Section of Neurology

President—GEOFFREY JEFFERSON, M.S.

[*January* 18, 1940]

Extrasellar Extensions of Pituitary Adenomas

PRESIDENT'S ADDRESS

By GEOFFREY JEFFERSON, M.S.

THE extensions of the pituitary adenomas beyond their average confines require definition. Although everyone knows roughly what is meant by the term, no description exists. Harvey Cushing illustrated one or two, in parentheses, in the text of papers describing the symptoms and the surgery of pituitary tumours, and Henderson (1939), in a detailed review of Cushing's cases, devoted a small section of his paper to them. Examples will be found scattered through the literature of the earlier writers, but since attention became focused on the surgical treatment of the " strumous adenomas " interest has been centred on the smaller types which give the best operative results. The influence of this happening on our conception of the adenomas will be discussed, and indeed this paper has the double purpose of calling attention to the less typical cases, and of suggesting that we do not know the story of the pituitary unless we include these others in our survey. That point does not seem, hitherto, to have been appreciated as fully as it deserves. Cushing himself was always most interested in the cases which gave the best results, and in his time it was proper that the emphasis should have been laid on that note. Other writers have, quite naturally, followed his lead. But to do so leaves the history but half told.

Every enlargement of the pituitary results in an encroachment on neighbouring tissues. One might correctly speak of extension as taking place in all directions, downwards into the sphenoidal air sinus, outwards towards or into the cavernous sinuses, upwards into the cranial chamber and then by further proliferation either in front of the chiasma into the anterior fossa, behind it into the 3rd ventricle and hypothalamus, or below it laterally into the middle fossa. In its most exaggerated form it is a fact that such extensions take place in several directions at once, and tumour tissue may find its way even into the posterior fossa, as will be illustrated later. It appears then that extension must be a name given to any exceptionally florid adenoma, which, once its restraining bonds are broken, might build a prodigious tumour were it not for the predecease of the patient. Such as retain a globular form (and some do so) I should prefer to call " massive " adenomas, reserving the term extension for those which take an hour-glass or irregular shape in which the extrasellar portion is at least as large, and almost always larger, than the intrasellar portion.

The most extensive adenomas are the malignant, those which burst their capsules and not only form an intracranial mass but also invade the cavernous sinuses. In order to curtail the present paper a full description of this important group must give place to a shorthand note, leaving them for another occasion. Great size alone is not a sign of malignancy. Theoretically it might be assumed that gradation from small to great would be the natural procedure of all adenomas. It is, in part, the thesis of this paper that this assumption is no less incorrect than that they are all the same, with a completely standardized clinical picture.

That intracranial extension must cause important variations in the clinical picture is self-evident ; they may indeed alter it until it is almost unrecognizable. What is more, the growth qualities of the tumour and its mass have a considerable bearing on prognosis, taking the long view, and on operative mortality. It is only the smaller tumours, chiefly intrasellar, which can be operated upon with the margin of safety which we desire. Considerations of this kind lead one to the description of an ordinary pituitary tumour, one that has no special characteristic attributable to its size and ramifications.

The Average Pituitary Tumour

The steps by which the various pituitary adenomas came to be recognized are well known: the publication on Christmas Eve of the year 1900 by Benda of his discovery of acidophile granules in three tumours from acromegalic patients, the designation of " chromophobe struma " to describe the neutrophil adenomas (Cushing, 1912) causing hypopituitarism and the description by the same author in 1932 of the basophilic syndrome in an inclusive statement.[1]

The importance of these discoveries has been that each type of adenoma has slowly had attached to it a typical syndrome. In the formation of these symptom-sign complexes, history shows a repetition of a certain train of events which does not vary in its plan, whatever the disease. After the preliminary state of complete ignorance comes one of puzzled awareness until an individual, by intuition, crystallizes a disease pattern out of an amorphous group of cases. After tentative acceptance comes a period of conflicting evidence, and of apparent inconsistencies, which in the end are found to be no longer antagonistic if the original plan is slightly modified. Next follows the period of codification and clarification. The simple facts are seized upon, the greatest common measure of similarity applicable to all cases is sought out, and a standardized picture formed, clear enough to be memorized. Such formulation has the advantage that it can be taught to students in a clear way and, with greater difficulty, grafted on to the knowledge of those already practising their art. These didactic pictures are drawn, as I have said, from the average of symptoms and signs, shorn of variants which might blur the clarity of the outline. But formulation, however praiseworthy its intention, and however useful its practical benefits, has certain dangers. We may come to believe that the simple picture represents the whole of something which is, in reality, very complex. We are unaware, or only vaguely conscious, that the typical case is a high abstraction of our minds. No little

