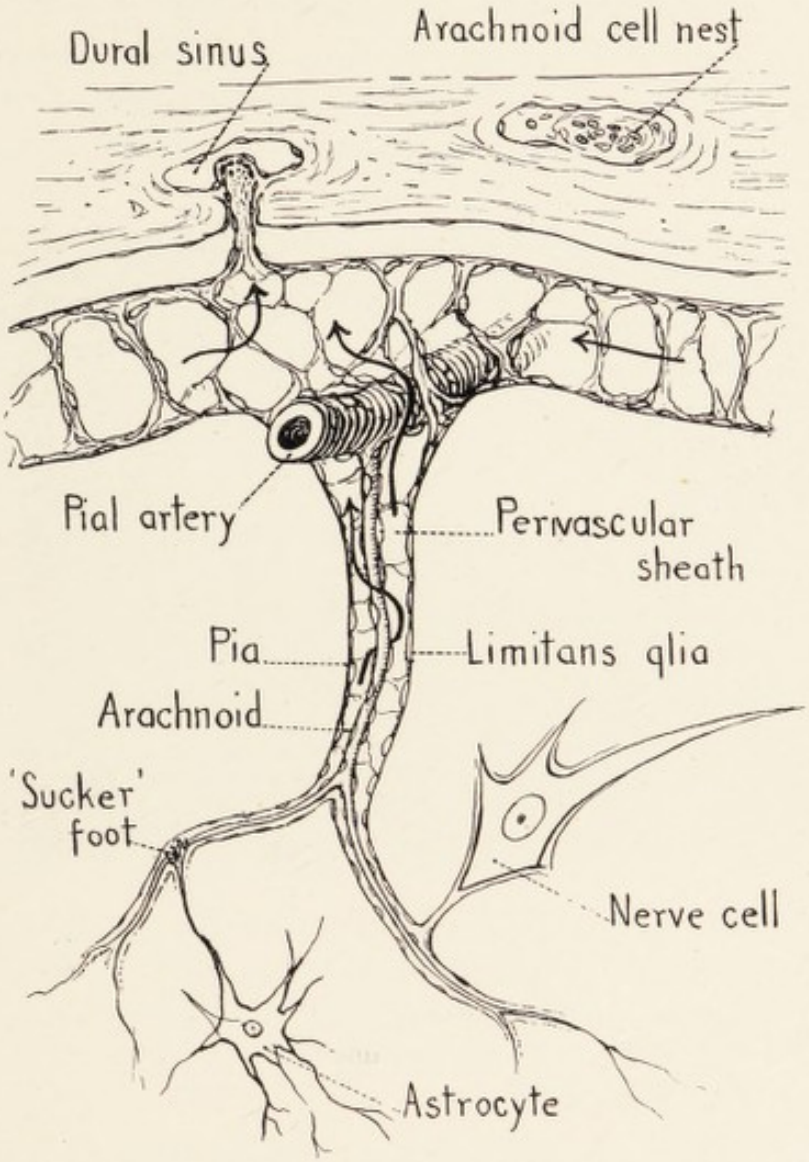

FIG. 3. Diagram to show the sleeve of pia-arachnoid constituting the space surrounding a branch of a pial artery (modified from Weed).

secundus but properly known as the Monro-Kellie doctrine, since it was further elaborated some years later by another Scotsman, Dr. George Kellie of Leith.* According to this

* I don't know how many members there be of the Medico-Chirurgical

famous doctrine, which introduces certain principles of physics relative to the flow of fluids through a closed box, the contents of the intracranial chamber with its three elements, nervous tissue, blood, and fluid, must always remain the same in bulk. Any increase in blood volume, for example, can only take place at the expense of one of the other elements, and conversely a diminished blood volume must be com-

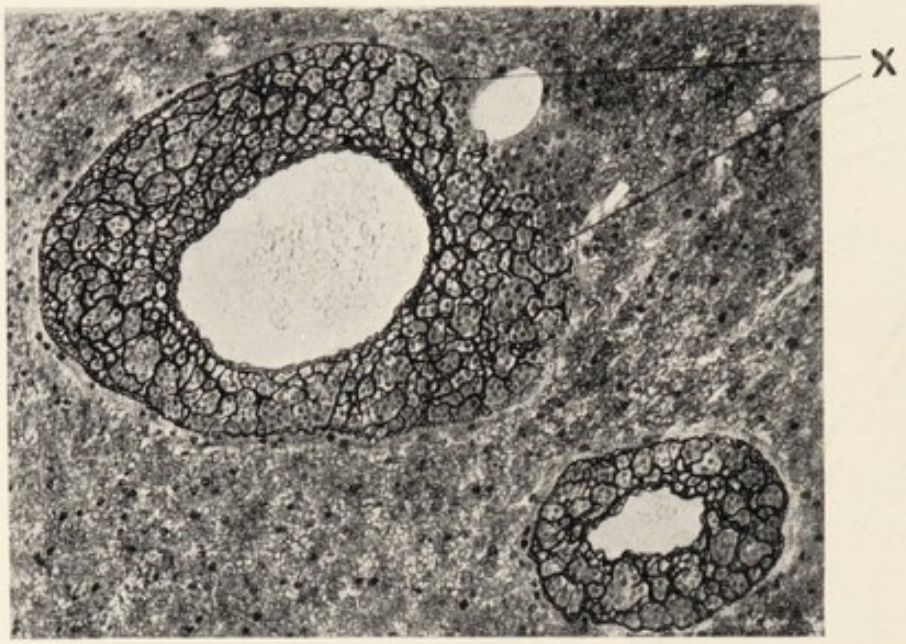

Fig. 4. From Spielmeyer: showing the so-called 'adventitial' (Virchow-Robin) spaces invaded and ruptured at × by the inflammatory cells of an encephalitic process, in this case experimental sleeping sickness (tannin-silver method).

Society of Edinburgh who ever had in their hands the first volume of the Transactions of that venerable society, now in its second century. To those who have not and who may be interested in the cerebral circulation, I would highly recommend the perusal of pp. 84–169, which contain George Kellie's 'Account of the appearances observed in the dissection of two or three individuals presumed to have perished in the storm of the 3rd, and whose bodies were discovered in the vicinity of Leith on the morning of the 4th November, 1821: with some reflections on the pathology of the brain', as read before the society on February 6 and March 20, 1822.

pensated either by an expansion of the brain, or by an increase of cerebrospinal fluid, which probably amounts to the same thing. Hence, if an animal is bled and the brain in consequence shrinks in size, it becomes, as Weed termed it, a 'thirsty brain', and the additional fluid which must necessarily be provided to compensate for the shrinking becomes sucked down into the perivascular channels.

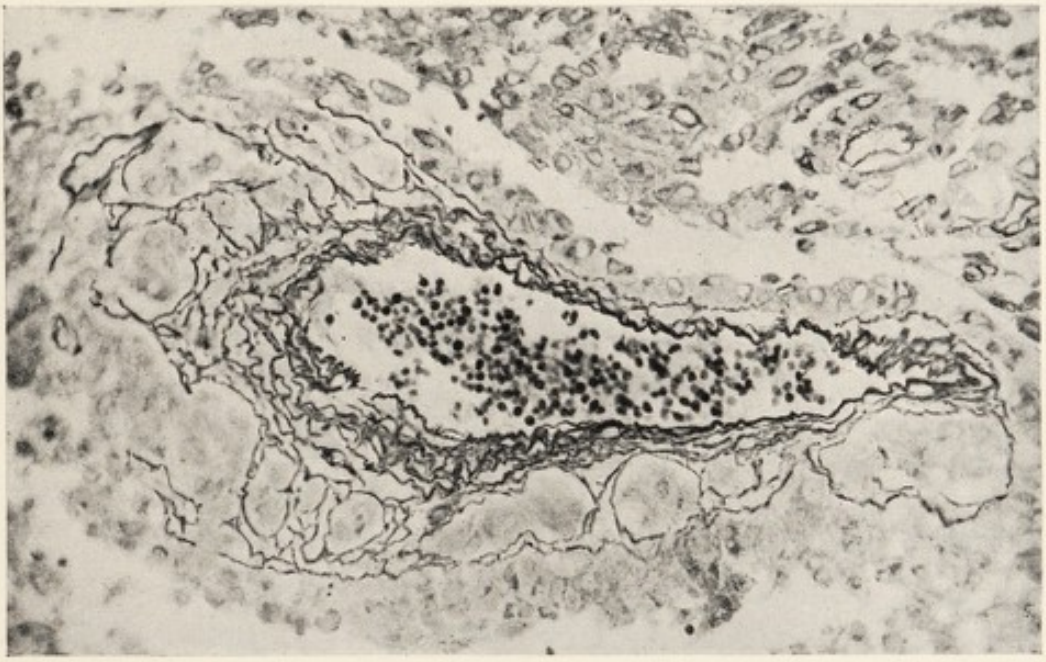

Fig. 5. To show the cerebral perivascular spaces invaded by, and to the left ruptured by, a primary perithelial sarcoma (B. Fried). Perdrau's silver nitrate method for connective tissue (× 133). Ghosts of unstained tumour cells are apparent.

Moreover, since these changes all take place rapidly—a matter of minutes—it is hardly possible that the great increase of fluid which the process entails could be the result of mere transudation. George Kellie was close to the facts a century ago when he said, in speaking of the effect of cerebral anaemia, that 'watery effusion within the head is a pretty constant concomitant or consequence of great sanguineous depletion'.

All this is part and parcel of the extraordinary phenomenon of cerebral oedema, for the brain, owing to its sponge-like structure, is apparently more capable than any other of the body tissues of taking up fluids with an enormous and rapid increase in its bulk; and it was perhaps, through some such sequence of ideas, that Dr. Weed, with his own pupils in turn, a few years later, while in charge of an experimental laboratory during the war, made the discovery [28] that prompt changes in brain volume ensue upon the intravenous injection of hypertonic and hypotonic fluids. This discovery not only has served to provide a new method of attack on many old problems associated with the Monro-Kellie doctrine,[48] but it has proved in the clinic to be a veritable boon for certain desperate states.

The practical applications of the discovery were obvious, and they were immediately pounced upon for therapeutic purposes. In the first place, it was apparent to the physician that drugs like salvarsan, to which the choroid plexus was impervious, might be brought more intimately in contact with the nervous tissues owing to the probable reversal of the current in the perivascular channels when the brain was shrunk by hypertonic solutions. The surgeon, on the other hand, promptly adopted the procedure as a means of lowering intracranial tension; and it is truly amazing how rapidly certain patients in deep stupor, even with Cheyne-Stokes respiration, may be brought back to consciousness after the intravenous administration of a hypertonic solution.

It was soon observed in my clinic [41] that the effect of the concentrated solutions could be produced even when salt was introduced in the alimentary canal; furthermore, that the effects were more noticeable when the increased intracranial tension was due to hydrocephalus rather than to a solid tumour, an observation which received early con-

firmatory evidence in Weed's laboratory by Nañagas.[50] We were a little dubious, consequently, whether what Weed had described as an actual shrinkage of the brain might not merely be due to the resorption of cerebrospinal fluid by some unnatural method of osmosis consequent upon the greatly increased salinity of the blood.

Remembering that Dandy and Blackfan [12] had shown that phenolsulphonephthalein, introduced into the ventricles of an hydrocephalic, might tardily be recovered in the urine, indicating that there must be some resorption through the ependyma, Dr. Foley undertook some experiments to answer the question, and was led to conclude[44] that the fluid under the abnormal conditions of increased blood-salinity became resorbed directly into the subependymal tissues. It was his impression that the process occurred largely by way of the choroid plexuses, but in this he was apparently mistaken, for Drs. Wislocki and Putnam,[46] who reinvestigated the matter, appear to have shown that the ependyma alone participates in the process and that the modified ependymal cells covering the plexus do not.*

Development of the arachnoidea. But I am getting far ahead of my story. Having proved to our satisfaction how it was that the fluid became absorbed, Dr. Weed on his return to Baltimore proceeded, as I have expressed it, to work 'upstream' and ere long completed his extensive and now classical monograph on the development of the meningeal spaces.[26] These spaces, as he convincingly demonstrated, are produced by a seepage, through the roof of the fourth ventricle, of fluid which permeates and breaks down the perimedullary mesenchymal syncytium. This occurrence

* These matters were subsequently investigated independently by L. H. Weed, and are fully discussed in two important papers,[56, 61] one chiefly devoted to the path of fluid absorption after hypertonic solution, the other on the effects of hypotonic solutions.

practically coincides, as we had anticipated, with the development of the choroidal tufts and supposedly therefore with the initial flow of cerebrospinal fluid, which comes to supplement the stagnant pre-existing fluid; for the undifferentiated cells of the ependyma up to this time may be assumed to have a secretory activity of some sort.

These illuminating studies of Dr. Weed's not only confirmed but greatly amplified the observations made by Reford ten years before. They serve to show with some finality:—that at about the fifth week of embryonic life fluid begins to percolate through the remaining fragment of the roof plate overlying the fourth ventricle; that it finds its way through leptomeningeal channels which are thereby formed in the mesenchyme; and finally that it escapes by way of persisting leptomeningeal communications, the villi, that project through the dura into its major venous sinuses. All of which assuredly indicates the birth of an actual circulation under the pressure of a secretion.

Meanwhile, in 1913–14, W. E. Dandy had been pursuing his ingenious studies of experimental hydrocephalus, in association with Kenneth Blackfan,[12, 20] and though our ideas, as stated, differed from theirs in regard to the process of absorption, Dandy succeeded in making two notably crucial experiments which filled gaps in our previous knowledge. One of these[34] was the demonstration that ventricular hydrops would occur if an inflammatory reaction were set up so as to encircle the cerebral peduncles at the level of the tentorium, which clearly indicates that the major course of the fluid, after its emergence from the foramina of Magendie and Luschka, is upward by way of the arachnoidea through the incisura tentorii to bathe the cerebrum.

The other of his crucial experiments relates to the actual

source of the fluid concerning which, from lack of exact proof, doubts have frequently been raised. In the spring of 1911, I had had a most suggestive surgical experience with a patient (J. H. H., Surg. No. 27733) who had a unilateral hydrocephalus due to a cystic intraventricular tumour arising near and occluding the right foramen of Monro. After two unsuccessful efforts to give pressure relief the ventricle, which proved to be filled with xanthochromic clotting fluid, was opened, emptied, and the choroid plexus laid bare. From the naked plexus thus exposed, fluid could be seen to be freely exuding, but when a silver ' clip ' was closed on the entering choroidal artery the organ became blanched and the secretion apparently ceased. The plexus was then excised, but unhappily the patient succumbed to a subsequent attempt to remove the tumour.

In his laboratory experiments Dr. Dandy was more fortunate in his demonstration that when one foramen of Monro is occluded a unilateral hydrocephalus results, whereas if the plexus is removed coincidentally the ventricle remains collapsed. This observation could hardly leave doubt in the mind of the most sceptical that the plexus is the active spring whence the river of cerebrospinal fluid arises, whether the actual process be one of filtration, secretion, or dialysation. There hardly seems need of belabouring the argument further, yet Weed has recently added additional evidence by his demonstration [61] that after the intravenous injection of hypotonic solutions, which greatly augment the amount of cerebrospinal fluid, the choroidal cells show histological evidence of its passage into the ventricle, even though this may not be a reversable process when hypertonic solutions are injected.

The increased intracranial tension which is provoked by the intravenous injections of watery fluids, and which must be due wholly to an increase of fluid in the cerebrospinal and

perivascular spaces, shows that there are definite limits to the rapidity with which the fluid thus augmented can escape through the arachnoidal filters into the venous sinuses. This brings up the question of whether under any circumstances such an effect can occur as a clinical entity, and one immediately calls to mind the so-called condition of meningitis serosa with its pseudo-tumour syndrome. But this is an obscure malady; and so far as I am aware, the only example of a condition, in which a pressure syndrome simulating tumour with hydrocephalus was produced by an apparent increase in fluid beyond what the system could care for, was in a case recently reported by Dr. L. E. Davis, in which a huge symmetrical hypertrophy of the plexus (Fig. 6) was the only post-mortem finding.[63]

Hydrocephalus, therefore, may apparently be produced in at least three major ways: (1) by occlusion of the villi through which the fluid is normally absorbed into the sinuses (and, as a corollary, extensive sinus thrombosis, should it be compatible to life, would have the same effect); (2) by obstructions easily produced by inflammation or tumour in the narrower portions of the pathway, notably at the foramina of Monro, in the aqueduct, at the fourth ventricle, and in the narrows of the incisura tentorii; and (3) more rarely, by an increase in the amount of fluid secreted in excess of what can be cared for by the normal portals of drainage; and this is what, hypothetically, would take place could the hypotonicity of the blood, under the conditions of Weed's experiments with the injection of watery fluids, be long maintained.

In connexion with these meningeal channels there remains to be discussed another matter, the importance of which has only been stressed of late years, namely the physiological activity of the cells which constitute the lining of the fluid pathway. Now it is a remarkable thing if one stops to think

of it, that Nature should have provided this watery fluid, which, on the general biophysical principle of osmosis, contains the salts and sugars of the blood, but practically none of its other elements. What could have been her reason for interposing in the blood stream this peculiar circulatory

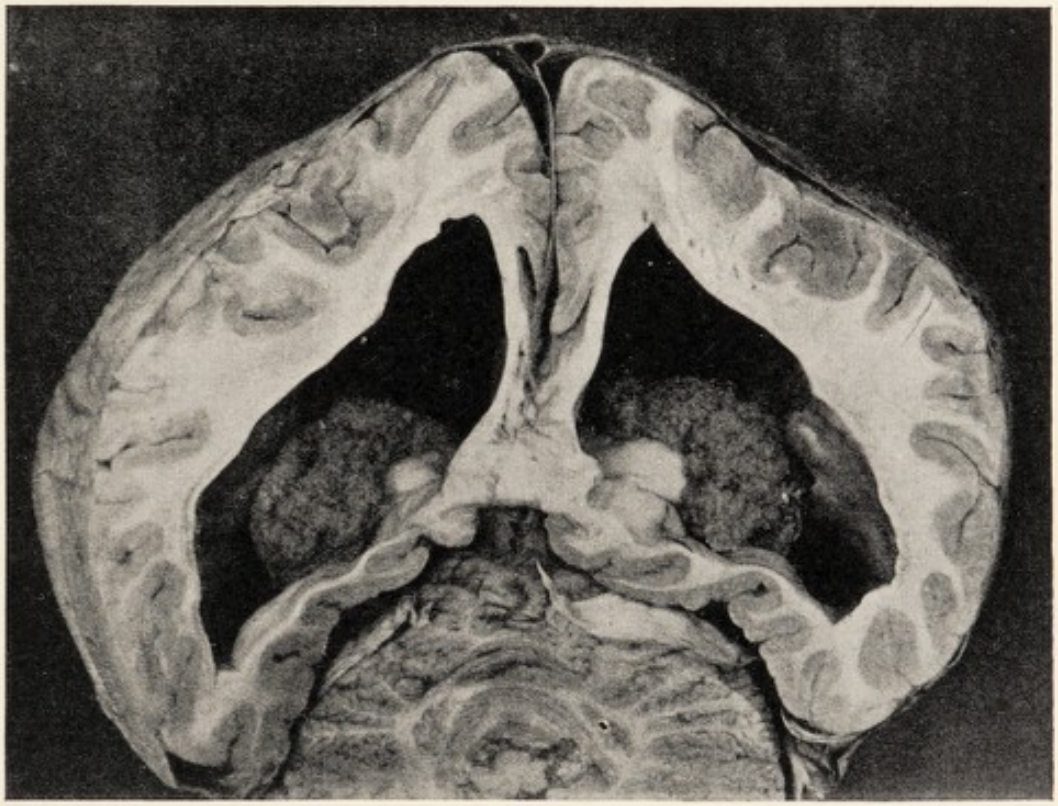

FIG. 6. Bilateral hypertrophy of choroid plexuses, producing hydrocephalus and the general pressure syndrome of pseudo-tumour cerebri. P. B. B. H., Surg. No. 11462 (from Davis).

switch with its choroidal barriers and impervious pia, which keeps the fluid free from practically all known substances, whether drugs or vital dyes, which may be put into the blood stream ? Unquestionably one purpose was to provide a medium for the washing out of products of metabolism—a substitute for a lymphatic apparatus if you will—for we have learned that the intraventricular and subarachnoid fluids have a slightly different chemical composition. Then,

too, it seems not improbable that something may be added to the fluid in transit which may be necessary to the economy.*

Vascular or lymphatic channels might well enough have served for both these purposes it would seem, and just why another medium had to be provided within spaces, which, as we shall see, are particularly intolerant of the presence of blood cells, remains unanswered. Moreover, as may be observed, there is no method whereby a collateral circulation for the cerebrospinal fluid can be spontaneously established in cases of obstruction, and since it passes through a very specialized pathway it is to Nature's provisions to keep the pathway in repair and free from foreign substances which might obstruct the fluid outlets that I wish to devote the remainder of this hour.

B. The Cellular Lining of the Meningeal Pathway

The 'meningocytes' and reparative processes. The mesothelial cells which line the extraventricular fluid spaces possess a most remarkable capacity for repair, as must have been observed by many. I may give an example.

The efforts which were made many years ago to drain the hydrocephalic ventricles by establishing a communication with the subaponeurotic layer of the scalp, in the expectation that the fluid would permanently escape into the lymphatic spaces, led to disappointments. For under these circumstances a very peculiar and striking thing happens. The scalp at first becomes widely oedematous, but in the course of a few days the oedema gradually subsides and finally a circular pool of fluid a few centimetres in diameter is all

* A discussion as to whether the active principle of the posterior lobe of the hypophysis is so added,[8] and whether this substance increases the flow of fluid, must be deferred to my second lecture.

that remains. This disc-like subaponeurotic pool, which continues in free communication with the ventricle, becomes promptly lined with a layer of glistening serosal cells, like those lining the dura, which are impervious to the further escape of fluid into the tissues.

Early in our surgical experiences, with what is known as a subtemporal decompression, a comparable observation was made, namely that a new dural membrane would promptly re-form without any adhesions to the brain, provided the leptomeninges over the surface of the exposed temporal lobe were not injured in the process of opening the dura. This neo-membrane would so perfectly repair the defect over the bulging lobe that any one who might happen after an interval to re-operate upon the patient or to conduct a post-mortem examination would be likely to doubt whether the pachymeninx had ever been opened.

Such disclosures as these threw new light upon the question of the desirability or otherwise of implanting tissues for the purpose of closing a dural defect—an old story, of course, which harks back to the once prevalent idea that cortico-meningeal adhesions, rather than a secondary cortical gliosis, were the cause of traumatic epilepsy. Substances without number have been advocated for the purpose. Some of them no doubt have done little harm, but many have probably done more harm than good owing to the extensive reaction which takes place around them during the process of their healing in.

An experience of interest in this connexion may be mentioned. There are times when in operations for the removal of a brain tumour it is advisable owing to the patient's condition to postpone the completion of the operation for a second, sometimes even for a third, session. It has long been customary under these circumstances to place over the raw surface of the brain a thin layer of gutta-

percha tissue (protective).* When a layer of this protective has been thus left in place it becomes possible to re-elevate the bone flap after an interval of some days without the separation of newly vascularized and organizing tissues which would start fresh bleeding. This is so because the non-irritating foreign tissue will have become enveloped by an outer and inner layer of transparent fibrin; and if a sufficient interval has passed, the two surfaces will have become covered by a neomembrane of serosal cells.