[1] My own interpretation of the various events is this : Cushing did not of course discover the chromophobe cell or even the adenoma. It was Flesch (1884) who first observed chromophils and Hauptzellen chromophobes. Schoenemann (1892) first called the former " eosinophils ", Benda (1900) preferred the name " acidophils ". It was Benda (1900) who first recognized the association of acidophil tumours with acromegaly, and Loewenstein (1907) who studied, in Ribberts' laboratory, the first chance findings of small chromophobe adenomas in a post-mortem study of pituitary glands from patients dead of disease elsewhere. The basophil cell was recognized first by Schoenemann (" zyanophil " 1892), and Erdheim first distinguished histologically a basophil adenoma (1917), having already (1903) suggested that anlage tumours and cysts were derived from Rathke's pouch. Cushing's Pituitary Body (1912) brought all the previous work on the adenomas to a focal point, presenting a series of clinical cases with chromophobe and acidophil tumours, the diagnosis having usually been established by biopsy during life. He compared their signs with those resulting from animal experiment. He found a parallel between the loss of pituitary function that accompanies the chromophobe adenoma and that following hypophysectomy in the dog. I have therefore given the chief credit to Cushing for the chromophobe picture because no one before 1912 had seen the problem so clearly or had had so much experience. Erdheim's basophil adenomas were probably cell aggregates ; he could not correlate them clearly with any clinical state. We have yet much to learn about " basophilism ". All the previous work on pituitary cytology has been superseded by the work of Severinghaus (1932–38) and Rasmussen (1933). Severinghaus has rebutted Benda's evidence of the existence of a fourth cell, containing mixed acidophil and basophil granules (Benda's " amphophils ", 1900).

of the thrill, which most of us have experienced, in encountering a typical or textbook case arises from its being a rare experience.[2]

This is true of most diseases ; in neurology the symptomatology of disseminated sclerosis and of cerebellar tumours comes to mind, but it is difficult to know what to exclude in any speciality.

The pituitary syndromes began with a heavy endocrinal emphasis, but attention has become more and more sharply focused on the ocular manifestations, and especially on the visual field disturbances, with the radiological picture important, but not dominant. This change marks the growing importance of the surgical therapeusis of pituitary adenomas.[3] Standardization of the clinical results of the lesion tends to make us regard all pituitary tumours as being standardized in shape and size—perhaps something the size of a walnut. We know that the operative results are, in the main, excellent and we are puzzled, and indeed rather hurt, if a case behaves in a manner outside its scheduled pattern. We might further come to regard the type of case with which this paper deals as a curiosity, as the corner of a corner in medicine. In this we should be wrong, for these cases with extrasellar extensions give us part of the life-history of the pituitary adenoma and we know but little of the latter if we do not know of extrasellar extensions as well.

Cause of Extrasellar Extensions

In the main there are three factors in the production of extrasellar extensions. They are (*a*) the growth urge of the adenoma, (*b*) the state of fixation of the chiasma, and (*c*) the shape of the pituitary fossa and the nature of its diaphragm. Each of these requires a few words of explanation.

(*a*) *The nature of the adenoma and its growth tendency.*—Undoubtedly the most important factor must be the innate urge of the adenoma to enlarge progressively or intermittently. We know that the tendency to enlargement is by no means uniform. In the " benign " type of acromegaly, known in Marie's time, an adenoma with toxic qualities produces skeletal and somatic alterations, then ceases to grow. Such an acromegalic may live a long life without evidences either of continued pituitary toxicity or of encroachment of the adenoma on neighbouring structures. This behaviour causes no surprise, for we are familiar with similar adenomatous masses in another endocrine gland, the thyroid, where an adenoma reaches a certain size and, with minor fluctuations, remains not only the same for decades but never at any time occasions any symptoms. It seems probable that the pituitary and thyroid adenomas are similar in their nature and in their origin.[4] The original title of " pituitary struma " was not entirely wrong, in that it suggests the pathogenesis of the lesion. In adenomas the tissue anarchy is a local one within the gland, and we suppose that all its other cells have at one time proliferated excessively,

[2] Much of the difficulty which the young doctor finds in his first contacts with the sick after qualification arises from the fact that he has been educated on theoretically typical cases. He is baffled by the variants which actually form the greater mass. The student prefers his teachers to be dogmatic and, as it turns out, tellers of but part of the truth.

[3] The implication that endocrinal changes are unimportant is not intended. Not only are they important to the sufferer but their study has led to great enrichment of physiological knowledge. It is in practical daily usage that they have proved confusing, as is illustrated by the reluctance of the ophthalmologist to make a diagnosis of pituitary tumour when endocrine changes are absent. This has been a handicap not so much to neurology as to the patients themselves ; fortunately a great advance can be made by the insistence that we should use as the title of our preliminary diagnosis " chiasmal lesion " and fill in the details of its causation only after full study. Confusion has arisen from the attempt to carry the diagnosis through to a conclusion on hasty examination and incomplete evidence ; the consequence has too often been either no diagnosis at all or a wrong one.

[4] The endocrinal inter-relationship of the pituitary and thyroid glands is established by both clinical and experimental evidence, and there is little reason to suppose that their activations are based on dissimilar principles.

though the majority have regressed. The pituitary is so small that an adenoma crushes its cells out of existence (though sometimes they may continue to function) and then what they have to tell, what traces of change they might show, is undiscoverable. Once established, the adenomas behave like tumours in their tendency to continue growing, although we can find no sign of continuous compulsion in the state of the body metabolism. The urge, therefore, appears to be intrinsic. Another, and different, comparison can be made between the adenomas of the two glands, their tendency to be solid, or to have diffluent, or again, cystic, contents. The diffluent pituitary adenoma is fortunately common and rarely large. It is the solid adenoma with a strongly marked fibrous stroma which at once builds the largest tumour and at the same time makes them most difficult of removal. We shall return

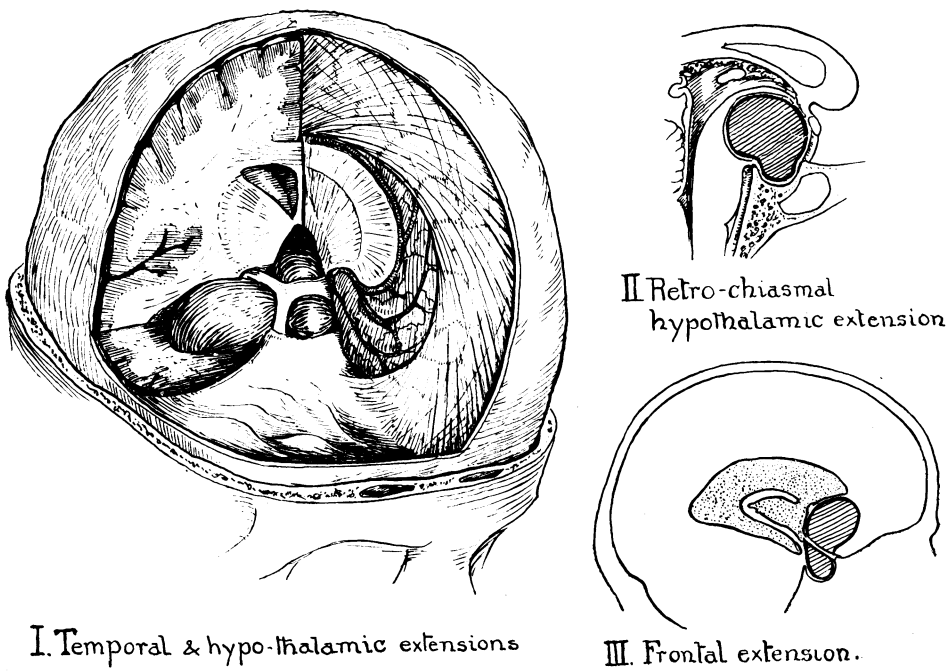


FIG. 1.—Diagram of pituitary extensions.

to the question of growth tendency when we come to discuss the so-called " malignant adenomas ". These reflections on the intrinsic growth urge of the adenoma may conclude with reference to Cushing's series (*see* Henderson, 1939). For whereas some of the cases survived for twenty years after operation, and over half the cases were well for long periods, others died relatively soon. Although it is comforting to the surgeon to believe that operation has greatly prolonged his patient's life, one must admit that the proliferative abilities of the tumour must always be the deciding factor in a situation where all of it cannot be completely extirpated.[5]

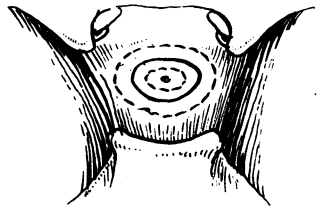
A distinction is made here between improvement of vision as a result of opera-

[5] My own experience and my own results are similar to Cushing's and give the impression that the rare pure cyst and the commoner diffluent adenomas sometimes allow of almost complete removal. But even in the most favourable example a few cells are left behind, and, if these have the necessary intra-cellular progressive energy, they can cause early recurrence with eventual death.