Practical applications have been made of this extraordinary capacity for the formation of neomembranes. For example, there is a common intracranial tumour (meningioma), to whose source of origin reference will subsequently be made, the removal of which often necessitates not only the leaving of a defect in bone but in dura as well, so that the scalp alone covers the raw and oedematous cortical area stripped of its pia-arachnoid. The natural consequences of this would be an adherent scar between scalp and brain with practically no re-formation of membranes, or at best of very imperfect ones, for some fluid will naturally be exuded through the intact perivascular spaces which would encourage their formation. However, should a piece of protective be placed over the raw area at the close of the operation, glistening serosal surfaces will form in the manner described in a surprisingly short time, a matter of days, perhaps of hours.

Before entering into a consideration of the particular cells which take part in these reactions there is something more to be said about the processes of meningeal healing in general. Much light has been thrown on the subject by the ingenious experiments of my former assistant, Dr. S. C.

* For the widespread employment in surgery of the substance known as 'protective', to prevent painful dressings, the profession owes a debt of gratitude to the late Professor Halsted.

Harvey, and his co-workers,[57, 64] who have shown the futility of patching a dural defect by the transplantation of fat or fascia, as is often advocated; for if the arachnoidea over the cortex remains intact, the dura will spontaneously re-form without adhesions, whereas should the pia-arachnoid and cortex have been damaged dense adhesions will form and incorporate the dura even though its inner surface had been uninjured. In other words, as Dr. Harvey puts it, 'the inner surface of the dura does not act as a limiting membrane in the presence of an attempted repair in the underlying meninges but on the contrary enters intimately into the process'; and he contends that there are not only morphological but actually functional differences in the two membranes, one of which merely lines a potential subdural space, whereas the other is a more highly differentiated structure.

My own explanation of the difference in the behaviour of the two surfaces to injury would have been that the arachnoid exudes fluid, thereby providing a space which, as we have seen, becomes promptly lined by cells that migrate from the mesenchyme to make a new membrane; the dura, on the other hand, does not exude fluid, and consequently adhesions form, since there is nothing to keep the surfaces apart when the pia-arachnoid has been damaged. But Dr. Harvey has recently brought forward additional proofs in support of his view.[66]

He conceived the idea that the cells of the leptomeninges might be derived from the same source as the sheath cells of the peripheral nerves, which arise, as R. G. Harrison had shown, from the embryonic neural crest, whereas the dura itself merely develops from the mesenchyme. Employing Harrison's methods he removed a bit of the cerebral hemisphere of one amblystoma embryo and transplanted it into the mesenchyme in the region of the fore-limb of

another where the explant during its subsequent growth came to be surrounded by an incompletely formed dura, but with no leptomeninx. On the other hand, when a portion of the neural crest was included in the explant, a choroid plexus developed and leptomeningeal spaces were formed in addition to the duraloid membrane of the control experiment. But here again we may have to consider the normal reactions of mesodermal tissues to the infiltration into them of cerebrospinal fluid with the inevitable formation around such fluid spaces of a serosal membrane.

This notable contribution by Dr. Harvey to experimental embryology and to that much-neglected part of it to which Weed had already contributed, namely the embryology of the meninges, is interesting and important from many points of view ; * but as a matter of fact we may be stretching matters in the endeavour to show differences between the endothelium of the vascular and lymphatic channels and of the mesothelium of the serous cavities and cerebrospinal fluid spaces ; for they all are but part and parcel of the

* It confirms, by experimental methods, a conception of the common origin of the leptomeninges and the sheath of Schwann cells originally propounded, as would appear on purely histopathological grounds, by Ch. Oberling (' Les Tumeurs des Méninges ', *Bulletin de l'Association Française pour l'Etude du Cancer*, 1922, vol. 11, No. 6). On the basis of a congenital disorder of this system, such a widespread malady as generalized neurofibromatosis (von Recklinghausen's Disease) becomes readily understood. It would perhaps explain also what has long been interpreted as a possible secondary route for the absorption of cerebrospinal fluid, namely by way of the perineural ' lymphatics '. These, however, are purely hypothetical structures, for it is histogenetically inconceivable that lymphatics can directly connect with the subarachnoid space. A conical sheath of dura and pia-arachnoid extends along the cranial and spinal nerves to their bony foramina of exit where the pia-arachnoid ends, and where arachnoidal villi and cell nests are found bearing the same relation to the sinusoidal veins of the region (cf. R. Elman [58]) which the comparable structures in the cerebral chamber possess.

circulatory apparatus as a whole. But even though the cerebrospinal fluid channels appear to be lined by supposedly fixed pavement cells, certain specialized cells are found to lie here and there in clusters, notably in association with the villi (Fig. 2), in nests incorporated within the fibrous mesh of the dura (Fig. 3), in the interforaminal prolongations of

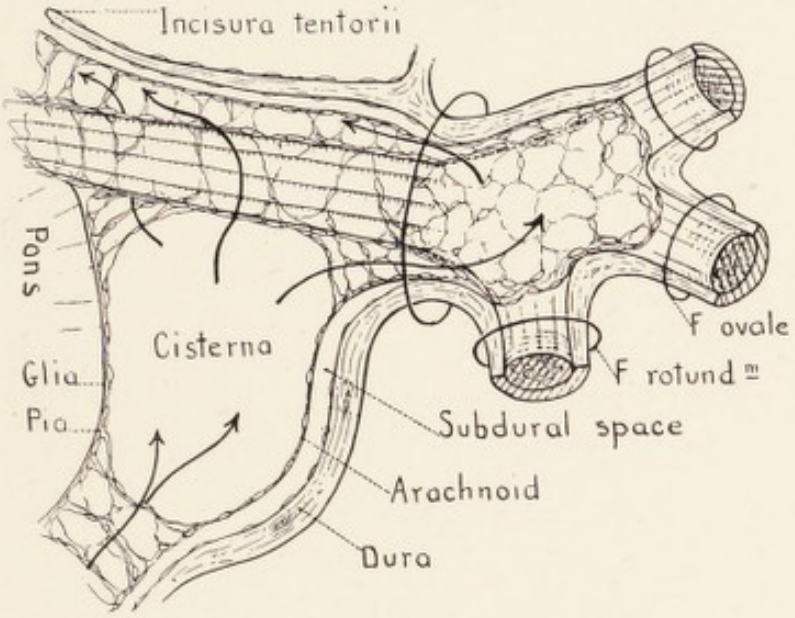

FIG. 7. Diagram to show relation of pia-arachnoid to the cranial and spinal nerves, in this instance the N. trigeminus, the ganglion itself being bathed by fluid in a subarachnoid extension which envelopes it. It is from this extension, both in the case of the trigeminal and the spinal nerves, that the meningiomas in these regions arise.

arachnoid enveloping the posterior root ganglia (Fig. 7), and in the leptomeningeal stalk of the plexus.

It would seem to me that Dr. Harvey's disclosure of the difference in origin of these cells from those lining the dura—the one being ectodermal in origin, the other mesodermal—is of particular significance. Let us for a moment consider some of the duties of these particular cells which, merely because of their situation and in com-

plete disregard of their histogenesis, we may for convenience call *meningocytes*.*

Phagocytic properties of the meningocyte. If the pathway for this specially elaborated fluid is as important as we are led to assume, there would certainly have been provided some method whereby its intricate channels could be kept clear of debris, especially of blood or inflammatory products of one kind or another which might get into the stream; for otherwise these foreign particles would inevitably be swept into the microscopic villi and effectually stopper them. The experimental observations of Dr Weed [36] and his co-worker Nañagas [50] in this direction have been mentioned in discussing hydrocephalus. Moreover, it is safe to say that the head of every infant is sufficiently traumatized during parturition to cause the extravasation into the fluid of red blood corpuscles, so that from the first moment of extrauterine life the mechanism for absorption of the fluid may be seriously interfered with.

An effective method of keeping these microscopic pathways open seems to have been provided through the phagocytic activity of the meningocytes under the stimulation of foreign particles. This property was first noted, it seems, by Quincke who found that cinnabar granules introduced in the fluid become engulfed by large phagocytic cells—the same cells that Goldmann subsequently found to be stained by vital dyes; but more recently it has been shown by

* In an excellent paper on this general subject by Mme. N. Zylberlast-Zand from Flatau's laboratory in Warsaw ('Rôle protecteur de la pie-mère et des plexus choroïdes,' *Revue neurologique*, Sept. 1924, An. 31, pp. 235–52), emphasis is laid on the fact that the pia represents the unbroken anatomical substratum which acts through the medium of the histiocytes as a barrier between the circulating blood and the nervous tissues. The author, however, subscribes to the view of Mott in so far as the manner of absorption of the fluid is concerned, and is apparently unacquainted with Weed's researches, which would have simplified her explanation of the general process.

Essick[35] in Weed's laboratory that though this reaction might be evoked by a great variety of substances it was particularly pronounced after the subarachnoid injection of laked blood, under the stimulus of which the cells enlarge, become vacuolated, and detach themselves from their moorings to swim out as free macrophages into the cerebrospinal current. Thus Nature saw to this need from the first, and the surgeon has only just tardily come to a realization that she can be considerably aided in her purpose by the prompt and repeated withdrawal of bloody cerebrospinal fluid.

It was apparently Essick's view that the fixed pavement cells of the membrane could become transformed into phagocytes, but doubt has been cast on this through the recent studies of the cellular reactions of the leptomeninges under supravital conditions of experimentation (a step farther than the vital staining of Goldmann) made by L. S. Kubie and G. M. Schultz.* These authors have shown that the flat pavement cells of the arachnoid membrane are interspersed with cells of another character, namely monocytes, which in all probability are the active agents in these phagocytic as well as in the reparative processes which have been mentioned, rather than the pavement cells themselves.

The *plasma cells* of Waldeyer, the *Mastzellen* of Ehrlich, the *endothelial leucocytes* of Mallory, the *pyrrol cells* of Goldmann, the *amoeboid macrophages* of Metchnikoff and Evans, the *polyblasts* of Maximow, the *histiocytes* of Aschoff, and the *clasmatocytes* of Ranvier (the term in most common use by American authors) are probably one and the same type of cell which possesses active migratory and phagocytic properties. But in regard to their source of origin, their

* 'Vital and supravital studies of the cells of the cerebrospinal fluid and of the meninges in cats.' *Bull. Johns Hopkins Hosp.*, August 1925, vol. 37, pp. 91–129.

relation to the phagocytic monocytes, and their capacity for transformation into more fixed cellular types when they have ceased their wanderings, there are divergences of opinion.

Maximow, for example, claims that the three cell types in inflammation have a single origin in the lymphocyte; Sabin and her co-workers, on the contrary, strongly favour the absolute specificity of the several cell strains; the Lewises are convinced that the macrophages (clasmatocytes) and the epithelioid cells are merely functional stages of the monocytes but make their position somewhat less clear in regard to the origin of the fibroblasts; whereas Carrel states he has definitely seen amoeboid macrophages become transformed into fibroblasts. The final decision in these matters unquestionably lies with the experimental cytologists, who have already devised and will further perfect methods of studying living cells in tissue cultures which permit direct observation not only of their behaviour and manner of division but also of their specific reactions to vital dyes.

What to the surgeon is of greater concern than the genesis of the active meningocyte, if we are justified in so specifying a cell which Goldmann first clearly showed to be a normal division of the meninges, is what it may be able to accomplish not only as a scavenger but also as a reparative agent. Certainly when it comes to the prompt replacement of a dural defect, say of 30 sq. cm., by a neomembrane, it is inconceivable that the pavement cells could grow in from the edges; and since it is doubtful whether these fixed cells are capable of further division, we must assume either that clasmatocytes or monocytes have wandered in from the mesoderm or else that, in the guise of ' meningocytes ', they are already present as normal denizens of the cerebrospinal spaces and ready to act as reparative agents. In either case we must assume further that they are capable of ultimate transforma-

tion not only into pavement cells but also into duraloid fibroblasts.

Whether the cells which participate in these activities are cells which wander in or cells which in a resting stage are normally moored in the leptomeninges perhaps makes very little practical difference, provided one appreciates their behaviour when called into action.

The formation of biliary pigments. There remains a further matter for consideration in connexion with these meningocytes. After Edwin E. Goldmann's discovery that the endothelial cells of the Kupffer-cell type which lie clustered in the blood channels of various organs have a selective affinity for the vital stains of the benzidine series, the suggestion, I believe, was first clearly formulated by H. M. Evans * that these cells as a group wherever they occur, within the blood stream or free in the tissues, should be looked upon as an endothelial organ of major physiological importance which in his belief is concerned in the production of immune bodies. It is this organ to which Aschoff has recently drawn renewed attention as the reticulo-endothelial apparatus, one of the functions of which—and there are probably many—is the phagocytosis and disposal of broken-down blood cells.

Little or no attention, however, seems to have been paid by those interested in this subject to the existence of a similar apparatus in the meninges, though Goldmann, whose early death was a great loss to experimental pathology, in the last of his remarkable papers † clearly described the pyrrol-staining monocytes which normally reside therein. Though misled as so many others have been into the belief that the

* 'The macrophages of mammals.' *Am. J. Physiol.*, 1915, vol. 37, pp. 243–58.

† 'Vitalfärbung am Zentralnervensystem.' *Abhandlung der K. P. Akad. d. Wissenschaften*, Berlin, 1913.

cerebrospinal fluid chiefly escaped by way of the pericranial lymphatics, he observed that, whereas the central nervous system itself remains unstained by vital dyes,* the choroid plexus as well as the anterior lobe of the hypophysis become highly coloured ; and at the same time certain cells of the meninges (in places which we now recognize to be those where clusters of meningocytes particularly abound) and also occasional cells of the same type scattered through the brain take the stain faintly. He regarded it as probable that these cells played the essential rôle of phagocytosis for the locality.

Let us for a moment return to a consideration of the fact that this specialized endothelial apparatus of the lepto-meningeal spaces appears to be called into action more effectively by the introduction of blood corpuscles than by any other foreign substance. And in this connexion attention may be drawn to the different behaviour of the pachymeningeal and leptomeningeal surfaces following the extravasation of blood into the subdural space, for as is well known the clot adheres to and begins to organize from the dural side, whereas it fails to adhere to the arachnoid. Now the subdural space as we have seen has an outer and inner lining of quite different origin, and the different

* MacCurdy and Evans subsequently showed that this was true only of the normal brain, for diseased cells become readily stained (*Berliner Klinische Wochenschrift*, Sept. 1912, vol. 49, p. 1695).

Wislocki and Putnam,[39] in the Surgical Laboratory at Harvard, on repeating Goldmann's experiments, discovered a minute bilateral area adjacent to the calamus scriptorius which is invariably stained. In these spots there proves to be a peculiar network of neuroglia which is highly vascularized and which they assumed to have some special function. This, from a developmental standpoint, is a very complicated area of the brain-stem—almost as complicated as the region of the infundibulum—and I suspect that certain of the rare tumours like the peritheliomas which arise from over the fourth ventricle may originate in the structures which Wislocki and Putnam have disclosed.

manner of reaction of the two surfaces to these subdural haematomas has been investigated anew by my recent assistant, Dr. Tracy Putnam.[70] He has shown how in the process of their digestion and organization from the dural side, communicating or non-communicating endothelial-lined spaces appear to be formed which are distinct from the newly-formed blood channels. But there is another feature of these subdural haematomas which seems to have escaped attention, namely the greenish surface colour which they acquire due to the deposition of biliverdin.

The presence of bile pigments indeed may be identified in cerebrospinal fluids after almost any extravasation of blood into the spaces. This is the more peculiar when one takes into consideration the fact that the bile pigments themselves do not normally pass the barrier of the choroid plexus, but are only found in the fluid in small traces in long-standing cases of deep jaundice, and perhaps only then because of functional damage to the choroidal epithelium. And though the information is not likely to be forthcoming, at least from clinical cases of icterus, I believe that even when a trace of bilirubin can be detected in the subarachnoid fluid it will not be found in the ventricles ; and if this should prove to be so, it would indicate that the pigment finds its way into the arachnoidea by way of the perivascular spaces rather than by passage through the filter of the plexus.

But leaving this aside, the demonstration in cases of subdural haematoma of an extrahepatic local icterus brings up in turn a subject which has of late occupied the attention of experimental pathologists. It was one of your fellow-countrymen, J. W. McNee, who first broke away from accepted tradition and ascribed the formation of bile pigments from haemoglobin to the reticulo-endothelial cells of the body rather than to the hepatic cells themselves. This view has been fully supported by the experiments of

G. H. Whipple and his co-workers and of F. C. Mann and his, and the proof now seems conclusive that the formation of bile is actually extra-hepatic. Though of course the Kupffer cells of the liver naturally participate with the endothelial cells elsewhere in the pigment formation, we need no longer accuse our much-maligned livers for all the melancholias the world has seen since the introduction of the humoral doctrine.

However this may be, it is to the fact of the meningocytes sharing in this capacity of producing bile salts, that I particularly desire to draw attention; and there is possibly no better place in which to study the activity of blood-devouring macrophages than in the cerebrospinal fluid where blood corpuscles represent foreign elements.*

The meningiomas. There remains one thing more to say of these meningocytes. It indirectly concerns the much mooted question as to whether the cells of the reticulo-endothelial apparatus can, as Marchand and Maximow and Carrel believe, become transformed into fibroblasts. Though this is a matter more likely to receive a definite answer by the modern methods of tissue culture and supravital staining which would permit the transformation to be actually observed, nevertheless clinical and histopathological experi-

* In a series of observations (unpublished) made by Mrs. Maddock upon a large number of fluids with the particular object of the detection of bilirubin by the method of Van den Bergh, she has shown that it is demonstrable after a certain length of time in all cases in which the arachnoid fluid becomes blood-stained as after an operation for tumour, whereas the ventricular fluid remains clear; that the mere mixture of cerebrospinal fluid and blood allowed to stand in vitro for many days gives no positive test; that it is probably, therefore, an action of living macrophages which abound in the fluids. It has been known of course since Mestrezat that an intense icterus may finally come to give in the cerebrospinal fluid a faintly positive test for bilirubin, and this we can corroborate. No tests have been made specifically for biliverdin though some of the fluids are distinctly green.

ences may add something to the subject. And this leads me to speak of the tumours which might be expected to take origin from the cells of the apparatus under consideration, if it actually possesses the important physiological functions ascribed to it.

Endotheliomata, so-called, are known to arise in the liver, spleen, bone marrow, and lymph glands where the cells of the apparatus in question abound, but in no situation are tumours of this category more common than in the meninges. They consequently are lesions long familiar to the pathologist and to the neurologist. A famous example, often referred to, was reported (as a sarcoma) by Byrom Bramwell in his early monograph on Intracranial Tumours (1888)—a young girl of twenty who had been admitted to the Newcastle Infirmary, January 5th, 1877, in a terminal stage of compression from a growth which had given no localizing symptoms. This, be it said, is a characteristic of these meningeal tumours—slowly to deform the brain, in which they make a nest for themselves, often without any local symptoms whatsoever, or indeed any pressure symptoms until the lesion may have attained an amazing bulk.

These tumours all have a common histogenesis, whether they occur in the spinal canal, taking their origin from the cells of the arachnoidal villi at the points of emergence of the spinal nerves, or, as is more frequent, from those which project into the venous sinuses of the cerebral dura. Unfortunately, however, they have been given by histopathologists so great a number of conflicting names that it has seemed best, partly for the purpose of emphasizing their common origin and partly to get away from the unfortunate misnomer of 'dural' endothelioma, to speak of them simply as meningiomas.[55]

To the fact that they undoubtedly arise from the arachnoid cell-clusters of meningocytes Dr. Weed and I called

attention in one of our early papers,[22] though, as we found, it was not an original observation, for the suggestion had been made before by M. B. Schmidt (1902), and also long before him (1864) by the late Professor Cleland of Glasgow. But no one seems to have offered any explanation of the remarkable fact that the tumours invariably take their origin from the arachnoid and never from the pial side of the fluid pathway, for though 'endothelial' tumours may in rare instances appear to arise from the pia they are of vascular and not mesothelial origin.

While examining the meninges in our experimental animals we had often observed local thickenings of the arachnoid produced by the heaping up of meningocytes, which tend to arrange themselves in whorls—an appearance suggestive of some antecedent local reaction. Dr. Weed subsequently made a special study of these arachnoidal cell-nests and traced them all the way from slight areas of thickening to actual tumefactions, and I am under the impression that the condition my colleague, Dr. Gilbert Horrax, has recently described as chronic cisternal arachnoiditis [62] may represent the residua of some similar physiological response which has called the meningocytes into activity, with a resultant thickening of the membrane sufficient in certain cases to impede seriously the flow of fluid.

But there is one final proof which I did not have, at the time of my Cavendish Lecture on the meningiomas, to show that they are actually of leptomeningeal and not of dural origin, namely a tumour of this category with no connexion whatsoever with the dura. Since then I have seen and removed one of the rare intraventricular tumours of the plexus (Figs. 8, 9), better known to comparative pathologists—a growth of precisely the same character as those that become incorporated with the dura, and which unquestionably

has arisen from the meningocytes which abound, as Sundwall observed,[11] in the arachnoidal fold constituting the stalk of the plexus.

Further light will doubtless come to be thrown on the genesis of these tumours and their relation to generalized neurofibromatosis by Harvey's embryological studies to

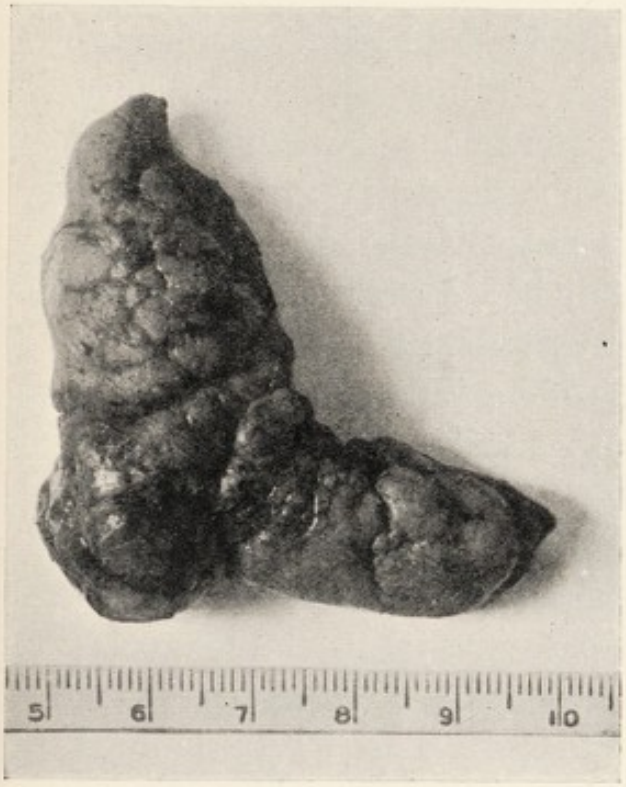

FIG. 8. Meningioma of right lateral choroid plexus, practically representing a cast of the dilated ventricle.

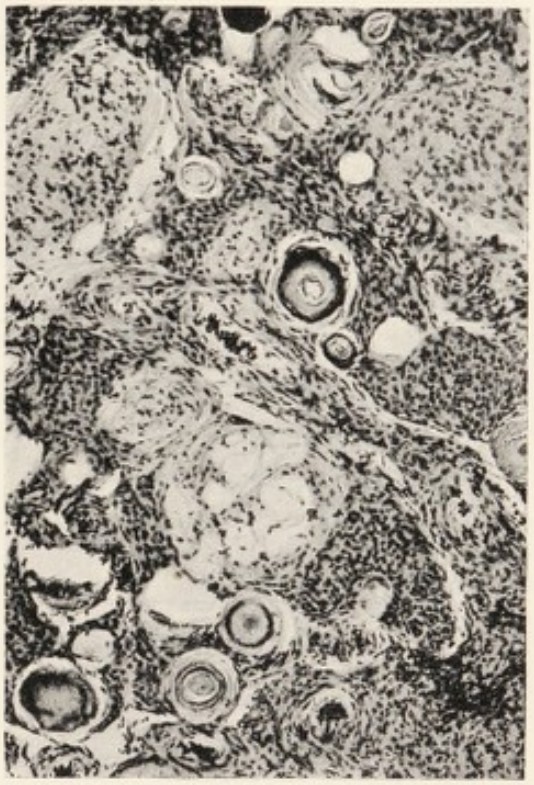

FIG. 9. Section of same, mag. × 80, showing typical so-called 'psammomatous endothelioma'.

which brief reference has been made; for if they originate from the neural crest they are ectodermal in origin and not mesodermal as long supposed.

Though we have only made a small beginning in the study of tumour cells by modern culture methods such as have permitted Alexis Carrel to see macrophages become transformed into sarcoma cells, we have at least succeeded in

cultivating the cells of a meningioma and have seen cells, which unstained were indistinguishable from tumour cells, engulf red blood corpuscles. Only by the employment of such methods can light be thrown on the much-mooted question as to whether the meningocytes actually become transformed into fibroblasts. The larger number of these clinically unmistakable tumours are almost wholly composed of endothelial cells, but certain of the older and psammomatous growths come to take on a fibrous change and may actually contain deposits of true bone; but even in the more purely fibrous examples one may always find nests of mesothelial cells. From this histological evidence, if it is dependable, one would certainly be led to conclude that the cells comprising the reticulo-endothelial apparatus of the body, of which the cell clusters of meningocytes are obviously important representatives, may actually undergo fibroblastic transformation.

Thus we have seen whence the cerebrospinal fluid takes its origin, how it comes to make pathways for itself by percolating through the primitive mesenchyme, how these pathways which originate from cells of the neural crest become lined with a specialized mesothelial membrane, and how minute outlets for the absorption of the fluid into the large venous channels are formed—in short, how this circulatory switch for a fluid peculiar to the ventricular and meningeal spaces comes into existence, and how it communicates with the deeper parts of the brain by perivascular tubes of the pia-arachnoid.

We have seen, too, that in addition to the fixed pavement cells lining these spaces certain other cells termed meningocytes tend to become deposited in clusters, which we may figuratively describe as moored fleets of destroyers ready to cast off and engage any objectionable invader. In this

respect the phagocytic functions of these cells are in every way comparable to those exercised, for example, by the clusters of Kupffer cells in the hepatic vessels, for they have the same affinity for vital dyes, the same capacity to engulf and destroy red blood corpuscles, elements which are foreign to the circulating medium of the meningeal spaces, and they possess also the capacity, in this process of blood destruction, of transforming haemoglobin into bilirubin. Hence these cells may be taken to represent the reticulo-endothelial apparatus for the meningeal spaces.

We have seen also how these clusters of meningocytes may become the seat of tumefactions which, because of their being in most cases incorporated with the dura, are commonly supposed to arise from it, but which actually take their origin from the meningocytes and may be conveniently designated as meningiomas. And it would appear from the study of these tumours that their endothelial ground cells may become metamorphosed into fibroblasts.

So, by a consideration of the cerebrospinal fluid and of the cells of the membranes which enclose it, one may be led into problems of wide concern in general pathology. But with the intended purpose of this lectureship in mind, it is improper to leave the subject without calling attention to the fact that, though we may not appear to be much nearer to a cure for congenital hydrocephalus, in quest of which we started out, we have at least learned many things on the way which are essentially of practical therapeutic value.

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LECTURE II

THE PITUITARY GLAND AS NOW KNOWN

In those creatures that have the *glandula pituitaria* large, (as in Calves, for instance) the two Carotid Arteries, meeting about the *sella* of the wedge-like bone, presently divide themselves into small twigs, which being interwoven . . . make on each side a notable *plexus*, called *Rete mirabile*. . . . So that in these creatures that gland seems to be of the same use to the *Rete mirabile*, as the *glandula pinealis* is to the *plexus choroides*, viz., to separate a serous matter from the Arterial Blood. But in Man, (according to the best Anatomists) this *Rete* is wholly wanting; so that . . . the *glandula pituitaria* is of less use in him, than in other creatures that have the *Rete*.

Thomas Gibson's *Anatomy* (1688).

The subject before us, in view of the time-honoured association of the pituitary body and the cerebrospinal fluid pathways, is not so far removed from that of the preceding lecture as might be supposed. Nor can we to-day, when there is so much that remains unknown, afford to smile at those who regarded this obscure structure as a strainer for the sedimented waste products of the brain, which passed out by the infundibulum as pituita or slime into the nasal cavities. This Galenic conception persisted for fifteen centuries; and as late as 1631, in his *Integrum Morborum*, Robert Flood explained the aetiology of coryza on the principle of the siphon action between the ventricles and the nose. Could he have known that the hypophysis is present in all vertebrates, and that in the low order of amphioxus a canal lined by ciliated epithelium affords a communication between the buccal and cerebral cavities, he would have had something more than tradition with which to substantiate his beliefs.

But Schneider (he of the membrane), in his *Liber de Osse Cribriformi* (1655), denied the existence of any demonstrable communications; nor could either Willis, or Richard Lower, or Vieussens find any by the experimental methods at their command. And yet how could a spontaneous cerebrospinal rhinorrhoea, of which these learned men must certainly have had knowledge, have been accounted for on any other basis? Even Magendie leaves one with the impression that the hypophysis may represent a sort of lymph gland interposed in the fluid pathway.*

Truth assuredly lies at the bottom of a well; and that out of these gropings in the dark, the pituitary body, in the past decade or two, should have come to occupy a position in medicine out of all proportion to its size is the more remarkable. Of this I need not remind the members of a School whose Professor of Physiology not only was a pioneer contributor to our knowledge of its functions, but who has inspired many of his fellow workers, Oliver, Vincent, Herring, Magnus, Cramer, Pringle, Dott, Hogben, and others, to the making of further discoveries. Indeed, if I am not mistaken, it was he who, in his admirable Lane Lectures in 1913, actually baptized the 'Endocrines' of which we hear so much to-day.

The modern period, which begins with Marie's description of acromegaly in 1886, is too well known to need retelling here, and it is scarcely possible in the time at my disposal more than to hint at the many problems, anatomical,

* Cf. 'Recherches sur le Liquide céphalo-rachidien', 1842. In this work he remarks (p. 77), 'Les auteurs anciens, tels que Brumer [Brunner ?], Litre, Haller, ont sans doute observé quelque chose d'analogue [i. e. a pituitary tumour] lorsqu'ils ont dit que l'hydrocéphale est souvent causée par *des obstacles au passage du fluide des ventricules par la glande pituitaire.*' The matter is gone into more fully in the historical appendix to Magendie's treatise, written by Dr. Jodin.

physiological, pharmacological, pathological, and clinical, which are awaiting solution. An attempt even to mention the names, much less to give due credit, to those who in the past ten years alone have made additions to our knowledge of the subject would read like Chapter I of the Fourth Book of Moses, for those to be numbered are many. Consequently, as in the preceding lecture, I shall pursue the easiest course and let a personal story lead where it will.

During the first decade of the century, great confusion prevailed in regard to the disorders of the gland. To be sure, acromegaly and gigantism were recognized as clinical entities known to be associated with hypophysial tumefactions, but Pechkranz (1899), Fröhlich (1901), Axenfeld (1903), Müller (1905), Brissaud (1907), and probably a good many others,[1] ophthalmologists and gynaecologists in particular, were calling attention to the existence of tumours of the gland or its neighbourhood associated with combinations of optic atrophy, amenorrhoea, infantilism, adiposity, and sometimes diabetes insipidus—in short, a most heterogeneous array of symptoms which had no apparent relation to acromegaly whatsoever.

The attempted reproduction of any of these mysterious syndromes by extirpation methods had been unavailing; and though physiologists had shown the existence of an active substance in the posterior lobe, it was generally believed that the organ must be vestigial, since those pioneers who had undertaken its experimental removal claimed that no symptoms whatsoever ensued. However, because of the gland's inaccessibility and small size, these experiments were particularly difficult to carry out, and the results, to say the least, were undependable. Certainly, were hypophysial tumours ever to be operated upon successfully, it was necessary to know something more about the function of the gland if for no other reason than to avoid

such mistakes as had been made in the process of developing the operation of thyroidectomy.

Experimental apituitarism. In 1907, a Roumanian investigator, Paulesco, devised a new operative approach to the canine hypophysis which enabled him to expose the gland so that it could be successfully and cleanly extirpated. The animals invariably died with a peculiar train of toxic symptoms, and he naturally concluded that the organ was essential to the maintenance of life. Here, then, out of all the vagueness of the past was something tangible, if the astonishing statement was to be believed. Dr. L. L. Reford and I in the same year undertook to repeat Paulesco's experiments and came to the same conclusions.[2] The animals with proven total removals all died with what, in imitation of Kocher's designation for the symptoms provoked by a total thyroidectomy, we termed *cachexia hypophysiopriva*.

Now, this fundamental question of the essentiality or otherwise of the gland to life would seem to be a very simple one to settle. Paulesco's contention has received support from Schafer (1909), Livon (1909), Biedl (1910), Ascoli and Legnani (1913), and Blair Bell (1917); but others who have studied the effects of these total-extirpation experiments, e. g. Gemelli (1908), Aschner (1909), Horsley with Handelsmann (1911), and more recently Brown (1923) and Dandy (1925),[48] have come to the opposite conclusion; and it is not impossible that both parties to the argument are in a measure right. We perhaps tended too strongly to ascribe the occasional survival to the presence of an accessory (pharyngeal) hypophysis, or to the incompleteness of the removal; those holding the opposite view have perhaps tended too strongly to explain away the early and fatal cachexia on the grounds of some hypothetical injury to structures at the base of the brain. After all, the important

thing to have shown is not whether the gland is actually essential to life, but that instead of its being merely a vestigial structure of no moment, as was claimed by Paulesco's predecessors, it is in reality an organ of extraordinary importance for the maintenance of a normal physiological equilibrium.

One would suppose, with the present-day activities of surgeons in operating upon the gland, that the clinic would by this time have provided corroboratory evidence bearing upon this matter one way or the other, just as the extirpation of the thyroid served to bring to light the essentiality of the parathyroid bodies to the maintenance of life; and though extensive operations for the removal of tumours such as the congenital lesions arising from the relics of Rathke's pouch are occasionally followed by fatality from inanition, I have never but once known of a clinical case in which the symptoms resembled the experimental cachexia hypophysiopriva which is so quickly fatal in animals.

> This case was that of a middle-aged woman who, while in normal health, had a sudden severe headache which was soon followed by stupor, coma, and death in three days. The abruptness of this unexplained illness led to a detailed medico-legal examination of the body. Nothing whatever was found which could possibly account for the death apart from a small and unsuspected pituitary adenoma. Into this adenoma a spontaneous haemorrhage had occurred with a seemingly complete intracapsular destruction of the gland.

But to return to our laboratory studies. We naturally felt that if the train of symptoms were actually due to the removal of the gland, they could be offset by a preliminary or coincidental glandular transplantation; and during the following year (1908–9), with Drs. S. J. Crowe and John Homans,[7] an attempt was made to answer this and the many other questions which crowded in upon us. In the course of these studies, we made a hundred or more total

or partial hypophysectomies, an operation at which my co-workers became particularly adept, for it is a procedure requiring both practice and skill, even now, when it may be greatly simplified through the coincidental shrinking of the brain by Weed's method.

When I re-read to-day our report on the prolongation of life by transplantation of the gland after total hypophysectomy,[4] I am less impressed with our partially successful results than I am with the many sources of confusion which beset us. We were vainly endeavouring to distinguish between the comparative importance for the maintenance of life of the epithelial *versus* the nervous portion of the gland; and in respect to the latter had been somewhat misled in regard to its relation to diuresis by the studies (1901) of Schafer and Magnus—an error which at least put us in very good company. There is, however, perhaps one thing in our report which is deserving of attention to-day, namely the appearance, in the vicinity of a transplant made into the cerebral cortex, of Herring's hyaline bodies, which we regarded as evidence of activity of the posterior lobe. But this concerns a mooted question to which I shall return.

Experimental hypopituitarism. During the course of these experiments we hit upon a matter of far greater interest than the mere question of essentiality of the gland to life. For it was observed that after incomplete hypophysectomies many of the animals became in time adipose, inactive, and sexually dystrophic. They showed, in other words, a train of symptoms that in many respects resembled the confusing clinical syndromes produced by tumours of the gland, which failed to cause acromegalic overgrowth but, on the contrary, were accompanied by an adiposogenital dystrophy. It is a curious fact that we had long been surrounded by these fat and lethargic animals before we really 'saw' them, and before the idea burst upon

us that we had actually produced states of pituitary insufficiency.

In an address given in June 1909[3] the idea was, I believe, first clearly formulated that the corresponding clinical states were due to glandular insufficiency (hypopituitarism) and that, as a corollary, acromegaly must in all probability represent a counter state, due, as had previously been suggested without experimental corroboration, to glandular over-activity (hyperpituitarism). In further support of this hypothesis was the fact that two cases of acromegaly had been operated upon at about this time (1908), the first by Hochenegg in Vienna, and the second at the Johns Hopkins,[5] in both of which there had been an apparent amelioration of many of the constitutional symptoms associated with the disease.

An array of problems was immediately exposed for attack by this disclosure. Could the symptoms, as in the case of thyroid deficiencies, be offset by feeding of extracts or by glandular transplantations? What was the active principle with which we were dealing, and where did it reside; in the posterior lobe, which alone possessed an active substance so far as physiologists could tell us, or in the anterior lobe, or in both, or were there several principles? Why should these experimental hypophysectomies have produced so many striking changes in the other ductless glands? What would be the effect on growth, provided the experiments were made on puppies rather than on the adult animals selected at random for our earliest series of experiments? Some of these questions, like the last, were soon answered; some of them still remain unanswered, for the riddles of physiology are not so easily solved as all that.

A series of hypophysectomies in puppies was soon carried out with Dr. Emil Goetsch, giving results, so far as the retardation of growth is concerned, in entire agreement

with those reported by Ascoli and Legnani (1911) and by Aschner (1912), whose admirable papers forestalled us. We, however, doubted the truth of Aschner's contention that the effects he had obtained were due to uncomplicated total removals, in view of the operative approach through the mouth which he had employed; and yet, though we still clung to the view of essentiality of the gland, we had to admit that the fatal cachexia following its total removal in puppies was much less prompt in onset than in older animals.[13]

But when it occurs, this state of apituitarism is unmistakable, characterized as it is by somnolence, a slowed pulse and respiration, and a subnormal body temperature which tends before the end to fall almost as low as that of the surroundings; and Dr. Goetsch observed that the hearts of some of these animals continue to beat after death much as does the heart of a batrachian. We naturally inferred that the loss of the gland leads to some profound disturbance of metabolism and heat regulation, and were inclined to ascribe these effects chiefly to deprivation of the anterior lobe; for, in confirmation of Paulesco's observation, we had found that the dislodgement of the infundibular lobe, leaving the pars anterior intact, led to no recognizable disturbances—an observation the more surprising in view of the active principle it was known to contain. We were not then aware, of course, that the infundibular stalk contains secretory pathways in connexion with the pars tuberalis resembling those for the pars intermedia in the posterior lobe, and also that extracts of this portion of the gland contain traces of the active principle. Even so, it is quite probable that all of this posterior lobe tissue, pars nervosa and intermedia included, can be spared, and no untoward symptoms supervene, provided the anterior lobe remains intact. Something comparable to this seems to be true

of the adrenal gland, for Wislocki and Crowe have shown * that the medulla, which contains the known active principle, may be destroyed—indeed the entire abdominal chromaffin system removed—without producing any recognizable symptoms, whereas they calculate that one-fifth of the total mass of the cortex is necessary for the maintenance of life.

Let us first of all turn our attention to this seemingly unimportant posterior lobe, to its secretory product, and the manner of its discharge.

The Pars Posterior

As later experiences taught us, we had been barking up the wrong tree in our original conjecture that it was deprivation of the anterior lobe which caused the serious alterations in physiological equilibrium in our extirpation experiments; but leaving this aside, a more important pursuit was that in connexion with the series of animals in which incomplete extirpations had been made, particularly those with stalk division, which Paulesco erroneously regarded as equivalent to a total extirpation.

In the quotation used as a caption to this lecture, Gibson makes reference to the *Rete mirabile* of the older anatomists, and Drs. Heuer, Goetsch, and Dandy made studies [10] of the circulation of the canine gland which showed that the entire supply to the anterior lobe passed down the infundibular stalk from the Willisian vessels, whereas the posterior lobe had an additional blood supply from vessels which enter it from behind. We therefore knew that it would be possible, in the dog at least, to divide or to obstruct the pituitary stalk without subsequent necrosis, and this led to a series of experiments the consequences of which may at this juncture be discussed.

* *Bulletin of the Johns Hopkins Hospital*, June 1924, vol. 35, pp. 187-93.

The formation and discharge of posterior lobe secretion. In the course of his studies here in Edinburgh on the cat's hypophysis, Herring had called attention (1908) to the faintly staining hyaline or colloidal masses in the loose tissue spaces of the pars nervosa, and suggested that these masses might represent the secretory product of the lobe. In properly fixed preparations of the canine hypophysis we found likewise that these amorphous masses, which appear to be a product of the epithelial investment of the lobe, are at times abundant and appear to be streaming through the loose tissue spaces which obviously radiate towards the tip of the infundibulum. Though these presumably colloidal bodies are very elusive and are easily dissolved out of the specimens, leaving the tissue spaces empty, we nevertheless, in full agreement with Herring, frequently saw the masses in the act of seeming to extrude themselves between the ependymal cells into the ventricles.[7]

This naturally led to an effort to detect the substance in the cerebrospinal fluid, and though we found it most difficult of experimental proof, capable of false interpretations and necessitating innumerable controls, Goetsch and I came to believe that posterior-lobe secretion was normally discharged into the cerebral ventricles ;* and ere long succeeded, as we thought, in demonstrating its presence in the cerebrospinal fluids secured from the hydrocephalic ventricles of clinical cases.[8]

Doubts as to the correctness of our conclusions promptly appeared. Edinger (1911), while admitting that the spaces in the pars nervosa appear to lead brainwards, had never seen an injection mass enter the ventricle. Carlson and

* Goldmann (*Verfärbung am Zentralnervensystem*, 1913, p. 25) conjectured without experimental proof that the secretion of the gland passed into the periglandular leptomeningeal spaces which Key and Retzius had discovered, and which have recently been accurately redescribed by Hughson (1924).

Martin took exception to our findings (1911), also Houssay (1918), and even in our own laboratory the subsequent studies of Dr. Conrad Jacobson, not published till ten years later,[37] failed to corroborate them. Dr. S. C. Harvey and I returned to the matter again in 1915–16, using the uterine muscle test (oxytocic), without results sufficiently uniform and dependable for publication, and there the matter on our part might have rested.

However, certain more successful studies were at the same time being carried out in the Pharmacological Laboratory in Cambridge by Douglas Cow (1915), who showed that the active substance in the fluid, which is most variable in amount, can be increased by the intravenous injection of certain extractives, particularly of the duodenal mucosa. And since the war, independently of one another, W. E. Dixon in Cambridge (1923) and Carl Trendelenburg* in Frankfurt (1924) have taken up the subject anew with results that lend firmer support to our original views than we were able to furnish ourselves.

Like many others (Capelletti, Petit and Gerard, Meek, Dixon and Halliburton, Frazier and Peet, to mention a few of them), we became engaged at one time or another in the course of our cerebrospinal fluid studies, in the elusive and uncertain pursuit of substances which might increase the flow of fluid. For reasons associated with the closed-chamber factors of the Monro-Kellie doctrine, experiments of this sort offer unusual difficulties and are prone to misin-

* Trendelenburg's studies have been subsequently extended by his pupil Yoshio Miura, who has shown (*Pflüger's Archiv*, 1925, vol. 207, p. 76) that a positive oxytocic response from the fluid of an animal (cat) would diminish or disappear after either an hypophysectomy or stalk division.

Dixon and Marshall have recently shown that ovarian extract is a powerful stimulant of the hypophysis, and causes the oxytocic principle to be passed into the fluid (*Journ. Phys.*, 1924, vol. 59, p. 276).

terpretation. However, we felt that we had avoided the more common sources of error by measuring the fluid production as it came from the ventricles rather than from the arachnoid cisternae; and, in our Cerebrospinal Fluid Studies, No. VIII, Weed and I reported (1915) that posterior-lobe extracts, presumably from their direct action on the plexus, had a particularly marked effect in producing what we called a 'choroidorrhoea'. As our conclusions in this respect were not confirmed by Dandy and Blackfan (1913) and were opposed also by Dixon and Halliburton (1916), we may well enough have been misled. This, however, is less important than the confirmation by Professors Dixon and Trendelenburg of the underlying assumption that under certain circumstances the cerebrospinal fluid actually contains demonstrable amounts of posterior-lobe secretion.

There are, however, evidences from another source which support our hypothesis and to which we may for a moment refer. In repeating Paulesco's experiments on stalk separation, we had found on subsequent histological examination, that the posterior lobe had become so extraordinarily cellular and so infiltrated with hyaline masses that we naturally came to regard this appearance as an evidence of secretory stasis, although we knew of no comparable process in connexion with any other organ of the body. We had at this time also been given opportunities to study a certain number of hypophyses from clinical cases of hydrocephalus due to tumour or otherwise, in which the posterior lobe had shown a similar invasion by cells from its epithelial investment. And since many of these patients, as explained in my monograph on the pituitary disorders,[13] had shown constitutional symptoms such as lethargy, adiposity, subnormal temperature, amenorrhoea, and so on, suggesting a deficiency of pituitary secretion, we were led to believe that

under these circumstances also there must be an obstruction to the normal discharge of the secretory product from the pars nervosa.