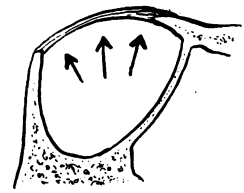
tion and long-range survival. It cannot be denied that operation must often retard the growth of a tumour (whether X-ray therapy helps we do not know with any certainty; Cushing's figures prove that it is helpful, though why it should be more so after operation than before is not clear). However this may be, an examination of the cases which follow deepens the impression that the most important single factor in the construction of large extensions of adenomatous tissue outside the sella is the vital urge of the cellular structure.

(*b*) *The fixation of the chiasma.*—There are objections, at first thought, in accepting the condition that fixation of the chiasma can have any influence on the size of a pituitary adenoma, for the chiasma is a structure which has, it is true, a not unimportant tensile strength, but not sufficient to restrain the growth of a tumour. When the chiasma is normally fixed an adenoma must make firm contact with it after it has risen 2·0 cm. above the level of the sellar diaphragm, and must then begin to cause some disturbance of vision (though, maybe, so slight a change as to pass unnoticed for a time). But if the chiasma is abnormally fixed the adenoma may grow for long before it seriously disturbs sight. Case 3 is an example of an adenoma being present for twenty years before it was finally operated upon, and in another (Case 9) it had presumably been present for twenty-four years. Both patients had, eventually, large but slowly growing adenomas; the only reason why the tumour had not caused symptoms before was because the chiasma was abnormally fixed (in one case post-, in the other pre-fixed). This is the explanation of the interesting series of cases of chiasmal lesion without optic atrophy reported by McConnell and Mooney (1938); the tumour does not make direct pressure on the optic nerves. Cushing (1933) hinted at the probability that central scotomata probably meant a retro-chiasmal extension (since the macular fibres appear to decussate in the posterior part of the chiasma) and Henderson (1939) in a further survey of Cushing's cases, supported the view, which is undoubtedly correct. I would go further and say that the tumour is always likely to be large when bilateral central scotomas are present. Although pre- and post-fixation of the chiasma are roughly equally frequent (4 and 5% respectively in Schaeffer's observations, as given by de Schweinitz) the surgeon is made more acutely conscious of pre-fixation, because it interferes so disastrously with his exposure of the tumour. But whichever the variant is, its tendency must be to allow of the unnoticed enlargement of the tumour. It is for these reasons that bilateral scotomatous fields suggest pre-fixation, and that fact again suggests that the tumour will be large. There is another possibility of scotoma formation, especially when unilateral, always to be borne in mind, that there may be a localized herniation of adenomatous tissue through the capsule impinging either on the chiasma or on one optic nerve. Such a happening may cause not only a scotoma but a monocular partial superior altitudinal hemianopia. Examples will be seen in the gross specimens illustrated in figs. 6 and 11. The significance of these tumour herniations will be discussed later.

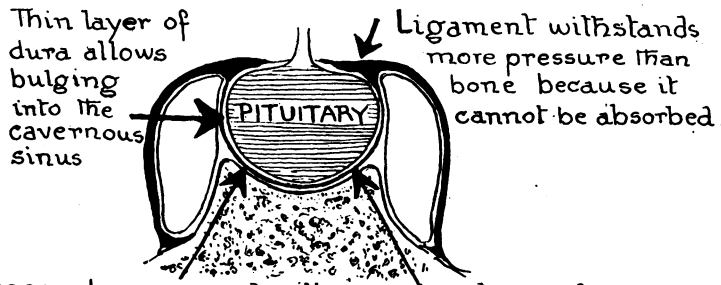
(*c*) *The sella and sellar diaphragm.*—Fig. 2 shows in diagrammatic form the alterations in the sella produced by pituitary adenomas and the influence of the sellar diaphragm in restraining extrusion. Little comment is necessary to amplify what the schema shows. The diaphragma sellæ is a thin fibrous sheet at its centre, where the pituitary stalk emerges through an opening which varies greatly in size. Sometimes nearly 1·0 cm. of the dorsal surface of the gland can be seen through the opening. At the sides it is thickened by the interclinoid ligaments which contribute to the strength of the diaphragma, fading in a mesial direction. But just as it is possible to hold down a tennis ball by two fingers widely separated, so these ligaments rather than the diaphragma take the chief thrust of the tumour, which balloons out sideways under them towards the cavernous sinuses on either side. Ligamentous tissue is not easily, if at all, destroyed by benign tumours (certainly not by plain pressure)