Not only did we find, in agreement with Herring, that these hyaline bodies were greatly increased in amount after thyroidectomy, but they seemed to be even more abundant after a 'near total' extirpation of the pancreas,[7] which

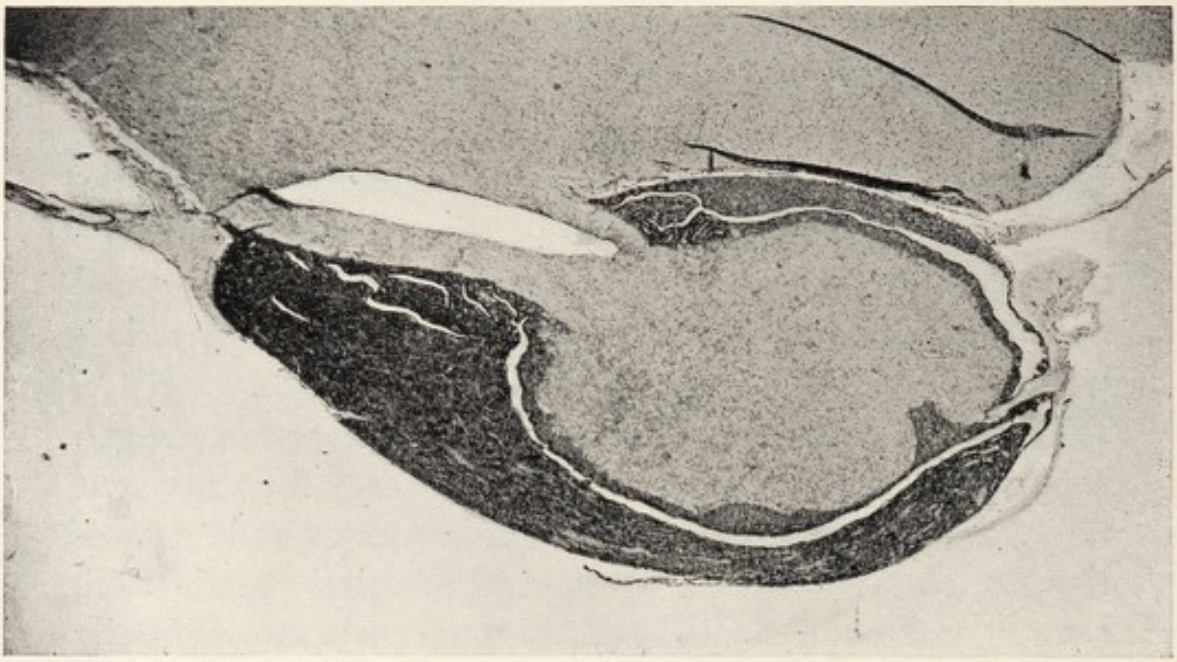

Fig. 10. Median section of normal canine hypophysis (×14). For comparison with Fig. 11.

merely goes to show how closely the endocrine organs are functionally inter-related. But the experiments, carried out with Emil Goetsch in our 1909–10 series, which gave us the most striking picture, were ones in which a silver-wire 'clip' was bloodlessly closed on the hypophysial stalk after exposing the gland by the usual operative method.

During the past year, with Dr. Maddock, a new series of these 'clip' experiments has been conducted for another purpose, to which we shall return; suffice it to say, the histological picture of extreme cellularity of the posterior

lobe with increase of hyaline, and the production of great masses of colloid in the inter-glandular cleft has been invariably obtained (Figs. 10 & 11). Certainly this striking appearance can only be interpreted as the result of an obstruction to the discharge of the products of posterior-

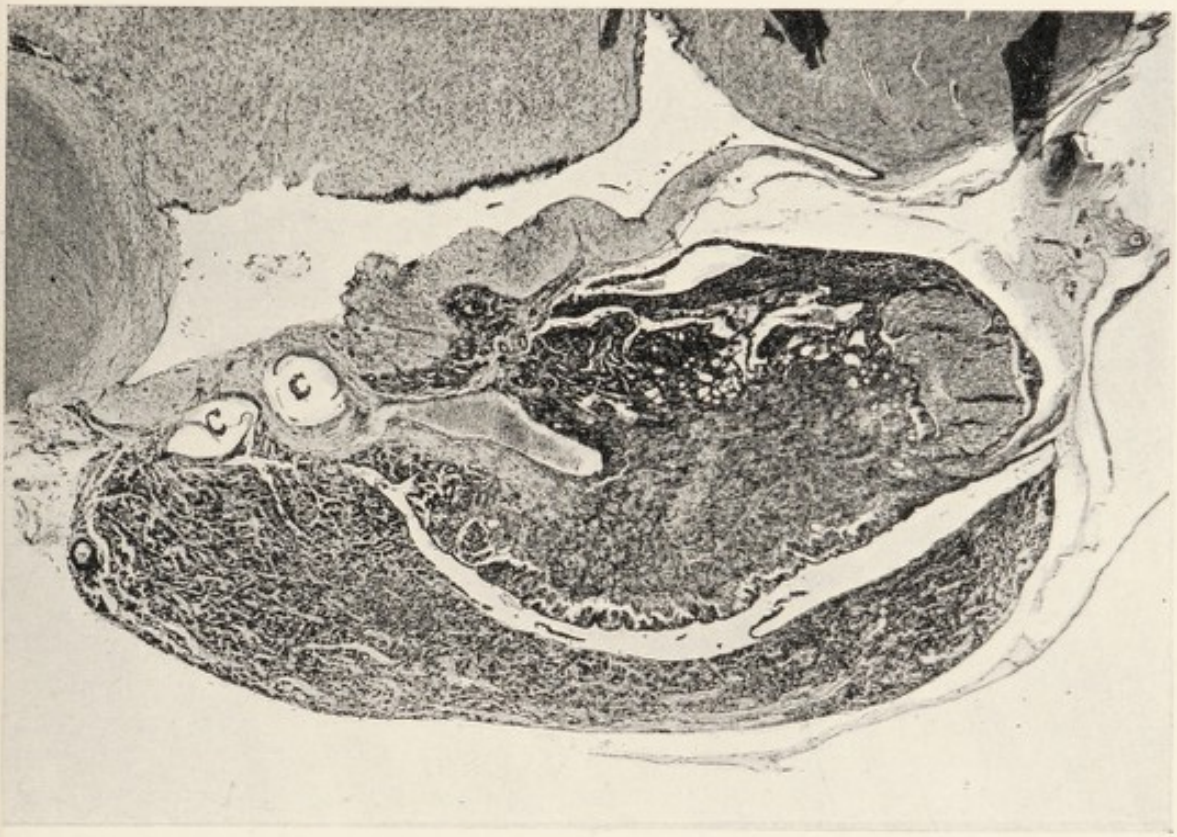

FIG. 11. Median section of canine hypophysis after closure of clip on stalk at C C, followed by persisting polyuria and 3 kg. increase in weight. Sacrificed on 26th day. Note the abnormal cellularity of the entire posterior lobe and the accumulations of colloid (×14).

lobe activity, or at least of products which are in transit through the lobe, for some destination or other.

Histogenesis of the pars nervosa. But we know lamentably little about the actual structure of the neuro-hypophysis. The pineal body, a far less important organ, is much better understood, and has an easily demonstrable basis of neuroglia ; but there are peculiar difficulties which stand

in the way of comparable studies of the pars nervosa. We have recently made an effort, with the specific dyes introduced by the school of Ramón y Cajal, to determine just what may be the nature of the loose tissue strands which radiate through the lobe towards the infundibulum and between which the hyaline masses accumulate. Though

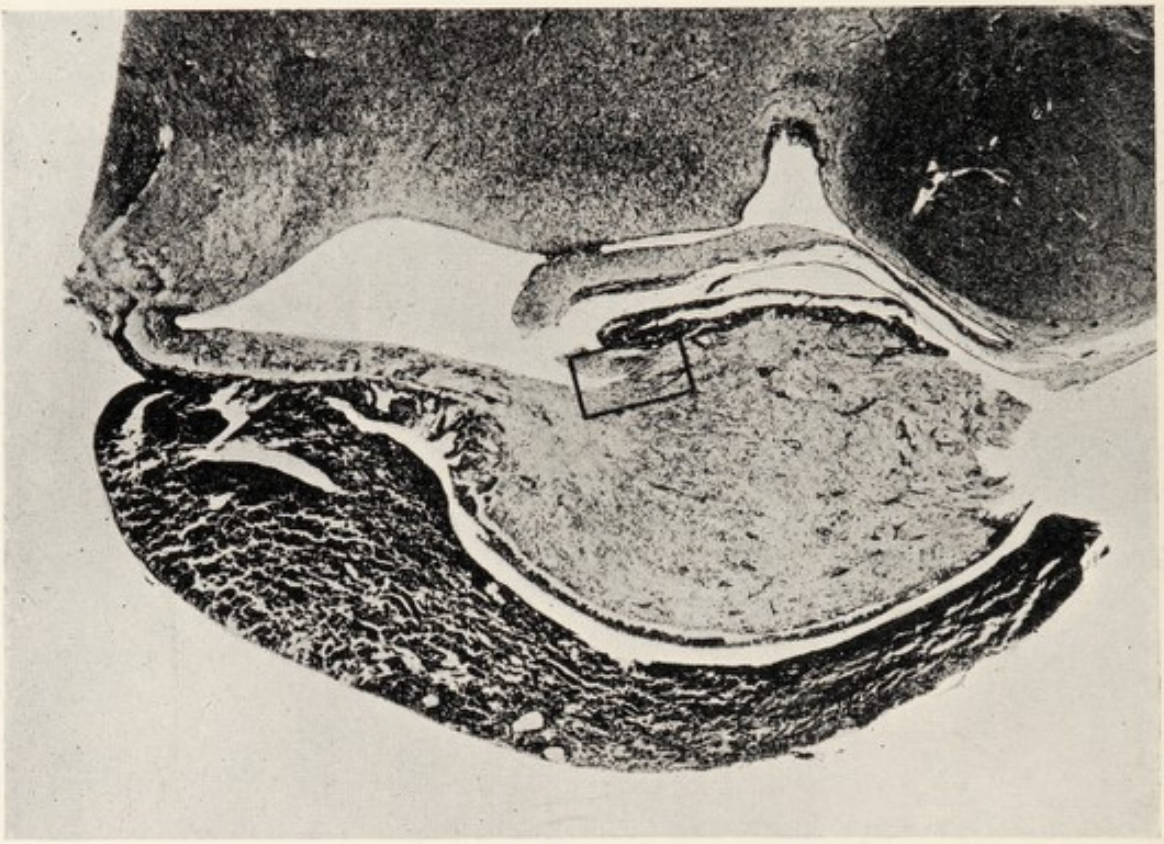

Fig. 12. Normal canine hypophysis (×15), stained by Cajal's nerve-fibre method. For squared area cf. Figs. 13 and 14.

supposed to represent neuroglial processes they do not take the specific stains for glia, and certainly the cells have none of the morphological characteristics of the glia cells.

Delicate nerve fibres of uncertain destination may be seen passing down the infundibular stalk to become lost in the upper portion of the lobe (Figs. 12, 13). Occasional fibrillae which take the specific glia stains are also demonstrable in the stalk, running for the most part crosswise to the course

of the nerve fibres (Fig. 14) ; but neither glia nor nerve cells can be demonstrated by methods at present at our command in the body of the lobe itself. It would appear that there must either be something in the chemistry of the substance which the gland holds that counteracts the effects of the usual tissue mordants, or else that the tissue, if actually

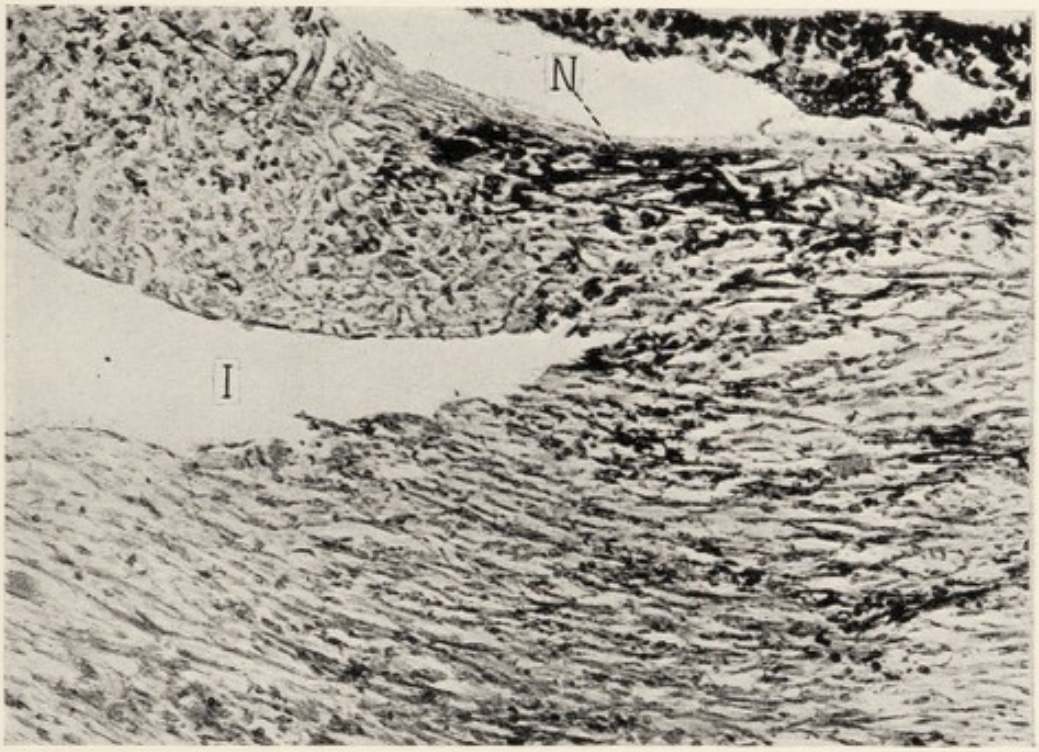

Fig. 13. Cajal's nerve-fibre stain. Squared area shown in Fig. 12 (×180). Bundles of fibres (N) shown coursing down posterior wall of the infundibulum (I) to become lost in lobe.

neuroglial, is of an unusual character.* The appearance and disposition of the faintly staining ground fibres would

* The literature on the subject is meagre in the extreme. In 1894 H. J. Berkeley (*Brain*, vol. 17, pp. 515–47) described not only the presence of neuroglia but of ganglion cells of several types in the infundibular lobe, as stained by the non-specific method of Golgi. In 1912 F. Tello (Cajal's *Trabajos*, vol. 10, pp. 145–83), using Achucarro's tannic silver method, was unable to substantiate Berkeley's claim, although unmyelinated nerve-fibres of uncertain distribution were observed in the region of the stalk. He

suggest that they are the modified tails of elongated ependymal cells, but it is a matter which needs further study.

Meanwhile, certain experimental zoologists in Germany, England, and America have hit upon a most significant consequence of posterior-lobe extirpation in the amphibia. They have shown that the lobe provides a substance which

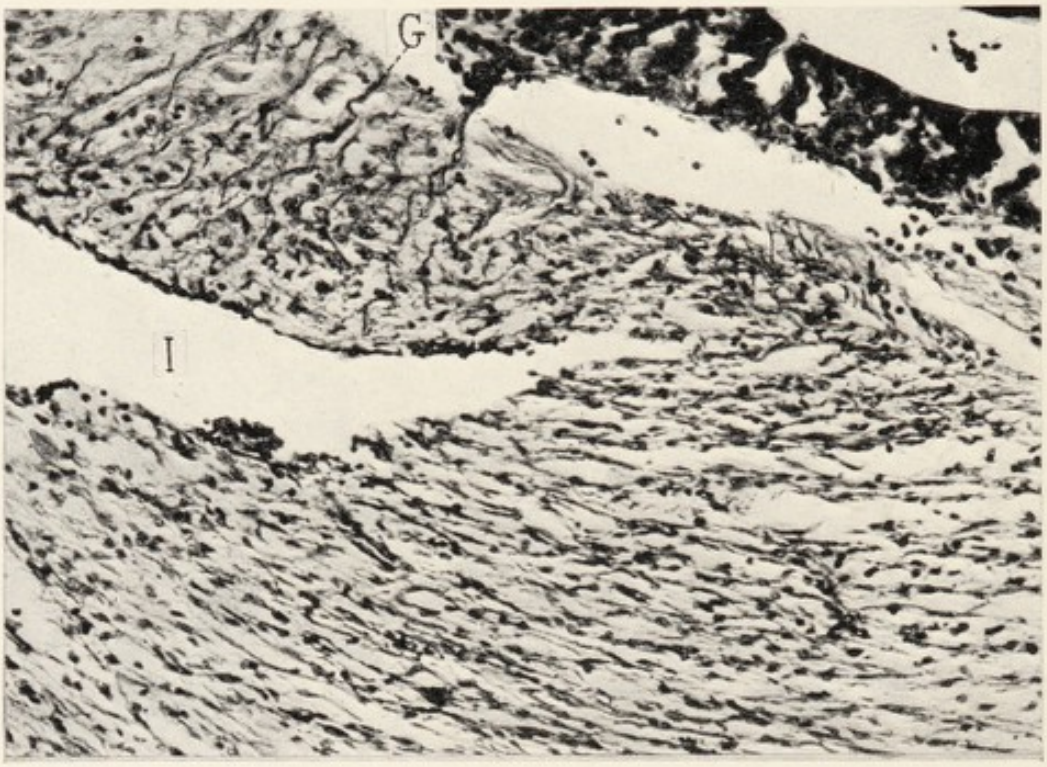

Fig. 14. Same area from Fig. 12 (×180). Stained by Bailey's ethyl violet-orange G method for neuroglia. Showing numerous glia fibrillae running perpendicular to the course of the nerve fibres shown in Fig. 13. No glia fibres demonstrable in posterior lobe, whose open spaces radiating towards the infundibulum are apparent.

controls the pigmentary responses in the skin, for after the removal from the embryo frog of the anlage of this portion

believed that Berkeley's cells were neuroglia cells. He traced the nerve fibres themselves to their terminations in pathological end bulbs which he believed underwent degenerative processes; and he thus accounted for the hyaline masses. A more recent paper by Ch. Hoenig (*Zeitschrift f. d. gesamte Neurologie u. Psychiatrie*, 1922, vol. 79, p. 197) adds nothing new.

of the gland, the tadpole not only becomes retarded in its growth but remains pale or albinoid owing to contraction of its cutaneous pigment cells [Adler (1914) ; Smith (1916) ; Allen (1917)].* These pale animals serve as a most delicate indicator for posterior-lobe (pars intermedia?) secretion, for on its injection in minute amounts the melanophores expand and the animal acquires the normal colour.

This melanophore reaction to posterior-lobe extracts has not as yet, so far as I am aware, been utilized as a test for the presence of this substance in the cerebrospinal fluid. But whatever future studies may bring forth in this respect, it may suffice to say that the posterior lobe is a unique organ surrounded by an investment of indolent-appearing epithelial cells, seemingly under the direct control of nerve fibres, and that stimuli of one sort or another cause these cells to divide and bud off directly into the loose tissue reticulum wherein they undergo some sort of amorphous transformation as they progress towards the stalk and the infundibular cavity. At this point they not only have the appearance of passing between the ependymal cells into the ventricle, but when this pathway is experimentally occluded, the gland becomes packed with the transforming cells and their secretory products.

With the exception of the last step in this process, our views I believe coincide with those of most others who have been interested in the subject. All agree that we are dealing with a secretion of extraordinary potency which accumulates in the loose tissue spaces of a poorly vascularized and unique organ. These tissue spaces obviously radiate towards the

* These observations have been greatly amplified by L. T. Hogben who has studied the effects of hypophysectomy on adult amphibians (*The Pigmentary Effector System*. Edinburgh, 1924).

infundibulum, and no explanation has been offered of the way in which this readily dialysable product—a hormone if you will—reaches the blood stream, unless it be by the mediation of the cerebrospinal-fluid switch described at such length in my first lecture.

Carbohydrate tolerance. But I must return again to our second series of hypophysectomies to pick up the threads of another pursuit conducted with Drs. Goetsch and Jacobson, which led us to investigate the carbohydrate tolerance of our experimental animals, and from this into studies of their basal metabolic rate, which in turn was indirectly responsible for the introduction of the calorimeter into the clinic.

As already stated, we had observed, in connexion with our first series of experiments (1908–9) that definite histological changes occurred in many of the other ductless glands, notably in the thyroid and gonads, as a consequence of the hypophysectomy ; and vice versa, as was well known, that changes in the hypophysis occurred subsequent to thyroidectomy, castration, and so on. We naturally wondered whether the syndrome which we had ascribed to a state of hypopituitarism, might not be due to these secondary changes rather than to the primary hypophysial lesion.

All this was part and parcel of a developing conception of the inter-relations of the ductless glands, so convincingly presented ere long by the work of Eppinger, Falta, and Rudinger. We had observed, for example, that a nearly total pancreatectomy appeared to activate posterior-lobe secretion if the associated increase in the hyaline bodies of the lobe could be so interpreted ; and we also found that our adipose and lethargic animals, with a pituitary deficiency, seemed to tolerate the loss of the major portion of the pancreas better than normal animals would have

done. We had learned also that the manipulation of the hypophysis sometimes caused a transient hyperglycaemia with glycosuria; that, corroborating Borchardt (1908), the injection of pituitrin, particularly in rabbits, had a similar effect; and, of course, we were aware that acromegaly, which we had come to ascribe to a state of glandular over-activity, was sometimes accompanied by symptoms resembling diabetes mellitus.

But when we came to investigate the sugar tolerance of our partially hypophysectomized animals, we were surprised to find that the temporarily lowered assimilation limit for carbohydrates ultimately became raised, and that this increased tolerance for the ingestion of sugar could only be overcome by the coincidental administration of either pituitary or thyroid extract. Since extracts of the anterior lobe had no influence in these reactions, we accordingly were led to explain the symptoms of pituitary deficiency—the adiposity, subnormal body temperature, and so on—to an impaired oxidizing or metabolizing capacity of the body from loss of posterior-lobe extract, with resultant transformation and storage of sugar as fat. A definite parallelism with these experiments was found to exist in clinical cases of hypopituitarism, though under these circumstances the precise extent and nature of the functional damage could only be surmised.

As was stated in our first paper (1911) on the subject:[11] 'If loss or diminution of the internal secretion of the pancreas robs the tissues of their power of metabolizing carbohydrates, certainly loss or diminution of the secretion of the hypophysial posterior lobe greatly enhances their power in this respect.' And this naturally led us to conjecture that an injection of the active principle of the pancreatic islets would lower the amount of sugar in the blood and that the active principle of the posterior lobe would

raise it—in other words, that the two substances counteract one another, which proves to be true.

Our observations in these matters led us to a reconsideration of the so-called encephalic glycosurias to which Claude Bernard first called attention. Though his celebrated sugar piqûre was well established as a physiological experiment, it had come to be appreciated in the clinic that lesions, traumatic or neoplastic, in the neighbourhood of the hypophysis were more likely to provoke glycosuria than similar lesions near the IVth ventricle, and as early as 1898 M. Loeb had postulated the existence of a sugar centre in the tuber cinereum.

We naturally turned to investigate the manner of the discharge and action of the posterior-lobe secretion in producing hyperglycaemia. In a study of the hypophysial nerve supply by Ehrlich's intra-vital methods, W. E. Dandy had shown (1913)[20] that sympathetic fibres radiate along with the numerous branches from the Willisian vessels towards the pituitary stalk, and we assumed, from what was known of the nervous control of the adrenal, that the glycosuric effects of these anterior piqûres might be due to a stimulation of the autonomic fibres to the gland. We accordingly undertook to determine the pathways of these impulses, and in an elaborate study conducted in the Laboratory of Surgical Research at Harvard, with L. H. Weed and Conrad Jacobson,[16] it was found, when what we termed ' available glycogen ' is present in the body, that :

1. A piqûre of the hypophysis in the rabbit is comparable, in its glycosuric response, to a piqûre of Bernard's so-called sugar centre in the IVth ventricle.

2. Stimulation of the superior cervical ganglion, by faradization or even by the manipulations necessary for its exposure, causes glycosuria in the rabbit, cat, and dog.

3. Stimulation of the superior cervical ganglion after exclusion

of all possible downward impulses to the abdominal viscera by way of the vagi, cervical sympathetic trunks, or spinal cord, leads to glycosuria.

4. Stimulation of the superior cervical ganglion after separation of all synapses of the sympathetic system by administration of nicotine, causes glycosuria.

5. Direct faradic stimulation of the hypophysis itself, after exposure by a trans-sphenoidal operation, gives glycosuria even after preliminary trans-section of the spinal cord and cervical sympathetic trunk.

6. If the posterior lobe of the hypophysis has previously been removed by operation the usual stimulation of the superior cervical ganglion fails to give glycosuria.

7. Direct faradic stimulation of the hypophysis provokes glycosuria even after trans-section of the spinal cord above the splanchnics.

8. A classical Bernard piqûre will likewise cause glycosuria even after trans-section of the spinal cord above the splanchnics.

We naturally concluded that the infundibular lobe acts under the influence of impulses which pass from Bernard's centre in the brain-stem and reach the gland by way of the cervical sympathetic, there to liberate a chemical messenger, which causes glycogenolysis, hyperglycaemia, and glycosuria ; and in view of what has gone before we assumed that this hormone was discharged into the cerebrospinal-fluid pathway.*

But with all this, should these findings come to be substantiated (and so far as I know they have never been repeated), they merely throw some further light on the physiology of the posterior lobe and leave us as far as ever from an answer to the pertinent question as to whether the glycosuria of acromegaly is hypophysial or pancreatic in origin.

* Three years later, employing the same methods, Dr. V. N. Shamoff showed that a temporary diuretic effect was also produced by stimulation of the superior cervical ganglion.[28]

In an attempt to answer this question your Mr. Dott applied himself a year ago while attached to the Brigham clinic, without coming to any definite conclusions. We know that acromegalic glycosuria is associated with a hyperglycaemia and that it reacts to insulin as does pancreatic diabetes. We also know that an acromegalic may die from diabetic coma and no histopathological changes be apparent in the islets—though this does not necessarily imply that they may not be seriously deranged from a functional standpoint. On the other hand, as was first pointed out by J. H. Burn,* pituitrin will counteract the effect of insulin, an observation our early studies would fully confirm ; and latterly R. C. Moehlig and H. B. Ainslee† have shown that the hypoglycaemic convulsions in rabbits produced by insulin may be checked by posterior-lobe extract, which causes a rise in the blood sugar. Moreover we know that acromegalic diabetes is capable of spontaneous recovery.

A clinical observation made in 1913 lends possible support to the view that glycosuria in acromegaly is primarily hypophysial rather than secondarily pancreatic :

(P. B. B. H. Surg. No. 61). A fisherman, aged 35, was admitted with ' acromegalism ' of unusual severity, to judge from a basal metabolism of well over +50 % and an associated diabetes of marked degree. After he had been under observation for some time with no change in his condition, both superior cervical sympathetic ganglia were excised. As in our animal experiments, there was an immediate temporary post-operative increase in the output of sugar (from 2·2 % to 4·8 %) followed in time by its ultimate complete disappearance from the urine. On his return to the hospital a year later the urine was found to be sugar free, without dietary precautions. He was too ill to make any dependable metabolism observations, and shortly died from the cardiac complications of

* *Journal of Physiology*, June 1923, vol. 57, p. 318.

† *Journ. Am. Med. Assoc.*, May 1925, vol. 84, p. 1398.

advanced acromegaly. At autopsy, in addition to a large intracranial extension of his hypophysial adenoma, marked hypertrophic and adenomatous alterations such as characterize this polyglandular disease were disclosed throughout the endocrine series; but there were no demonstrable histological alterations in the pancreatic islets.

This experience was very suggestive, but of course one cannot venture to lay undue stress on an isolated observation in a complex malady like acromegaly. Nor does the absence of any demonstrable lesion in the islets mean anything in a disease with such an unsatisfactory pathological basis as has diabetes mellitus. Moreover, since we have seen the diabetes spontaneously disappear from other cases of acromegaly, the effect of the sympathectomy in this man's case may be open to question. Nevertheless, there are enough grounds to justify the statement that 'diabetes mellitus' of definitely pituitary origin may occur.

Before leaving this general discussion of the posterior lobe and its manifold activities, there is still another subject which deserves discussion, for it has led to discordant views. It concerns the much mooted question of the hypophysial polyurias.

Diabetes insipidus. Is this disorder primarily neurogenic or primarily hypophysial in origin? This question has divided students of the subject into two opposing camps. Indeed, as may be recalled, a similar discussion once raged in regard to Graves's disease, which some still attribute to a neurogenic disorder in which the thyroid plays merely a secondary rôle.*

* In this connexion should be recalled Cannon's ingenious experiments on cats, in which the phrenic nerve and the cervical sympathetic were anastomosed low on one side of the neck. By this procedure the rhythmic, efferent impulses associated with respiration passed along the sympathetic, presumably to the thyroid, and provoked a most curious state with excitability, rapid pulse, increased metabolism and so on, which was interpreted as an evidence of

It must have occurred coincidently, to many of those who were interested in the subject of diabetes insipidus, that the supposed renal sources of the disease would have to be abandoned. For our own part, the early experimental hypophysectomies, with their resultant polyuria, had led us definitely to associate this symptom with a functional derangement of the gland, and this view was supported by certain clinical observations, in which patients with bitemporal hemianopsia and primary optic atrophy unmistakably due to tumour in the region of the hypophysis, had at the same time a persistent polyuria of high degree.[18]

We have seen that nerve fibres pass down the infundibular stalk, and it is perhaps natural that the hypothalamus (tuber cinereum) whence they may originate should be a favourite place for the predication of centres such as the sugar centre of Loeb of which mention has already been made. Erdheim, I believe, was among the first to suggest that an injury of these centres was responsible for these polyurias, rather than that they were due to an actual pituitary derangement ; in other words, that they were of nervous rather than glandular origin. He had arrived at this conclusion, I assume, during the course of his well-known studies of the congenital cysts of the infundibular region rather than from the actual identification of any centres by physiological experiments. However this may be, the view doubtless influenced other Viennese investigators, among them Aschner, who explained the polyurias following his experimental hypophysectomies on the same basis, just as did Narbut the diminished oxygen consumption shown by these same animals.

experimental hyperthyroidism. Dr. Gilbert Horrax in 1914 at my suggestion repeated these experiments, and, as a control, removed the thyroid lobe on the side of the anastomosis. His results (unpublished) were the same as those obtained by Cannon. We naturally claimed that our friend the hypophysis was more concerned than Cannon's friend the thyroid. There the matter rests.

A new fillip has been given to this matter by the publications of Camus and Roussy (1913–1922),* whose views have received unqualified support by Drs. Bailey and Bremer.[43] These paired investigators have both shown that an enduring polyuria (experimental diabetes insipidus) might be produced by a minute lesion of the hypothalamus which did not in any way injure the pituitary gland or its immediate stalk. Moreover, they go even farther than this and express the belief that the other symptoms which have been ascribed to hypopituitarism and probably to a posterior-lobe defect, namely the somnolence and the adiposity, are also of the same neurogenic origin.

Personally I find myself in discord with these views both on experimental and clinical grounds; for I cannot understand how a tumour, for example, which so seriously interferes with the function of the gland as to produce all the manifestations of infantile hypopituitarism, yet remains absolutely confined within its dural capsule, can possibly press upon the tuber cinereum. Moreover, on a pure neurogenic basis it is difficult to explain why the supposedly hypothalamic polyuria should be promptly checked by the administration of posterior-lobe extract. After all, it is perhaps an academic question, whether an injury to adjacent nerve centres, whose very proximity is enough to suggest that they preside over the activities of the gland, or whether damage of the gland itself by injury or disease, is the actual cause of a given syndrome.

But the whole subject of the non-diabetic polyurias has from the first been in a tangle of inconsistencies,[18] and indeed it was not until 1912 that studies such as those by E. Frank in Minkowski's laboratory served to point strongly towards their hypophysial rather than renal origin. The

* Cf. Léon Binet's review of these researches in his tribute to the lamented Jean Camus (*La Presse Médicale* for July 1, 1925, pp. 876–8).

chief source of confusion lay in the fact that diuresis provoked by posterior-lobe extracts is but a transient effect, and it was not until the acute physiological experiments on which this opinion was based * were checked by long-enduring observations, that the extract was found to have precisely the reverse effect, namely to provoke an oliguria rather than a polyuria. The experiments of Ketil Motzfeldt carried out in the Harvard Laboratory (1917) [32] were among the first to make clear the existence of these anti-diuretic properties, and thus to explain the apparent disharmony of the physiologists and clinicians; for it had been clinically observed by both Farini and Von den Velden (1913) that the extract given hypodermically, contrary to expectation, would actually inhibit the polyuria of diabetes insipidus.

This was a disclosure which justifies all the time and thought which many have given to the subject of these polyurias, for it has put into our hands what Andrew Cameron was after, namely a practical therapeutic treatment for the amelioration of a most distressing disease. Still, we are no nearer an actual explanation of diabetes insipidus. For if the disorder is due to an injury of some centre in the tuber cinereum, it is remarkable that it is so rarely an accompaniment of the craniopharyngeal-pouch tumours which compress and deform not only the tuber where the centres supposedly lie but the hypophysis itself.

It was for the purpose of reconsidering the interpretations which Bailey and Bremer had put upon their experiments,

* The results are now partly explainable by the action of posterior-lobe extracts in contracting smooth muscle other than of the blood vessels [Dale for the uterus (1906), Cramer for the eye (1908), Blair Bell and Hick for the bladder (1909), Houssay for stomach and intestine (1911)]: and with this interpretation many of the studies of experimental hypophysial diuresis like those of Shamoff [28] may still be regarded as positive in so far as they suggest the liberation of posterior-lobe extract and its action on the bladder musculature, even though there may not have been an actual diuresis.

and in the hope of reconciling our conflicting views on the subject, that Dr. Maddock and I this winter have made a control series of experiments in which, as stated, we have reverted to the method employed in our earlier studies of placing a silver ' clip ' on the hypophysial stalk. By the aid of Weed's brain-shrinking method these operations are conducted more easily to-day than they formerly were, and the ' clip ' can be closed on the stalk of the dangling canine gland quite bloodlessly and without any appreciable or histologically demonstrable injury of any adjacent structures. When this procedure is carried out, precisely the same train of symptoms is evoked that Bailey and Bremer describe, viz., a prolonged polyuria with subsequent tendency to adiposity.*

Probably, therefore, the effects are the same whether produced by: (1) an injury to the hypothalamic centres, (2) a ' block ' of the nervous impulses with obstruction of the secretory products in the posterior lobe, or (3) a partial hypophysectomy with actual removal of the lobe. In other words, a break in the mechanism of posterior-lobe secretion from nerve centre to gland, produced by any agency, tends to upset the normal water balance and to cause an hypophysial polyuria; and conversely, the administration of posterior-lobe extract serves to check the experimental polyuria thus produced wherever the break in the mechanism may have occurred.

This explanation at least harmonizes the differences which lay between my own preconception in this matter and the views of my pupils. But it will not, I fear, quite satisfy those who, like J. J. Abel, if I understand him correctly, believe

* We are of course aware that in these experiments not all of the pars intermedia, and of that portion of the infundibular tube containing active posterior-lobe substance, lies distal to the obstructing ' clip '. But the major portion of the gland is ' blocked ', and this suffices to produce the symptoms in question.

that the responses are entirely by chemical messengers and that the direct nervous influences may be wholly disregarded.

The anti-diuretic property we have been discussing is but one of many which extracts of the posterior lobe possess, and some of which are already utilized for practical therapeutic purposes. The attention of the pharmacologist has tardily become focussed on a study of the bio-chemical nature of the substance or substances responsible for these various reactions. Some have postulated the existence of three or four separate hormones. Others, like Professor Abel,* believe that there is only one specific hormone which, alone, as appears to be the case with his tartrate, is capable of evoking all the known responses, cardiovascular, anti-diuretic, oxytocic, respiratory and melanophore-expanding.

The Pars Anterior

In what has gone before, over-much has perhaps been said in regard to the physiology of the pars nervosa, and we may now turn to the epithelial lobe, where there are fewer functional straws at which to grasp, though there are many reasons for ascribing to this portion of the gland the premier rôle among the endocrines—if, with all said and done, we are entitled to consider separately the function of the two or three anatomical subdivisions of the gland. However this may be, the customary physiological weapons of attack are unavailing in the case of the pars anterior, and we must have recourse to roundabout ways if we would spy into its secrets. The fact that we are not all in agreement as to whether the various cellular elements, chromophile and chromophobe, comprising this highly vascularized lobe represent different stages of activity of a single cell type or

* Cf. Abel's Harvey Lecture on 'The Pituitary Principles'. *Johns Hopkins Hospital Bulletin*, October 1914, vol. 35, p. 305.

are cells of quite different function, shows the present great limitations of our knowledge. As J. J. Abel has said in regard to the posterior lobe hormone, there are Unitarians and Trinitarians among us.

Metabolism observations. In considering the relation of the posterior lobe to the utilization of sugars, the question was discussed whether the glycosuria of pituitary disease should properly be regarded as an hypophysial or a pancreatic effect. A similar question is naturally raised in regard to the alterations which the clinical cases show in their metabolic rate. Are they primarily hypophysial or secondarily thyroid in origin? To this subject we may now turn for a moment.

While we were engaged in our studies of carbohydrate tolerance in 1908–10, I knew nothing about metabolism estimations, hardly knew, indeed, what the term with its modern implications signified. We had observed in the clinic that outspoken states of hypopituitarism, in addition to the adiposity and sexual dystrophy which they showed, were accompanied by periods of profound and long-enduring somnolence, by a slowed pulse and respiration, by a subnormal body temperature and by an apparent insensitivity to external stimuli—states comparable to those of our experimentally hypophysectomized animals. Certainly these individuals were burning their tissues at a low fire, and it was perhaps not unnatural that the clinical syndrome should have suggested resemblances to the state of hibernation. Since the experimental extirpation of no other ductless gland except the hypophysis, so far as we knew, caused this particular train of symptoms, Dr. Goetsch and I were led to make some studies in this direction,[25] and we found, as others had found before us, that in the hibernating state the ductless glands, notably the hypophysis and gonads, appear to be in a resting stage, whereas at the period of

awakening they become markedly hypertrophied; but aside from the simple histological studies which served to disclose these facts, we found ourselves dealing with a subject of unanticipated difficulties, intertwined with chemico-metabolic problems beyond our reach.

A more important lead came from another direction, for Dr. John Homans after his year in the Hunterian Laboratory enlisted the interest of Francis Benedict in the subject of our dyspituitary dogs; whereupon Dr. Benedict devised a respiration calorimeter for determining the carbon dioxide production of small animals. With the aid of this apparatus, as described in their detailed report (1912) from the Carnegie Nutrition Laboratory,[12] they observed, among the other general effects of a partial hypophysectomy in puppies heretofore discussed, that in the course of time there was a marked post-operative fall of the total metabolism as measured by the carbon dioxide production per kg. of body weight per hour, a fall which was the more striking owing to the amount of inert body fat the animals gradually acquired.

All of this has led to the supersession of our crude carbohydrate estimations as a measure of the degree of hyper- and hypopituitarism by the numerically more accurate studies of basal metabolism. And I feel that the present widespread clinical employment of these estimations on patients with endocrine disorders of all kinds is largely an outgrowth of the pioneer work conducted in the Brigham Hospital during the next few years by Dr. Walter M. Boothby and his co-worker Miss Irene Sandiford. For it was in the course of their routine studies of these cases that the surprising excursions of metabolic rate in hyperthyroidism were I believe first disclosed.[31] Overshadowed by the importance of this finding, an analysis of the estimations made on the hypophysial cases became side-tracked, and

has never been published in detail although this was the primary object of our researches.

It may suffice to say after this lapse of a dozen years that the hypopituitary cases show, as did Homans' animals, a lowered rate, whereas the metabolism in the active stages of acromegaly is raised, though never to so high a percentage as may be seen in hyperthyroidism. The extremes which have been observed are −39 for the former and +65 for the latter.

But this does not answer the question at hand—is the increased rate in acromegaly due to a secondary thyroid hyperplasia rather than to some influence on metabolism possessed by the hypophysis itself? We, of course, are all aware that acromegaly has notable polyglandular manifestations, and I believe the view is held in the Mayo Clinic, where Dr. Boothby and Miss Sandiford have gone, that the increased metabolic rate shown by these cases is a secondary phenomenon; for it has been observed that removal of the enlarged thyroid of an acromegalic lowers the rate. But even this does not settle the point. The only proof could come from a lowering of metabolism by the partial removal of a hypophysial adenoma leaving the enlarged thyroid untouched; and an example of such an effect has been cited in a recent study of the pituitary adenomas by Dr. Bailey and Mr. Dott.[49]

I fully realize that there are inconsistencies in discussing metabolism as essentially an anterior-lobe effect, for not only is the basal metabolism commonly raised in acromegaly but glycosuria occurs as well, and this we have laboured to ascribe to the pars nervosa. And herein lies another inconsistency, for glycosuria (being a process supposedly evoked by stimulation of the autonomic nervous system whose fibres so far as is known are distributed to the pars anterior alone) we have discussed as a pars nervosa problem,

mentioning at the same time that the only demonstrable nerve fibres which pass to, and become lost in, this infundibular lobe are non-myelinated fibres which appear to arise in the tuber. Doubtless some explanation of these inconsistencies will be forthcoming; and we may well enough leave the subject, after this admission, for an anterior-lobe foothold on less uncertain ground.

The hypophysial relation to the glands of sex. Among the most definite consequences of hypopituitarism, whether produced by experimental procedures, by glandular tumours, even by hydrocephalus, so frequent a source of interference with the gland's activity, are the secondary effects on the gonads to which attention has often been called.[13] Infants fail to acquire normal sexual adolescence; adults lose their sexual desires and potency; amenorrhoea in women is one of the first tell-tales of disturbed function.

It is difficult to tell whether these symptoms and the histological changes which accompany them are ascribable to the anterior or posterior lobe, or to the combined action of both, but reversible effects show at least that the anterior lobe is an important element. Erdheim and Stumme, for example, first fully described (1909) the remarkable alteration in the cells of the anterior lobe associated with the amenorrhoea of pregnancy. The secondary enlargement of the hypophysis in eunuchs had been noted before this by Fischera (1905) and by Tandler and Gross (1905); and it is stated that in castrated hens the gland almost doubles in size. Indeed, the hen's plumage acquires male characteristics just as in certain clinical endocrine disorders we may see a suggestive reversion of the female to the male type and vice versa. The accounts of experimental masculinization and feminization produced by crossed transplantation of the gonads both in mammals and birds read like a story from the Arabian Nights.

Naturally while we have been waiting for the biochemist to isolate the active principle or principles of the gland, efforts have been made both in man and animals to see what would be the effect of prolonged feeding of pituitary substance and of glandular transplantations. The attempts have been innumerable and the results, so far as growth is concerned, quite negative, though Professor Schafer was led to believe that 'the addition of a small amount of pituitary substance to the food appears to favour the growth of young animals'.

But it was not until some studies were undertaken by Emil Goetsch that attention was given to the effect of prolonged feeding on the development of the sex glands as something apart from growth.[14] We had been encouraged to pursue this subject by an experience in 1909–10 when prolonged anterior-lobe feeding had been given to one of two female puppies of the same litter. At the expiration of seven months the animals were sacrificed, and the only notable difference in the two was that the ovaries of the control contained unripe Graafian follicles whereas numerous fully developed corpora lutea were present in the subject of the experiment.

A remarkable clinical experience was had shortly after this in the case of a boy nine years of age with adiposogenital dystrophy and overgrowth in the absence of tumour * who had come under observation in 1911. During the next three years, without interruption, he was given orally 18 grains of Armour's 'whole gland' preparation. When brought back for observation at the expiration of this period, it was found that a most unexpected *Frühreife* (for he was then just twelve) had taken place in the interval (Figs. 15 and 16).

In 1913–14, Dr. Goetsch took this matter up anew. In

* Case XXXIV, 'The Pituitary Body and Its Disorders.'

a time-consuming and most carefully controlled study on a series of young rats of known pedigree and growth curve, he found that the daily oral administration of bovine anterior-lobe extract during the preadolescent period had a remarkably stimulating effect upon the development of the reproductive glands of both sexes, shown not only by their early maturity and their precocity in raising families but by demonstrable histological evidences of precocious ovulation and spermatogenesis. Other glandular extracts, similarly fed to control animals, had no such effect, as may be learned from Dr. Goetsch's report,[14] in which scant emphasis is laid on the fact that all handling, feeding, and care of the animals had been personally attended to by the experimenter. In this detailed and altogether admirable paper, only brief mention is made of the fact, in corroboration of Professor Schafer's earlier studies, that the animals subjected to anterior-lobe feeding attained a more vigorous body growth than the controls.

The hypophysis and growth. The experimental zoologists have turned their attention to the relation of the pars anterior to growth, and P. E. Smith (1917) showed that the retarded development of hypophysectomized tadpoles could be accelerated if they were fed upon certain residues of the anterior lobe. But the most convincing experiments yet conducted have been those of Herbert M. Evans (1922–5). Dubious of the effects to be expected from the oral administration of pituitary extracts in the higher animals, Evans gave to a series of rats daily intraperitoneal injections of the emulsion of fresh bovine glands and succeeded in producing such marked overgrowth as to justify him in designating the condition as one of actual gigantism. Thus the assumption that the overgrowth of clinical acromegaly and gigantism is an expression of hyperpituitarism receives its first really striking experimental proof.

Though, as told above, generous anterior-lobe feeding over long intervals may have some influence in hastening sexual ripening, certainly no one has reported any definite clinical effects on growth from the oral administration of any glandular preparations. It is a very astonishing thing, that

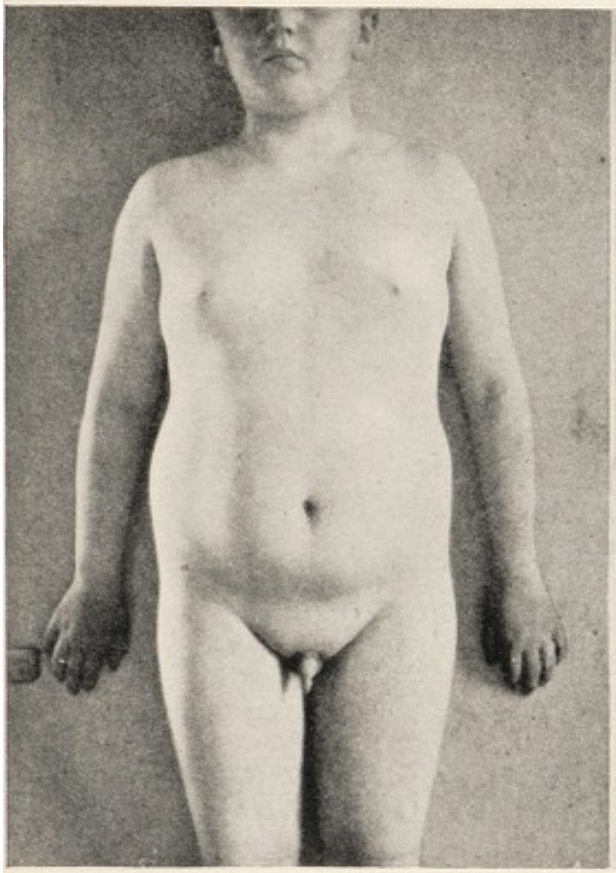

FIG. 15. Patient, age 9 yrs. 2 mo., with the combined symptoms of adiposogenital dystrophy and overgrowth. Height 4′ 10″ (av. normal for age 4′ 2″). Weight 118 lb. (av. normal for age 60 lb.).

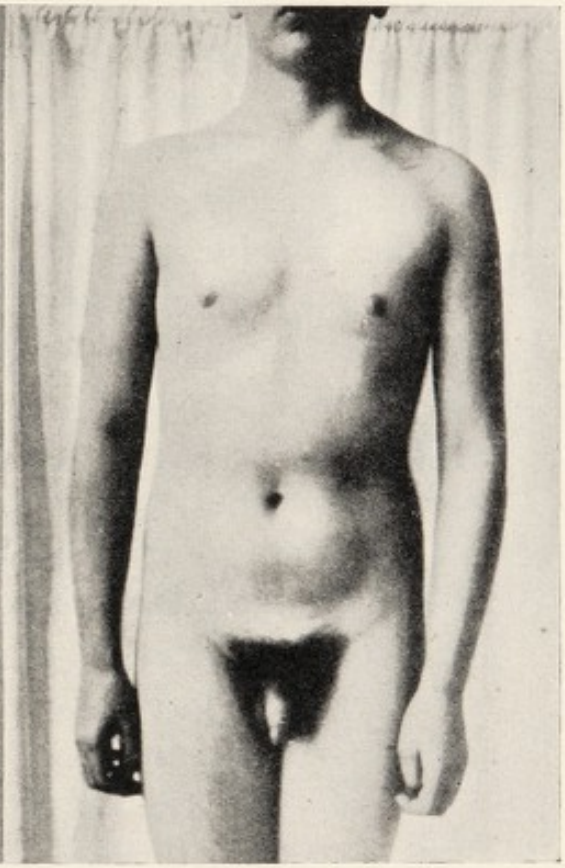

FIG. 16. Same patient, age 12 yrs. 2 mo., after three years' uninterrupted pituitary feeding. Height 5′ 2·5″ (av. normal for age 4′ 8″). Weight 133 lb. (av. normal for age 80 lb.).

this growth principle, which we may now safely ascribe to a hormone, should reside in this tiny epithelial lobe of an obscure gland. It is a matter which was bound to intrigue the interest of the clinician, to the extent at times, be it said, of overcoming his critical judgement; and, for the

nonce, endocrine therapeutics has striven to jump over the moon. Still one may condone this tendency; for it must be particularly wearisome for those who have had no personal experience with the difficulties which beset the laboratory worker, patiently to await his reports while the therapeutic possibilities of the glandular extracts float like iridescent bubbles before their eyes.

Encouraged, as others doubtless have been, by Dr. Evans's remarkable results, we have undertaken on our own account some further studies in regard to growth. Dr. Leo Davidoff, who has for the past two years been concentrating his attention on our series of acromegalics, undertook to see, by using Evans's methods, whether in animals, which had presumably attained their full stature, acromegalic characteristics might not be observed. But this proves to be a most difficult quest; and since preparations such as Evans employed are not tolerated by larger animals such as rabbits, cats, and dogs, when given intraperitoneally, we cast about to find some standard pharmaceutical preparation which at least might appear to possess traces of an active anterior-lobe principle.

One of these preparations we found to have a prompt effect in checking the oestral cycle in female rats, and though this in the light of Goetsch's experiments would seem contradictory, it at least showed the presence of an active substance of some sort.* Accordingly, a series of rats was subjected to prolonged intraperitoneal injections with results which suggested, at least, that the preparation

* The fact that posterior-lobe extracts have been shown to possess both diuretic and antidiuretic properties, may encourage us to expect that other seemingly contradictory responses to hypophysial extracts will come to be explained. The effect on the menstrual cycle is one of them. Amenorrhoea, as would be expected, is one of the early signs of hypopituitarism in women; but so is it an early symptom of acromegaly, the reverse state, accredited to hyperpituitarism.

contains the growth principle as well. The experiments, indeed, taken in conjunction with P. E. Smith's experiences with hypophysectomized tadpoles, were regarded as sufficiently encouraging to justify an attempt in the clinic to stimulate growth in one of our little patients whose stature for the two years following a successful removal of a Rathke's pouch-cyst had remained unchanged.

These children are peculiarly co-operative and intelligent patients,* and this particular child submitted, with his parents' consent, to receiving an intraperitoneal injection of 5 c.cm. of this substance every second day for a period of over two months. We had hoped that the effect of the substance, were it actually present, would be more marked in a case of pituitary infantilism than in a normally developing individual; but no effect whatsoever was observed. We evidently have much more to learn about these extracts before we can adopt them to clinical use, and the many apparent contradictions had far better first be untangled, so far as possible, in the laboratory, where observations can be controlled.

I may give an example from the clinic of how one might be misled into believing that he had influenced growth if the patients had coincidentally happened to be under anterior-lobe substitution therapy. On two or three occasions we have observed a most surprising accession of growth after successful operations for cerebellar tumours in children in whom the secondary hydrocephalus had provoked the usual hypopituitary manifestations. But still more remarkable are the occasional examples of unexpected growth observed in older persons after the successful

* Perhaps no one of the glands has a greater influence, direct and indirect, upon the psychic and physical responses of the individual to the environment. Cf. C. Macfie Campbell: 'Psychical Disturbances in the Diseases of the Glands of Internal Secretion', *Endocrinology*, May–June 1925, vol. 9, p. 201.

removal of parahypophysial tumours which more obviously have interfered with the normal function of the gland. The clinical story of one of these cases may deserve brief recital.

A young man, 23 years of age but of childish appearance, was brought to the hospital (Surg. No. 17148) in August 1922. He had grown up as any other normal child until his twelfth year when, for a period of six months, he suffered from severe headaches accompanied by bouts of projectile vomiting. A marked polydipsia with polyuria was observed during this period and it was found also that he had a temporary bitemporal loss of vision.

He slowly recovered from this illness, but during the 11 years which had intervened 8 to 10 similar attacks periodically occurred, the last, which led to his admission, having been the most prolonged and severe of the series.

To outward appearances, this young man looked like a preadolescent boy 12 or 13 years of age. His genitalia were infantile and the secondary characters of sex wanting. According to his parents, if there has been any increase in his stature since he was 12, it has been imperceptible ; no careful measurements had been taken. His height on admission was 4 ft. $11\frac{1}{2}$ inches.

Examination showed a primary optic atrophy with bitemporal hemianopsia ; an enlarged sella with suprasellar calcifications was disclosed by stereoscopic radiograms ; the temperature tended to be subnormal with registrations of 97°, and there was an occasional slowing of the pulse to 60. He was somnolent ; his metabolism was -23 % and it was difficult to keep him subjectively warm. Though not excessively adipose he was plump and weighed 47·2 kg., considerably overweight for his stature. He had a marked polydipsia and polyuria which, though variable, amounted at its height to nearly 5 litres.

At operation a typical craniopharyngeal pouch-cyst was exposed and a large part of the wall successfully withdrawn. He made an excellent recovery with relief of headaches, with restoration of normal fields of vision, and, in the course of a few weeks, with disappearance of his polydipsia and polyuria.

But what was more out of the ordinary were the subsequent reports from his parents of a surprising and unexpected accession

of growth. By August of 1924 he had passed 5 ft. and at the present writing, August 1925, his height is 5 ft. 2½ inches. In other words at the time of his hospital admission when 23 years of age he measured 151·5 cm. and now measures 159 cm. During the three years since his operation, therefore, this young adult has grown just three inches.

The time when we can accomplish like results at will by substitution therapy is not yet; meanwhile, theorists among us yield readily to the temptation to construct new clinical syndromes and to prescribe various extracts accordingly.[40] I once was led myself into this speculative trap by a tempting bait, and described a composite state * accredited to a combination of hyperplasia of the anterior lobe, owing to the existent overgrowth, with insufficiency of the posterior lobe, because of the associated adiposity and high sugar tolerance.[17] True, most of our primary hints in regard to the ductless glands have come originally from clinical observations, as the names of such as Addison, Gull, Graves, and Marie serve to recall; but even the comparatively simple disorders associated with these names have put laboratory workers to a vast deal of trouble, and lesser people can overdo this matter of describing clinical syndromes as entities.

Looking upon the ductless gland diseases as in a sense all polyglandular, though chiefly affecting and probably originating in one organ, the possible combinations for the eight or more glands of the series, both for men and for women, for children and for grown-ups, would run into hundreds of thousands did we attempt with too much refinement to describe them all. There are as yet only two dependable signposts that point the way: one, an evident destruction of the gland by injury or disease; the other, a tumefaction of one sort or another. Without the tumour,

* Such as is shown in Fig. 15.

as I have frequently stated, we would have been nowhere, so far at least as our knowledge of the hypophysis goes. And this naturally suggests the surgical aspects of pituitary disorders, with which I shall briefly deal in concluding this lecture.

Surgical Considerations

The tumours. As emphasized in many places[13, 23, 40, 45] had it not been for the tumour and its local pressure effects, the surgeon would hardly have come to meddle with the questions which up to this point have been under consideration. Having been drawn in, because there were mechanical difficulties to overcome, it was inevitable that he should take something more than a mechanical interest in the subject. So it was with the thyroid. Certain goitres, by displacing and flattening the trachea, caused a mechanical dyspnoea which could only be relieved by some surgical procedure. Kocher and the Reverdins first had the temerity to undertake operations under these desperate circumstances, and it is common knowledge that clues for solving some of the thyroid and parathyroid puzzles were thereby supplied.

But the thyroid goitre offered a simple problem compared to that of the hypophysial goitre. One was exposed to view for the layman to diagnose; the other was concealed, and affected not only the eyes of its victim, but obscured the vision of the professional observer as well. Consequently those who now have on their hands the responsibility of tardily developing the operative treatment of hypophysial disorders may comfort themselves by the recollection that those who have relayed to their successors the surgery of the thyroid adenomas had a twenty-year head-start, and our problem is a far more complicated and difficult one. We meanwhile have profited greatly by their experiences, have

more or less followed in their footsteps and avoided some of the pitfalls they had pointed out.

I have already touched on the fact that one or two of the earliest operations on the hypophysis were in cases of acromegaly, and that those who had undertaken them were led to believe that there had been a definite amelioration of the constitutional as well as the local symptoms. But these were precocious steps taken in imitation of partial thyroidectomy for Graves's Disease, and as we now understand the matter they were steps taken out of turn. For even to-day one may as well admit that the treatment of pituitary disease consists of little more than the prevention or relief of the local pressure-effects of pituitary or parapituitary tumours. True, this is a great boon, and the neurosurgeon now shares with ophthalmic surgeons the thrills and satisfactions of restoring vision to persons on the verge of blindness.

But in his desire to share in this satisfaction, the surgeon may get into infinite trouble unless he has some knowledge of just what he is after. I recall the remark made by a companion while watching a small dog bounding across the fields in pursuit of a railroad train: 'I wonder what he'll do with it when he catches it.' So it behoves us to be thoroughly aware of the nature of the various tumours of the hypophysial neighbourhood, and there are perhaps three main groups: the suprasellar meningiomas, and craniopharyngeal pouch tumours which, in addition to their local pressure effects, may evoke typical hypopituitary syndromes; and thirdly the hypophysial adenomas proper, some of which give the reverse clinical picture. Without a definite understanding of the precise situation, behaviour and manner of growth of these several lesions, it would be foolhardy to attack them; and the surgeon consequently must know his morbid anatomy no less well than his physiology of the gland.

We of course are indebted to the pathologist for our primary conception of these several lesions, but by the time they have come under his observation it is inconceivable that they could ever have had any surgical bearings. The fairly common suprasellar meningioma, which takes its origin from the arachnoidal cell-nests as described in the preceding lecture, may slowly in the course of years attain the size of a fist before it causes death ; and yet these lesions when small are not only capable of being diagnosed but can be exposed and totally removed with preservation of vision, in spite of their awkward position between hypophysis and chiasm.

The congenital cysts. And the same is true of the more common craniopharyngeal pouch cysts first clearly described by Erdheim in 1904, though there is very little in the literature concerning the surgical treatment for these remarkable congenital lesions.[45] They usually, though not invariably,* begin to manifest their presence in preadolescent life both by local signs of tumour as well as by their pressure effects on the hypophysis as a whole. Hence in these little patients one may see in most outspoken form the combined syndrome of anterior lobe disturbance (sexual and skeletal infantilism) and of posterior lobe disturbance (adiposity, a high sugar tolerance, a low metabolism and sometimes diabetes insipidus).

These lesions, moreover, are usually suprasellar and need not in any way deform the sellar outlines as shown by the X-ray. But there is a tell-tale of their presence[22] which to-day is demonstrable in fully 80 per cent. of the cases

* I have just (Sept. 29th) operated upon a woman 60 years of age who was becoming blind from the pressure of one of these congenital tumours. It had given no symptoms whatsoever till seven months ago. A seamstress, she had earned her living by fine needlework and enjoyed unusually good vision till that time.

owing to the refinements of roentgenological technique which the invention of the Potter-Bucky diaphragm has made possible.[46] This concerns the deposits of lime salts which occur in connexion with the keratinized epithelial lining of the cysts.[42] The diagnosis, however, is not quite so easy as all this, for sometimes the congenital tumour does not ride so high, but may actually develop within the capsule and distend the sella precisely as does the more common adenoma.

Though hypopituitarism in adults is usually caused by adenomas and in children by these craniopharyngeal pouch cysts, it is not always so. In a recent paper [40] reference has been made to two cases which entered the clinic together—one a child having adiposogenital dystrophy with a large ballooned sella, and the other an adult with a small sella, both cases showing primary optic atrophy, bitemporal hemianopic field defects, and evident hypopituitarism. The child proved to have an adenoma : the adult a pharyngeal pouch cyst ; quite the reverse of the preoperative diagnoses, so there are exceptions to the rule—as to most rules—and one must be on his guard.

With the congenital cysts, however, the difficulty is not so much in the diagnosis, as in knowing how to deal with the lesion when it is exposed. The mere evacuation of its contents gives only temporary relief, since there is an early refilling. Extirpation is necessary, and this is difficult because of the relation of the tumour to the optic nerves. These cases, of course, are operated upon from above by an osteoplastic approach ; different surgeons advocate different procedures, but personally I prefer to come down upon the lesion from in front rather than from the side.

The chiasm, in justification of its name, represents the crux of the matter, and though some of the cysts have sufficiently thin and tough walls so that after evacuation

they may be drawn out from between the distorted optic nerves practically intact, more often the calcareous and keratinized part of the wall is so adherent and extensive as to make this impossible. I have never quite had the courage to take what may be the proper step under these circumstances: namely, to split the chiasm fore and aft, thereby committing the patient to a permanent bitemporal hemianopsia, but at the same time giving free access to the mesially placed tumour, which at times may assume astonishing proportions. We have seen such a cyst as large as a tennis ball, its walls a solid mass of calcification.

After all, a permanent bitemporal hemianopsia is preferable to the recurrence of symptoms so apt to take place. Only one anatomical structure stands in the way of such an operation—the anterior communicating artery which lies stretched out across the elevated surface of the chiasm, but this vessel, as I have found, can be easily 'clipped' and divided. Thomas Willis would be interested to know that a portion of his circle, from which the spokes of the *rete mirabile* of his predecessors pass to the hypophysis, has actually come, after all these years, to be an important factor in a surgical operation.

The adenomas. These present quite a different surgical problem from the congenital cysts and strictly speaking should be the main object of our discourse, for they are by far the more common lesion and primarily rather than secondarily affect pituitary function. They have so recently been made the subject of a detailed report by Mr. Dott and Dr. Bailey [49] that it is hardly necessary to say more. Dr. Bailey has come to believe from a histopathological review of the adenomatous tissues in our collection that he can identify a 'mixed type' of adenoma. This differs from the chromophile adenoma of acromegaly [47] and the chromophobe adenoma characterizing hypopituitarism, in that

a peripheral rim of eosinophilic granules still persists about the cell; and he and Mr. Dott feel confident that this particular type of adenoma serves to explain those mixed clinical syndromes in which traces of acromegaly are seen commingled with the clinical evidences of hypopituitarism.*

It is our custom and preference to approach these glandular tumours by a method called trans-sphenoidal.[23] A small incision is made under the lip; the mucous membrane is separated on each side so that the operative approach is by way of the nose, but does not actually enter the nasal cavities. A speculum is inserted, the anterior wall of the sphenoidal cells removed, the thin bulging floor of the sella chipped away, the dural encasement incised, and such an amount of the gland as is thought sufficient to relieve pressure is then spooned or sucked away.† It sounds simple and in a favourable case may be so. What is more, the

* Personally I am not very clear in mind as to whether the pituitary adenomas arise from a definite focus within the gland, as do the so-called 'foetal' adenomas of the thyroid, or whether the entire epithelial lobe becomes involved in the process at the outset. Embryologists have shown [e. g. Baumgarten (1916)] that the pars intermedia and the pars distalis (anterior lobe) are ontogenetically and phylogenetically distinct, and that generally speaking the former may be considered to be the chief chromophobic and the latter the chief chromophilic portion of the gland. But we have no reason to assume that the typical chromophobe adenomas arise from the pars intermedia, indeed a very definite reason to believe that they do not, for otherwise we would frequently run across evidences of a compressed pars distalis in the ordinary trans-sphenoidal operation for adenoma. As a matter of fact, the histological examination in all of our cases shows the same kind of tissue throughout, with never any areas of normal-appearing glandular tissue.

† There is nothing wholly original in using a 'sucker', which is the most satisfactory agent for this purpose. If I am correctly informed, the ancient Egyptian embalmers used the trans-sphenoidal and sellar route to suck out the entire brain. Children, moreover, use the same principle in preserving birds' eggs.

convalescence is usually rapid and uneventful with rapidly widening fields of vision.

One would suppose that these operations, which necessarily open the enveloping arachnoidea of the gland, would be attended by great risk of meningitis. As a matter of fact, they are not, and the mortality of the series taken as a whole, including the early operations, which were foolishly done on patients often in extremis due to a then poorly-understood intracranial extension of the growth, is now approximately seven per cent.* However, in the last fifty successive trans-sphenoidal operations there has been only one fatality, which brings the operative mortality of the more recent years well within bounds, namely at two per cent. But what is of more importance is the fact that in about seventy per cent. of all these cases there has been a vast improvement of vision. This of course is the proof of the pudding.

In the days when we first began to study these cases on the surgical wards at the Johns Hopkins, the perimeter was a dusty instrument on a shelf, rarely used except for demonstration either in the neurological or ophthalmological clinics. To-day we could not get on without it, and the perfected technique of taking the field peripheries which was elaborated by Clifford Walker [26, 30, 33, 34, 36] during the years he was a member of my staff continues to be employed, so far as they are capable of it, by my successive neuro-surgical residents.

And a neuro-surgical group has scarcely less need of the ophthalmoscope and the calorimeter and other instruments of precision. Nor should the microscope be forgotten, for

* Out of 219 cases of pituitary adenoma, 214 have been operated upon. The trans-sphenoidal route has been used in 203 cases with 15 fatalities, giving a mortality of 7·38 per cent. The transfrontal route has been used in 35 cases with 2 fatalities, giving a mortality of 5·7 per cent. The total operative mortality for the entire series is therefore 7·1 per cent.

the histopathology of these lesions is no less important to the operating surgeon for diagnosis and prognosis. Subdivisions of responsibility in the routine handling of large groups of patients is probably necessary—diagnostic tests by a series of special people, an operation by another set, the pathological report by still another. But any such system, when progress is to be made in a new field, is unworkable.

I was once told by Professor Kocher, who I suppose had his experiences with the thyroid in mind, that no satisfactions in medicine were so great as those which came from concentration upon and the mastery of a small subject, and that this necessitated an approach from all aspects, diagnostic, experimental, pathological, and therapeutic, not the least important part of which at one time or another in the history of the subject was likely to be surgical.

It will be given to few to play such an important part in the history of any subject as that which he played in the case of the thyroid disorders. The best that people of lesser intellects and industry than he possessed can do is to come as near to this goal as their abilities permit. But the surgery of the hypophysis at the present time, as I am sure he felt about the surgery of the thyroid in his early days, is practically in the 'stone age' of its development. The time will come ere long, perhaps, when the biochemist will have shown us how to cure most of the common functional adenomas of both of these glands without surgery. Prevention will then come in its turn to supplant even these eagerly sought medicinal cures, and this will represent the 'golden age' of the subject which not even the youngest of us here are likely to see.

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LECTURE III

INTRACRANIAL TUMOURS AND THE SURGEON

In einem gewissen Gegensatze steht die Operation der Hirnabscesse zu der der Hirngeschwülste. Für die erstere leistet die Diagnose noch zu wenig, die chirurgische Technik aber genug, für die letztere hat umgekehrt die Diagnose schon so viel gegeben, dass Nothnagel z. B. sie für eine verhältnissmässig leichte erklärt, unsere Technik aber, soweit sie sich auf eine ausreichende Umschneidung, Blutstillung und Vermeidung des gefährlichen Hirnödems bezieht, ist durchaus noch im Rückstande. Vielleicht gelingt es, sie zu bessern und zu vervollkommnen.

ERNST VON BERGMANN, 1889.

NEURO-SURGERY: OLD AND NEW

IT has been said that three stages—optimism, pessimism, and adaptation—must invariably be passed before any revolutionizing principles of surgery can become firmly established. After the introduction of surgical anaesthesia, in which Edinburgh had a hand in the person of James Young Simpson, under whose spell Andrew Cameron must have sat; and after the still more important discovery of surgical cleanliness, the outgrowth of Lister's work which Cameron did not live to see; there was a widespread feeling that the chief obstacles to operations on any part of the body had been overcome. This in a measure was true; but when the surgeon came to attack such non-traumatic lesions within the body cavities as the physician was encouraged to surrender to him, difficulties unthought of were encountered. It was necessary by slow and devious steps to devise a special technique to overcome these difficulties before the stage of pessimism on the part of the profession as a whole could be overcome.

The first successes were in the pelvis, and operative gynaecology, in which another Scotsman, Lawson Tait, had no small part, came into being. Since then, the surgeon has been slowly working his way from the lower to the upper abdomen, where the liver and gall-bladder, the stomach and pylorus, the kidney and spleen, have in turn delayed him. Perfected methods and a novel technique had to be devised before he ventured above the diaphragm into the chest for purposes other than to drain suppurating cavities ; and he is now, last of all, coming to feel very much at home in the cranial chamber. But this is so recent a happening that many of us have vivid recollections of the wave of discouragement and pessimism which came on the heels of the generally unsuccessful operations for brain tumours undertaken during the last two decades of the century just gone.

There were some neurologists, among them that Nestor of your local profession, Byrom Bramwell, who, insisting even at that time (1888) that intracranial tumours were common, remarked that the soft brain tissue would seem to be ' as fine a forcing and feeding ground for new growths as Koch's nutrient jelly is for micrococci and allied organisms ' ; and it was stated by Bruns, I believe, not long after, that for a physician to assert he had never encountered a brain tumour in his wards or practice was equivalent to an admission that it had passed under his eyes undiagnosed.

But these were voices in the wilderness, unheeded ; and in the days before the Wassermann reaction every obscure intracranial lesion was regarded as a potential case of cerebral syphilis. This at least was the more probable diagnosis, and at any rate something might be done for it therapeutically. Better so than to run the risks of a surgical exploration with its almost inevitable sequence of a broken-down scalp wound, a fungus cerebri, a cerebrospinal fluid leak and ultimate fatality, should the condition actually have been

due to tumour. Such was the lamentable outcome of that first operation for a clinically localizable tumour, which Hughes Bennett had the courage to advocate, and which, on November 25, 1884, Rickman J. Godlee performed.

The young neuro-surgeon of the present day who only gathers from hearsay or from pictures in his text-books what the horrors of a fungus cerebri used to be, can have no conception of the calamities which commonly followed the intracranial operations for tumour as they were done thirty years ago—unless he looks about him in clinics where old-time methods are still practised by general surgeons blind to what has been going on about them in the development of a specialized technique for these complicated procedures.

Among many others in Great Britain who were pioneers in this work we may salute two outstanding figures: Sir William Macewen, whose major contribution was on the subject of the intracranial infections, now the smallest part of our work; and Sir Victor Horsley, whose troubles are for all to read in the contemporary pages of the British medical weeklies. He was outspoken in ascribing them, right or wrong, to the reluctance of his medical colleagues in surrendering their tumour cases except as a last resort when it was too late for surgery to accomplish much of anything. But even the echoes of a dispute as to how long a patient suspected of tumour should undergo a course of mercurial treatment before the surgeon was called in, have long since died away; * and looking back on all this from our present standpoint, one hardly knows which of the two parties

* Horsley in 1890 pleaded with the clinicians to agree on a definite probation period of drug treatment and suggested six to eight weeks, instead of as many months, as the time limit. Three years later, Allen Starr proposed, as a compromise, a preliminary three months' trial with drugs, after which, if cure had not resulted, surgical measures should be resorted to.

needed the more sympathy—doubtless a third party, the patient, most of all. In any event, at the National Hospital the physicians gained their point, with the result that in that deservedly famous institution, which has been a veritable incubator for neurologists, the neuro-surgeon, if I am correctly informed, continues to be looked upon merely as a therapeutic agent, rather than as a co-equal with the privilege of arriving at an independent opinion as to what may be wrong with the patients admitted to his own hospital beds and what should be done for them.

In illustration of the sort of thing Horsley was so outspoken against, I may tell the lamentable story of a young married woman just now under my observation, on whose life much depends (she has a six-months-old baby she can now barely see). She came to us bedridden and practically blind after long months of intracranial pressure from a tumour whose existence and location should have been sufficiently evident by the mere history of its inaugural symptoms. It is easy to play the game from the grand stand; and there were, one must admit, many reasons for confusion —the vomiting of pregnancy, the absence of nystagmus, and so on. Still, it would, I am sure, have astonished my neurologist friend who had attended her, had he known that shortly after her admission, a few pertinent questions about the symptoms of onset followed by a superficial examination had led a junior surgical house-officer to report that a patient with advanced hydrocephalus from a mid-cerebellar glioma was in the wards in need of prompt intervention; and no less would my pathological colleague have raised his eyebrows at the young man's additional comment that it was probably a cystic astrocytoma of the IVth ventricle.

In cases of brain tumour such a story of delay is becoming rare, I rejoice to say, but it is still too common a story. It

could have been told ten years ago about many a patient broken down from prolonged thyreotoxicosis ; twenty years ago about many another with pyloric obstruction or neglected biliary disease ; thirty years ago about many a neglected appendix ; forty years ago about many a pelvic tumour :—in regard to which the facts were not yet faced that a proper surgeon comes to be something more than a mere operator to be called upon as a last resort, and that because of his exceptional opportunities to observe pathological lesions exposed during life at the operating table rather than at autopsy he must necessarily have acquired diagnostic acumen and therapeutic judgement, of which early advantage might well be taken.

That differences of opinion would arise between neurologist and surgeon on these matters was inevitable, for they were only an historical repetition of differences that had impeded progress ever since Surgery had ceased to be purely external (*médecine externe*), as distinct from Medicine which was internal. The great Billroth once expressed the idea in another way : ' Die innere Medizin muss mehr chirurgisch werden.' This, as I take it, merely means that certain internists come in time to do their own surgery, as is quite proper; and it is but human, for those who do not, to resent an apparent trespass on their bailiwick.

Those of my generation, who as young surgeons with a leaning towards neurology grew up aware of this situation, realized that there were two essential steps to be taken : one, to become good neurologists themselves if that were possible ; the other, so to improve the technique of intracranial procedures as to restore the waning confidence of the profession in general, not only as to the therapeutic value of operations for brain tumours, but also as to their comparative safety.

In the course of a sojourn in the Hallerianum in Berne,

spoken of in my first lecture, I had learned many things about states of intracranial pressure which were subsequently of more value to me than the acute tension phenomena which were made the chief subject of my reports.[1] They were things, I am sure, long known to others, though new to me: that the sinuses are not rigid but easily collapsed; that respiratory cessation long precedes cardiac failure; that the falx may be markedly distorted by pressure against one hemisphere; that the brain can be widely dislocated without damage if there are contralateral openings; that pressure is not equally distributed throughout the cranial chamber; that choked disc and exophthalmus can be produced by intracranial tension, and so on.

Some degree of familiarity with these matters proved invaluable in my early intracranial operations, and I cannot too strongly emphasize the desirability of any one proposing to engage in the field of neuro-surgery getting his first experience with operations on the central nervous system in an experimental laboratory, particularly should it be one where the ritual of surgical asepsis is observed. I had the further good fortune at the end of this period to pass some months with Professor Sherrington at the time when he was re-mapping the motor cortex of the higher anthropoids and, as I was permitted to assist at some of these historic operations, I became familiar with his methods of unipolar cortical stimulation which subsequently stood me in great stead.[7, 9]

Armed with these experiences and with a practical, home-made haemodynometer—an instrument the model of which I had seen in use during a visit to Riva-Rocci's clinic in Pavia, and which promised to enable one, during the course of a serious intracranial operation, to keep a fairly continuous plotted record [2, 3] * comparable to the kymographic tracings

* When using a general anaesthetic we plot the ether tension [16] which

on which I had come to depend; armed, I say, with this small equipment, untutored in clinical neurology and wholly ignorant of neuropathology, I returned to Baltimore and lay in wait for I knew not what. Certainly brain tumours could offer no expectation of livelihood, for up to that time, a dozen years since the opening of the Johns Hopkins, there had been admitted to the surgical service only twelve cases of brain tumour, most of which had been brought to light at autopsy.

A successful brain-tumour operation was a rarity, not the rule; and up to the beginning of the century treatises on the subject were apt to tabulate the fifty-odd cases which had so far been reported in the entire literature as having survived an attempted extirpation. However, though the early hopes, that these performances might safely rest on the tripod of anaesthesia, antisepsis, and localization of function, had been dashed, these pioneer operations of the '80's and '90's, in spite of their discouragingly high mortality, had disclosed an important fact which proved the beginning of a new era.

Matters technical. Needless to say, the victims of intracranial tumours ordinarily have headaches and in course of time get blind; but many had observed that even though a cranial opening might have failed to disclose a tumour—as it usually did—and even though paralysis or worse might ensue, the patient's discomforts for a time might not only be greatly alleviated but, what was more surprising, his choked discs might subside with preservation of vision. These, then, must be purely pressure and not toxic effects of the growth; and Horsley's brilliant mind was quick to grasp and promulgate the idea of a premeditated craniectomy for the purpose of palliating the more distressing

the Connell apparatus makes possible, as well as the systolic and diastolic blood prsesure, pulse rate and respiration.

symptoms of these common lesions, irrespective of their nature and situation.

These early palliative operations, for which Jaboulay I believe introduced the term *trépanation décompressive* (1896), were usually made haphazard in any convenient portion of the skull, until Sänger of Hamburg suggested that the bone defects had better be made over the right posterior hemisphere, a relatively unimportant area of the brain from a functional standpoint. But the resulting protrusions covered by scalp alone were often so unnecessarily large and unsightly that other silent areas were sought, particularly ones where an undue herniation might be restrained by a securely closed muscle covering.

So it was that the temporal and suboccipital regions—on the one hand for supratentorial, and on the other for infratentorial lesions—were hit upon as preferential areas for the purposes of decompression.[5, 6, 30] And though these purely palliative procedures are nowadays less and less often requisitioned, they served a most useful purpose and saved a deal of suffering in their time. What is more, they served so to alter the attitude of the profession towards tumour operations that for a patient to become blind from an intracranial growth without some effort having been made to prevent this disaster, whatever else might be accomplished, came to be looked upon as reprehensible.

The old-time exploratory trepanations, which had unexpectedly resulted in giving relief from pressure, had usually been designed to expose lesions of the paracentral convolutions, and it was customary for the neurologist, in accordance with prescribed measurements and angulations, to mark out the fissure of Rolando on the scalp prior to the operation. Unfortunately, however, the very fact that tumours in this surgically accessible region were most frequently diagnosed, made it inevitable that a hemiplegia would ensue from

discontinuity of the pyramidal fibres in the subsequent herniation.

Wagner, to be sure, had long before introduced the idea of an osteoplastic flap (1889), but this in the hands of those who first attempted it was a matter largely of mallet and chisel, or of slowly nibbling a gutter in the bone with special forceps, of which there were many ingenious patterns; and it was not until the wire saw of Gigli was employed (1897) for the cutting of these bone flaps that the temporary osteoplastic cranial resection for exploratory purposes came to be a really practicable operation.[6]

Neither patient nor surgeon likes the idea of a large cranial defect, however great the relief from pressure headaches; and both parties were in equal dread of the paralytic consequences of a protrusion involving the paracentral convolutions. The Wagnerian procedure promised to offset these complications, but unfortunately it was soon found that when an osteoplastic flap was turned down and the dura subsequently opened in the presence of tension which could not be relieved, it might be impossible to replace the flap because of the bulging brain; and it was for this reason, I assume, that Horsley abandoned the making of these flaps as a matter of general principle. The difficulties, however, can usually be overcome by what is known as 'a combined procedure',[11] in which the large flap essential for thorough exploration of the hemisphere is reflected with its base to the temporal region where, under the protecting muscle, a bone defect with opened dura can be made in the same situation and with the same purpose in view as when the ordinary subtemporal decompression is made from outside in. In the general run of cases the outward dislocation of the relatively 'silent' temporal lobe then makes possible the replacement of the bone flap.

Operative surgery is little more than a composite of

devices; whosoever is most ingenious in using them is apt to be not only the most resourceful and skilful operator, but the one who secures the best results with the least damage to his patient. And though their therapeutic purpose may be clear, even comparatively simple operations, such as those designed for the limited purpose of a cerebral decompression, may go wrong in the hands of one who does not know the tricks of the craft, however clear may be his understanding of the principles involved. So, when it comes to the slow, painstaking enucleation of a tumour with as little loss of blood, as little damage to the brain, as inconspicuous a scar as possible, craftsmanship is really put to the test, and it is not a job for the inexperienced.

I would like, therefore, to doff my cap to the sole survivor of the pioneers in this work, my fellow countryman, W. W. Keen, who was one of the very first (1888) successfully to localize and remove a large meningeal tumour, yet had neither bone wax to use, nor muscle to implant, nor hypertonic saline at his command; no knowledge of intrapharyngeal narcosis, far less of local anaesthesia; no instrument of precision with which to follow the patient's condition from moment to moment; no provision for transfusion in case of need—and who simply made a sufficiently large hole in the skull, removed the exposed tumour with his finger, ligated the bleeding vessels; drained the wound; and in spite of a subsequent fungus cerebri the patient, with the same help that Paré relied upon, ultimately recovered. But both Dr. Keen and this celebrated case, the end result of which he recorded thirty years later,* are exceptions to all rules; neither is likely to be duplicated.

* As models of vivid case-reporting, I would recommend the reading of Dr. Keen's two accounts of this case, in the *American Journal of Medical Sciences* for 1888, vol. 96, p. 329; and in the *Journal of the American Medical Association*, 1918, vol. 70, p. 1905.

To-day such an operation is attended with the most intricate details of an osteoplastic resection, preferably under novocain, complete haemostasis during the dislodgement of the growth, replacement of the flap without drainage, and a wound closure so exact as to leave an almost invisible scar. Every neuro-surgeon has his particular method of accomplishing these things, but most of them have come to employ certain useful devices which are quite foreign to anything the general surgeon utilizes in his work, though he well might: cotton-wool pledgets wet in Ringer's solution instead of gauze; the implantation of muscle and the use of minute silver 'clips' instead of ligatures as haemostatic agents; the separate closure of the galea aponeurotica by buried fine silk sutures;[15] and a suction apparatus[54] in lieu of sponging, not only for the cleansing of the wound of fluids and blood, for the emptying of cysts and the sucking out of soft gliomatous tumours, but also for the collection of blood to be replaced, should there have been enough bleeding to cause anxiety—a rare happening, as a matter of fact, in these days of careful haemostasis.

Personally, of all these trifling contributions to operative technique, I think the separate closure of the galea aponeurotica is the most valuable, for it has prevented many a wound from separating under tension and thereby spared many a patient from a fungus cerebri. My assistants, however, who are scarcely aware of what used to happen in this respect, think the manifold uses to which the so-called 'sucker' is now put in the course of these operations makes it far the most important of our bundle of devices. However, if the clinic is to go down to posterity for anything, I hope it won't be through 'a sucker'.

But essential as the technical features of craniocerebral operations may be, these are dull matters to most people,

and I prefer to dwell on what goes before and what follows them: on the preliminary studies which lead up to the diagnosis; and on the histopathological nature of the lesion so far as it affects prognosis and the surgical end results. If the tumour question is to be covered as a whole, these are its more intellectual aspects; and my pupils, I am proud to say, have made contributions to diagnosis and symptomatology,[18, 25, 33, 43, 50, 51] which are no less important than the additions which may have been made to mere craftsmanship.

Matters diagnostic. There were two important instruments—the ophthalmoscope and the perimeter—with which at the outset we had to familiarize ourselves, for it was an imposition to ask our ophthalmological colleagues to give the time necessary for the often daily observations of the changes in eye-grounds and fields that we were anxious to follow. Fortunately for us the invention of the electric ophthalmoscope at about this time made possible the bedside employment of this indispensable instrument and did more to popularize its use than the vigorous though vain appeals to the profession, even of such as Hughlings Jackson and Clifford Allbutt in the years gone by.

The perimeter of the two is the more difficult instrument, for it entails an interpretation of the patient's subjective responses, and Dr. Bordley and I were led at the very outset into a misinterpretation of our findings in describing the interlacing of the colour fields as an early evidence of pressure.[12] However, this error, soon corrected, proved to be not wholly a liability for it encouraged us and others to employ perimetry in the routine examination of all tumour cases; and this led to a series of papers on the distortions of the visual fields with Dr. George Heuer[14] and with Dr. C. B. Walker whose contributions to the subject are well known to ophthalmologists. Perhaps the most valuable

disclosures were: (1) the progressive changes in the fields mentioned in my last lecture as accompanying the usual hypophysial adenoma; and (2) the advancing homonymous defects on which we place great reliance in the diagnosis of temporal lobe lesions.[35]

Though a brain-tumour, even a large tumour as is well known, may be accompanied by no changes in the eye-grounds or fields, yet when these changes are present, as one or both usually are, and are followed from day to day, they prove the best possible gauge as to whether the process is advancing or receding. The neuro-surgeon, in short, needs for his daily use the ophthalmoscope and perimeter no less than the physician, in following the condition of a consolidated lung, needs his stethoscope. No disinterested second party can be satisfactorily called upon for these purposes. What happened when the anatomist ceased to make his own dissections and employed a barber for the purpose is a matter of history; nor is this a far-fetched comparison.

These instruments, to be sure, the ophthalmoscope and perimeter, were in the hands of our predecessors, over whom, however, we are enormously advantaged by another instrumental aid to diagnosis, the X-ray. Stereoscopy and the improvements in röntgenography which have followed the introduction of the moving diaphragm enable us in many cases not only to confirm our clinical diagnoses, to assure us by tumour shadows of the nature of the lesion and its precise situation,[59] to lateralize it either by what Dr. Naffziger calls the pineal 'shift',[55] or by Dr. Dandy's method of ventriculography,[25] but at the same time the rays give us promise of therapeutic aid as well.[53] But with all said and done, no instrumental aid to diagnosis can equal in importance a detailed and exact history of the symptoms in the chronological order of their appearance. This must ever remain our chief reliance, and the ability to elicit

a dependable and correct clinical story is an art requiring perhaps even greater experience and skill than the making of a detailed neurological examination.

In assembling the clinical and laboratory data he regards as essential, the neuro-surgeon has evolved his own peculiar programme. This differs considerably from that generally followed by neurologists, since we have a somewhat different therapeutic objective; and in view of the great number of patients under the suspicion of harbouring a brain tumour who pass through our hands it would be humiliating did we not become more adept in making a diagnosis and giving a prognosis than those who see these cases less often, even had we not the added advantage of immediately checking our conclusions and correcting our mistakes by the invaluable experiences of exposing and dealing with the lesion on the living subject.

An operating surgeon is a peculiar animal. Of this perhaps no one is more aware than surgeons themselves, should they stop to analyse their conditioned reflexes. There is an unexplainable mental process that precedes what is known as a surgical inspiration, or to use an undergraduate vulgarism, a surgical 'hunch'. This means nothing more than that, after blindly puzzling and agonizing over a difficult problem in the effort to determine just what course to pursue, there is a sudden and unaccountable clearing of obscurities, and an operator enters upon his task with a conviction of just what he will encounter and just what will happen, as though he were possessed of a sixth sense.

I think most surgeons are more or less conscious of this state of mental preparedness for what to others may seem a desperate throw. But there is nothing uncanny about it; it is little more than the subconscious fusion of past experience which concentration brings to bear on a given problem.

And as these inspirations in difficult cases are the outgrowth of personal and repeated bedside studies of the patient whose equation also enters into them, he who neglects this portion of his task and merely operates at the behest of another misses much.

Nor should the surgeon and his staff shirk the responsibility of the detailed subsequent study of the tissues. Only by familiarizing himself with the microscopic appearance of the lesions with which he is to deal and by making his own post-mortem examination of his fatal cases can the operator's experience be properly rounded out. He otherwise becomes a mere tool, misses all the intellectual satisfaction which should pertain to his work, and his technical facility is prone to become developed out of all proportion to the soundness of his judgement.

Matters pathological. On the old basis, when one group pronounced on the diagnosis, another group performed the operation, and a third was left to study the histopathology of the lesion, no one was sufficiently concerned to study the case thoroughly as a whole and to follow the victim of the disease to the end, for better or for worse. The surgeon unquestionably is, or should be, the person most vitally interested, the person most likely to take the trouble to assemble and weigh all the facts on which subsequent operations and the patient's ultimate fate may depend, the person moreover whom the patient is most likely to keep informed of his progress.

Twenty years ago it was the usual custom for the brain on its removal at autopsy to be promptly sectioned according to the time-honoured method of Virchow, which would assuredly bring to light a concealed lesion but would at the same time permanently destroy the topographical relations of the lesion and its effect upon the brain as a whole, which to the surgeon is a matter of paramount interest. I therefore

cannot sufficiently express the obligations due to my pathological colleagues, first at the Johns Hopkins and in after years at the Brigham Hospital for their generosity in making it possible for us to conduct our own post-mortem examinations on these cases.[10]

This privilege has put in our hands a rare collection of tissues which are continually worked over; and since the brains have all been 'fixed' *in situ* before their removal, it has been possible for us to study and re-study them at our leisure. There could scarcely be a more informing process than to review the clinical history with such a specimen in hand, and the gross examination of these tissues in this process has incidentally led to certain observations of interest relating to foraminal herniation, the vascular strangulation of nerves as a source of false localizing signs,[13, 23] and so on.

But of even greater value has been the opportunity this collection of specimens gives for the periodical re-investigation and reclassification of the tumours from a histological point of view as our familiarity with their differing clinical behaviour widens.

I do not wish unduly to labour this matter which seems to me so important: namely, that the surgeon no less than any other who is pioneering in a given subject must attack it from all sides and not confine his attention to what the scalpel may do. Certainly the neuro-surgeon of the present day must take the wide view if he ever is to attain the goal he should strive for, of foretelling before the operation not only the precise situation of a given lesion but its probable character as well.

What this implies is well illustrated by the story of the acoustic 'neurinomas',[24] the common tumour of the cerebello-pontile angle, for which a short time ago there were confusing histopathological diagnoses, ranging all the way from neurofibroma and gliosarcoma to endothelioma,

depending on the portion of the tumour which happened to have been microscopically studied, and on the conflicting terminology of pathologists. It was not until this matter was taken in hand for purely surgical reasons and the finer anatomy of a long series of cases reviewed, that these particular tumours were shown almost invariably to arise from the VIIIth nerve and to have a uniform cellular architecture, akin to that characterizing the von Recklinghausen tumours elsewhere in the body.

This information has cleared away many obscurities in regard to these common lesions and permits an exactitude of diagnosis hitherto impossible. The fact that one surgeon[31] may be more conservative and another [58] more radical in the measures he advocates does not in the least modify the soundness of the principle that it is of enormous advantage to know beforehand precisely the sort of lesion he is to attack, and to be prepared accordingly. Ten years ago an operation for a cerebello-pontile tumour, so diagnosed, might have uncovered anything.*

So it is the neuro-surgeon's present ambition to concentrate upon one kind of tumour after another in a given situation, rather than to discourse as we were once accustomed to do upon brain tumours of all kinds on a broad

* As a matter of fact, subtentorial tumours as a whole were then looked upon as most formidable procedures—ones for which surgery offered the least. It seems incredible that M. Allen Starr, who first advocated a cerebellar operation on one of his patients in 1893, should have had to wait until 1910 before he could record a favourable result—the intracapsular removal of an acoustic tumour from a patient who still survives fifteen years later. A perusal of his article (*Am. J. Med. Sc.*, April 1910) gives a good idea of the bad results of these operations in the hands of even the most expert general surgeons. Without a satisfactory table suitable for a face-down position, without a wide suboccipital craniectomy from mastoid to mastoid and from torcular to foramen magnum, without a coincidental puncture of the lateral ventricle to relieve tension, operations for cerebellar tumours, generally speaking, were doomed to failure.

front ;[20] for though they have certain behaviouristic features in common, their dissimilarities rather than their resemblances are the important thing. And there is an ever increasing number of lesions which we can now with a fair degree of accuracy actually visualize and so be the better prepared to approach with the fewest strokes. One may gauge his shots better and be less likely to get into the rough when he is familiar with the course.

This allusion prompts me to mention still another element in all this not to be ignored. The results of a series of operations for a given lesion in a given situation provide a score for the surgeon to play against ; and an audience north of the Tweed need not be reminded of the importance of this as an incentive in improving one's game. Only by a carefully checked and posted score, such as is now available both for the acoustic tumours and for the pituitary adenomas, can a tentative ' par ' for the procedure in question be established. So we are constantly striving to better our record on the double basis of lower mortality percentages and of longer and more livable survival periods in the case of the more rapidly-growing tumours. A neuro-surgeon's responsibilities would be insufferable if he did not feel that his knowledge of an intricate subject was constantly growing —that his game was improving.

Certain midcerebellar gliomas of childhood, which Dr. Bailey and I have recently described as ' medulloblastomas ',[57] may serve to illustrate my meaning. These tumours composed of undifferentiated cells are among the most malignant and, from their situation over the roof of the fourth ventricle, rapidly fatal of all intracranial new-growths. Five years ago we would no more have presumed to foretell the presence of one of these lesions than we would have ventured to remove it if it happened to be exposed in the course of an exploration. The average survival period

of these cases, if left to run their course, proves to be six months from the time of onset of symptoms ; this period may be prolonged on the average for another six months by a suboccipital decompression, with or without fragmentary removal of the tumour, whose activity meanwhile may perhaps be checked by radiation.

With this fore-knowledge, we have become more and more radical in attacking these particular lesions and now have a case living three years after what appears to be a total removal at a second operation ; and there are a number of other children who remain free from symptoms well over the six months' period, which encourages us to feel that we are making progress, and that the isolated three years' case was not purely accidental.

But this matter of score, even for brain tumours of a single kind, becomes increasingly complicated as our tumour list has grown ; and to keep abreast of our changing percentages and shifting diagnoses requires the undivided attention of a highly trained secretary, who keeps in close touch with the living patients and their physicians.

Some one has remarked that all this attention being paid to brain tumours has caused them to multiply. There is a modicum of truth in this somewhat Hibernian statement, for tumours unsuspected in times gone by are now uncovered, and it is not an exaggeration to say that more patients with presumed or proven intracranial tumours annually pass through a modern neuro-surgical clinic than were seen in a lifetime by those of a past generation who were interested in the subject. But though we may be more alert than our predecessors to recognize them for reasons that I have mentioned, the tumours with which we have to deal to-day, and which we have thus unwittingly bred, are from a percentage basis quite different from those of thirty years ago.

In a much-quoted paper read by Byrom Bramwell before the Medico-Chirurgical Society of Edinburgh on February 21, 1894, there is recorded a series of fifty personally observed intracranial tumours which had been disclosed at autopsy. In half of these cases the lesion was secondary to a scrofulous, malignant, or syphilitic process elsewhere in the body, and most of the others were clearly inoperable gliomas. Only six of these fifty cases, it is stated, might have been favourable for operation, had a localizing diagnosis been possible—a sorry outlook indeed for the surgeon of those days.

Nor were the tumour lists subsequently compiled by others from the general literature of the subject any more encouraging. One of the most optimistic of neurologists in his unchanging advocacy of surgical intervention in brain tumours has been M. Allen Starr of New York, and yet in his compilation (1893) of 300 tumours there were 193 tuberculomas, mostly in children : indeed, tuberculous and luetic lesions comprised 71 per cent. of his assembled cases, whereas they represent less than 4 per cent. of our present-day tumour list.

Tumour Classification

One essential to the dissemination of information is the coincidental adoption of some convenient terms which serve to convey a definite meaning, however ill-chosen they may happen to be. In our early efforts to subdivide and tabulate our growing list of tumour cases we came to group them in the following three major categories : (1) the *tumour suspects* ; (2) the *unverified tumours* ; and (3) those *histologically verified*. The purpose of these subdivisions has been made clear from time to time by one or other of us,[32, 34] and needs at this time only a brief word of explanation.

In their desire to eliminate the possibility of an intracranial growth as the cause of persistent headache, disturbances of vision, convulsions, and so on, many physicians send their patients primarily to the surgical clinic for examination, and this group of cases puts our diagnostic capacity for differentiation severely to the test. They represent the old-time ' pseudo tumour ' group, and among them occur examples of cerebral arteriosclerosis, chronic abscess, aneurysm,[39] cisternal arachnoiditis,[51] subdural haematomas, multiple sclerosis, retrobulbar neuritis, mental derangements, and a multitude of other disorders which may be exceedingly difficult to distinguish from tumour and which are listed as ' suspects ' to be kept track of until the diagnosis comes to be assured in one way or another, should there be any immediate doubt about it. I don't know which is the greater source of humiliation, to operate unnecessarily upon a patient for a pseudo-tumour syndrome and to find merely an oedematous and arteriosclerotic brain, or to refer a case to a psychiatrist and learn a year or so afterwards that a frontal meningioma has been found at autopsy.

The unverified cases comprise the group of unlocalizable or inaccessible tumours whose existence is betrayed by an unmistakable tumour syndrome and for which temporary palliative measures may have been carried out. The list naturally contains many examples of tumour which will subsequently become verified by secondary operation or by autopsy, but it also includes those cases in which the story has already been closed and no post-mortem examination made. The criterion of verification rests on the microscopic examination of tumour tissue, for even if the lesion has been exposed at operation and its presumable nature recognized, without the actual histological study of a fragment removed for this purpose, it is classed as unverified.*

* We were led into making a single exception to this rule in the case of the

I may give an example of the way in which the diagnosis on our index-cards may shift from one category to another. Word has just come to me from Professor Brouwer in Amsterdam of the death of a little girl in whom I have long been interested. Five years ago she was operated upon for a presumed cerebellar tumour, for the few localizing symptoms she then had suggested a lesion below the tentorium. A hydrocephalus was disclosed but no tumour, and the diagnosis of 'cerebellar tumour unverified' was recorded. She made a remarkably good recovery with subsidence of her choked disc. On the expiration of a three years' period she had continued to do so well that the diagnosis was shifted to 'tumour suspect: probable arachnoiditis'. A few months ago she began to fail. To the end there were no recognizable localizing symptoms. The autopsy has disclosed a glioma [unclassified as yet] of the third ventricle, so that the case will now come to be included among the verified tumours.

With this preliminary explanation to account for the presence in our records up to September 1st of 513 tumour suspects and of 584 unverified tumours, we may turn to a more detailed consideration of the list of verified tumours grouped in the table on p. 126 under their family names.

What will first of all be noted is the subordination, in this modern list, of the lesions which dominated those of some years ago. It is gratifying to see that the infectious granulomata represent so small a percentage of the cases. Whether this means that these lesions are disappearing as tuberculosis and syphilis are getting under control is not

gliomatous cysts, whose yellow, clotting fluid contents are sufficiently characteristic to justify the diagnosis of glioma 99 times in 100. However, had we then known that the benign peritheliomas may undergo a similar cystic degeneration, we would probably not have made even this exception, though these latter tumours are exceedingly rare.

VERIFIED TUMOURS TO SEPT. 1, 1925

Gliomas (varia)		492
Pituitary adenomas		219
Chromophile	50	
Chromophobe	154	
Mixed	15	
Meningiomas (dural endotheliomas)		141
Neurinomas (acoustic)		100
Congenital tumours		67
Craniopharyngeal pouch cysts	55	
Cholesteatomas and dermoids	8	
Teratomas	4	
Metastatic and invasive tumours		44
Carcinomas	27	
Sarcomas	13	
Hypernephroma, &c.	4	
Granulomatous tumours		37
Tuberculomas	24	
Syphilomas	13	
Blood vessel tumours (pial)		17
Angiomas	9	
Angioendotheliomas	5	
Peritheliomas	3	
Papillomas (choroid plexus)		7
Miscellaneous and unclassified		22
Total		1146

certain, but we may at least assume this to be the case. Certain of the other tumours, the papillomas and the meningiomas, have been sufficiently commented upon in their connexion with the cerebrospinal fluid pathway, as have the hypophysial adenomas and the craniopharyngeal cysts in their relation to the pituitary question. Special reports have been made on the cholesteatomas in the series,[29, 36, 37, 48] and during the past year Dr. Boris Fried [61] has undertaken a review of the blood-vessel tumours, some of which had gravitated to the group of unclassified tumours;

and a few others, through inadequate study, had come to be included among the gliomas. Moreover, the familiar acoustic tumours, which I have just cited as an illustration of the importance of concentrating upon neoplasms of a single type in a single situation, have perhaps already had sufficient attention paid to them for a short address, particularly since I wish for the remainder of the hour to dwell upon the hitherto much neglected growths which outnumber all others—the gliomata.

The Gliomas in Particular

Mere numbers of cases, however, mean little. It is what is done with the few that actually counts; and numbers, even though they add to personal experience, may in reality prove a handicap to the advancement of knowledge by absorbing the time which might otherwise be spent in assuaging curiosity. All neuro-surgeons must certainly have had their curiosity aroused by the undependable behaviour of the gliomas after operation. Why were some apparently so favourable, others so malignant? How could one possibly account for divergent experiences such as were had in cases like the following?

1. From the cerebellum of a young man of 23, a large tumour was removed in 1910. The diagnosis was 'glioma'. He was given a *bad* prognosis, but there has been no recurrence and he remains well and free from symptoms now fifteen years later.

2. An apparently benign tumour was enucleated from the right hemisphere of a man of middle age. He was given a *good* prognosis. The pathological diagnosis again was 'glioma'; and he died of an extensive recurrence within three months.

3. Two years ago, a large subcortical tumour mass was removed from the left hemisphere of a woman of 43 who was rendered thereby almost completely hemiplegic and aphasic. It proved to be a 'glioma' and the prognosis seemed hopeless on the double score of incapacitation and malignancy. Yet she has recovered and,

except for a slight residual paralysis, considers herself well, and is earning her livelihood as an expert photographer.

4. In a young man with advanced cerebellar symptoms a large 'gliomatous cyst' of the right cerebellar hemisphere was merely tapped and evacuated. He remained well for 13 years, when a return of his former symptoms led to a secondary operation, and a solid 'glioma' was successfully removed from the situation of his former cyst.

5. A woman of 36 was operated upon in 1916 because of persistent Jacksonian seizures beginning in the right face. There were no evidences of tumour and the bone flap was replaced. Nine years passed before she again came under observation. Her attacks during this long interval had been moderately well controlled by drugs, but she had begun to notice a progressive weakness of her face and arm and a defect in speech. Re-exploration disclosed an infiltrating 'glioma' of the cortex.

These inexplicable experiences come readily to mind, and the list might be indefinitely prolonged. Generally speaking, the gliomas have heretofore not only been the *bête noire* of the surgeon but a most amorphous subject to the pathologist. Yet from many points of view they are unquestionably the most interesting of all intracranial tumours. In our efforts to classify them from their surgical aspects in years gone by, about the best we could do was to divide them into the gliomatous cysts, the cystic gliomas, and the non-cystic gliomas.

We were aware, of course, that a tendency to cystic degeneration was not only common but was in a certain respect favourable; and three years ago Dr. Paul Martin made a special end-result study of the gliomatous cysts,[42] which served to show that the expectation of life after operation in these cases was at least as good as that for malignant tumours elsewhere in the body, such as cancer of the breast, for example. This was an encouraging disclosure, but it was not based on a histopathological study of the varieties of

glioma which were concerned, nor were we then capable of differentiating them. Moreover, we had hit upon a most baffling type of lesion in our first effort to discourse upon a specific glioma in a given situation, namely that involving the optic nerves and chiasm.[40]

It is commonly assumed that a glioma, in spite of its degenerative tendencies, is a tumour of such hopeless malignancy that its attempted extirpation, however radical, is inevitably followed by recurrence; and there was some reason to believe that the mere operative meddling with the growth was likely to stir it into increased activity. Here, then, was a lesion representing the chief bulk of our work, so far as tumour operations were concerned, cut off from the prospect of any surgico-therapeutic aid apart from the temporary palliation of symptoms.

But in the course of a long and largely discouraging experience in dealing with these lesions, there had been a number of most unaccountable happenings. There were mystifying cases in the series like some of those just cited, in which: either an extensive tumour, unquestionably glioma, had been found on the surface of the brain and abandoned as hopeless, or in which a similar tumour was encountered and an obviously incomplete removal undertaken; or ones in which after a radical extirpation a pathological report of 'glioma certain to recur' was returned; and yet the patients had remained well for years, free from any indications either of progression or return of the growth. From this, only one conclusion could be drawn: that gliomas differed markedly in their behaviour under variable influences which were unknown, or else that there were many different kinds of them.

To the unpromising task of disentangling these true tumours of the nervous system which so greatly preponderate over all other intracranial neoplasms, Dr. Percival Bailey

and I set ourselves three years ago, he devoting himself to an investigation of their finer histology, far the most onerous and specialized part of the work, my small portion being to correlate his findings with the clinical histories and surgical experiences.

To be sure, many different varieties of glioma have been described in the past, and in a sense no two of them are precisely alike if one takes into consideration size, manner of growth, situation, gross appearance, and microscopical architecture. But so complex had the matter of histopathological differentiation become that in our own pathological laboratory, as in most others, I assume, the simple diagnosis of glioma with little attempt at characterization served to cover the entire group. The only exception to this was in the case of certain distinctive tumours called neuroblastomas,[45] which, as a matter of fact, we have now come to believe are not composed of neuroblasts.

It was necessary of course to begin at the beginning, and Dr. Bailey set out to familiarize himself with the normal glial elements and their reaction to the specific stains,[41, 49] it being a natural expectation on our part that, could the several varieties of cells known to constitute the supporting substance of the central nervous system be identified in the normal tissues, the cytoplasm of these cells would not lose its specific tinctorial affinities even when they had acquired neoplastic tendencies.

Needless to say, the several glial elements have long been objects of study, even though neuro-histologists, following Golgi, have been more interested in the neural than in the supporting tissues. The difficulty has been to find dyes with a specific affinity for the cytoplasm of the several glial elements which would leave the remainder of the tissue largely unstained; and to the contributions of Ramón y Cajal and his pupils neurology is almost wholly indebted for

success in overcoming these difficulties. Others of course had been intrigued by the same problem, one of them that brilliant Scot, the late W. Ford Robertson, who twenty-five years ago described and pictured as ' mesoglia ' what Cajal calls the third element, and Hortega the oligodendroglia—those small round cells whose insignificant cytoplasm is so difficult to stain and which abound near blood-vessels in the long fibre tracts of the central nervous system. But his method is one of the lost arts ; at least the platinum salt he employed, or believed that he employed, even in Bailey's practised hands gives mediocre results not to be compared with Robertson's original preparations, some of which his son has been kind enough to send to us.

But not only was it necessary to find ways of identifying these fully developed interstitial elements like the oligodendroglia, the microglia, the protoplasmic and fibrillary astrocytes and the adult cells of pineal and ependymal type, but, what was more difficult, to trace their less differentiated precursors. This of course meant delving into the histogenesis of the central nervous system, and, to make a long story short, after many setbacks and discouragements Dr. Bailey finally began to see daylight in his part of the problem, and a classification of the tumours on a purely histogenetic basis was gradually evolved. On the pegs of this schema we have come to hang, at least as a temporary working arrangement, the various tumours in which the mother, daughter, or granddaughter cells of the various cell types happen to predominate, even though there still remain a goodly number of cases in which transitional or mixed cellular types leave their position on the schema doubtful.

During the progress of this work, descriptions of some of the more easily identifiable tumours such as those composed of ependymal[46, 60] cells and of the pineal elements[56] have

been published; and more recently the common mid-cerebellar gliomas of children,* composed of undifferentiated cells, have been made the subject of a special report.[57]

Meanwhile the tissues of all the glioma cases in our possession were being re-cut and reinvestigated by the newer histological methods; and as the series up to January 1924 proved to contain of the various types a sufficient number (viz. 412) of examples for the purposes of clinical correlation, this was then separately undertaken. Accordingly from the clinical histories tabulations were made of the survival-periods from the onset of symptoms as well as from the time of operation for the cases up to this date in correspondence with each of the histopathological subdivisions.

We had no preconception of what the results would show, though, had we been inclined to make prophecies before the figures were spread before us, it might have been anticipated that, other things being equal, the tumours composed of less well-differentiated elements would have the shortest antecedent history with the briefest post-operative survival period, and conversely that those composed of the more highly differentiated glial types would have a longer pre- and post-operative story. We were, however, quite unprepared to find what the following highly condensed table betrays, that certain definite tumour types show a longevity far and away beyond what one would expect for a glioma. The

* These are rapidly-growing tumours which have been the source of great confusion since they have been variously described as 'neuroblastomas', which is distinctly a misnomer, or as 'round-celled sarcomas' because of their tendency to 'infect' the leptomeninges, which is still worse. Dr. Bailey originally gave to these unmistakable tumours the name *spongioblastoma indifferentiale*, but, since Strauss and Globus first used the term *spongioblastoma* for quite another lesion, we have gladly given way to them and have settled upon the term *medulloblastoma* as a suitable designation.

table, in other words, serves to show us the kinds of glioma that had seemingly responded so favourably to surgical intervention and to roentgenization [53] as to have been the source of our previous confusion.

AVERAGE SURVIVAL PERIODS IN MONTHS
FOR THE CLASSIFIED GLIOMATA

1. Medulloepithelioma	8	months
2. Pineoblastoma	12	,,
3. Spongioblastoma multiforme	12	,,
4. Medulloblastoma	17	,,
5. Pinealoma	18	,,
6. Ependymoblastoma	19	,,
7. Neuroblastoma	25	,,
8. Astroblastoma	28	,,
9. Ependymoma	32	,,
10. Spongioblastoma unipolare	46	,,
11. Oligodendroglioma	66+	,,
12. Astrocytoma protoplasmaticum	67+	,,
13. Astrocytoma fibrillare	86+	,,

The details of this long study which is in process of publication [62] need not detain us; it may suffice to say here that up to January 1, 1924, we had 412 so-called verified gliomas with which to deal. From these many eliminations had to be made: the cases 'verified' merely on the basis of cystic fluid; those in which tissues had been insufficiently well preserved for our purposes; certain atypical tumours which as yet baffle classification, and so on.

The table on p. 134, which lists the total number of verified gliomas in the series brought up to date, gives a sufficiently clear idea of the proportion of the tumours we have succeeded in classifying, and our reasons for discarding about a third of them which as yet fail to meet the criteria essential for the purpose.

VERIFIED GLIOMAS TO SEPT. 1, 1925

Verified by cystic fluid alone		54
Unclassified because differential study impossible		61
Unclassified gliomas of optic chiasm, pons or midbrain		31
Optic chiasm	12	
Brain stem	19	
Unclassified for other reasons		30
Atypical gliomas	24	
Transitional forms	6	
Classified		316
Medulloepithelioma	2	
Medulloblastoma	41	
Pineoblastoma	4	
Pinealoma	7	
Ependymoblastoma	6	
Ependymoma	8	
Spongioblastoma		
Multiforme	100	
Unipolare	9	
Neuroblastoma	3	
Astroblastoma	15	
Astrocytoma		
Protoplasmaticum	61	
Fibrillare	49	
Oligodendroglioma	11	
Total		492

Tables of classification are forbidding objects with which to punctuate a lecture. But there are one or two things to which in passing I may call attention. It will be seen in the first place that the 316 ' classified ' gliomas fall into three major groups—41 medulloblastomas, 109 spongioblastomas, and 110 astrocytomas. The medulloblastomas, to which I have already referred, are so malignant that when they once break through the limiting pia they tend to spread in the sub-arachnoid spaces in such a fashion as to have led to the term ' sarcomatosis of the meninges '. The spongioblastomas are scarcely less malignant and represent the

so-called gliosarcomas of the older literature which have given their bad name to these tumours as a whole. But with the astrocytomas it is an entirely different story in view of their average survival period exceeding 86 months or over seven years. And when one considers that these 110 astrocytomas, together with the oligodendrogliomas which are equally favourable, represent approximately 40 per cent. of all the gliomas, the neuro-surgeon may feel much heartened in his tasks.

What all this means to us from the important standpoint of prognosis no less than of treatment is incalculable. But there is one thing more of which we are greatly in need: namely, the development of more rapid laboratory methods, if the clinic is to get the full benefit of these classified diagnoses.* What the surgeon must cultivate is the ability to tell with some exactitude just what kind of glioma he has exposed, and in the past it has taken so long to mordant, to cut and differentially to stain the tissues that his picture-memory of the gross characteristics of the tumour, in spite of an operative sketch and a careful description, has become so faded before the exact returns come in, as to have lost much of its permanence. The patient meanwhile, as likely as not, has been discharged, and since the recollection of his particular lesion has become overlain by other impressions, it is difficult to get a dependable composite of one's operative and microscopical pictures.

I may give an illustration of what this all implies by the story of a patient who at the moment has just left the hospital after the removal of a glioma from her left hemisphere. She is the wife of a physician whose experience with brain tumours had led him to expect the worst, and when

* Some tentative short cuts in this direction with promising results have been made by Miss Grace Hiller, who has become highly efficient in the specialized technique of staining these tissues.

what I took to be a large spongioblastoma was uncovered, I feared that his apprehensions would be fully realized. The soft, infiltrating tumour, so far as possible, was removed partly by dissection and partly by suction, and a thin block sent to the laboratory was put through by a shortened process in three days. It shows a pure protoplasmic astrocytoma, which completely alters the prognosis in the case, to the great relief of all concerned. What we must search for, however, is a still more rapid process than this—one which will make it possible to get the histopathological returns while the operation is still in progress.

These then are some of the objectives towards which we are striving. I have from time to time put into writing some generalizations about the special field of neurological surgery.[4] The first of these papers, written just twenty years ago, sounds on re-perusal very juvenile in its discussion of the aetiology of choked disk; of palliative operations for purposes of decompression; in its chance remark that possibly some one might some day even venture to operate on a pituitary tumour. By slow processes we have come to broaden our horizon, but we do not for a moment forget that we are merely standing on the clustered shoulders of those here unnumbered and unnamed persons who laboriously worked out for the benefit of our generation the development and finer anatomy of the brain, who discovered the localization of its functions, untangled the pathways of its impulses, determined the clinical expression of its lesions, bequeathed to us the instruments of precision we depend upon, laid the foundation-stones of modern craniocerebral surgery, and much more besides. We would betray their expectations of us had we not managed to cultivate a few flowering plants in the large field of neurology in which they did the spade work.

There is, therefore, nothing novel in all this that I have laid before you—nothing, I fear, that Andrew Cameron would have felt was a distinct contribution to practical therapeutics. The complicated act of diagnosing, of localizing, and of removing a brain tumour is based on long-established anatomical and physiological principles, and it is time we paid more attention to a detailed study of the lesions themselves. This will require a more intimate knowledge than we possess of their cellular composition, for which purpose aid must be sought from chemistry and biophysics, all of which merely shows how closely interlocked with other sciences any research in clinical medicine has come to be. And in closing, I would like to quote a statement made by Ranvier in addressing the histologists in regard to his discovery of the clasmatocytes :

> Tous savent [he said] que des objets même très apparents échappent à leur observation quand ils ne les connaissent pas encore, tandis qu'ils les voient de suite lorsqu'ils ont appris à les observer. C'est pour cela qu'il est si difficile de faire des découvertes, qui semblent ensuite si simples que l'on se demande s'il y a quelques mérites à les avoir faites. Quoi de plus aisé que de montrer aujourd'hui la présence du glycogène dans le foie. Cependant Claude Bernard, qui était sans conteste un homme de génie, n'y est arrivé qu'après bien des années de recherches et par une série de tâtonnements.

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