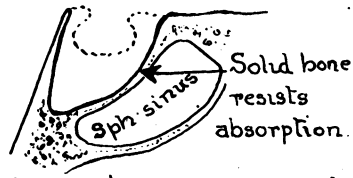
Variations in size of stalk opening in sellar diaphragm



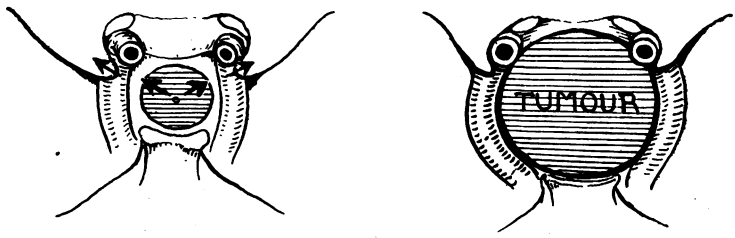
Elevation of anterior clinoids by pull of ligaments



Spongy bone covered with very thin layer of dura is easily absorbed.



Spongy bone is more easily absorbed than compact bone



Erosion of the anterior clinoid processes by the carotids

FIG. 2.—Mechanism of sellar alterations.
(E. W. Twining.)

and bone, unexpectedly, proves to be much more malleable. As for the bone itself the cancellous (and thicker) variety proves to be physiologically less resistant than the compact kind, so that the tumour enlarges more easily downwards and backwards towards the basi-sphenoid than forwards into the sphenoidal air-sinus. Thus arises the eccentric V-shape sella, characteristic of the pituitary adenoma. In fig. 12 for example the thin compact bone roofing the sphenoidal air-sinus has proved itself remarkably resistant to depression by the large overlying tumour.

In those cases where the sella is saucer-shaped and shallow a suprasellar extension is the natural result, though its size chiefly depends, at the time seen, on the other two factors just discussed (especially the first). The lateral walls of the sella, and the breaking through of adenomatous tissue into the cavernous sinus, will be described in its proper place. A last word must be added on " sharpening " of the anterior clinoid processes. The figure shows the late E. W. Twining's explanation: that the tumour presses the internal carotids against these bones and wears them away by the water-hammer of the pulse, and not by the direct pressure of the adenoma itself. That observer's figure of the elevation of the clinoids by the drag of the interclinoid ligaments is also illustrated.

We may now pass to the discussion of the various extensions. It will be realized that they are all examples, and only variants, of the same thing but although their classification is, in a wide philosophical sense, quite artificial, there is good clinical reason for grouping them because their symptoms and their signs differ. Fig. 1 shows schematically some of the various intracranial extensions which may be classified as—Hypothalamic, Frontal, Temporal, Pharyngeal, and Posterior fossa protrusions.[6]

It was mentioned earlier that a distinction should be made between mere massiveness in a tumour and extension proper. I regard a " massive " tumour as one which is merely a very large tumour, the diameters of which are equal.

Hypothalamic Extension

Most of the more massive tumours in the series have extended towards the hypothalamus, usually behind a prefixed chiasma. In this series there is one excellent example of an hour-glass extension, which is, on the contrary, so frequent in the pituitary anlage series. There have been several of that nature in this material (e.g. Cases 9 and 11).

The outstanding features of these extensions are headache and somnolence, thirst, polyuria, temperature variations; alterations in cardiac and respiratory rhythm are less common. As a rule tumours which merely indent the hypothalamus without invading it do not produce outspoken hypothalamic disturbances, though this is not an invariable rule. Severe headache is rare in chromophobe adenomas and should always raise the suspicion that an extension is present. Neither headache nor hypersomnia are sure indications of the direction of the extension, but since a hypothalamic extension, of all others, is most likely to produce internal hydrocephalus the severest headache should occur in this type.

Case 1.—*Chromophobe pituitary adenoma. Amenorrhœa.*

Right homonymous hemianopia. Bilateral optic pallor. Very severe periodic headaches. Fugitive left abducens weakness. Operation. Death from hæmorrhage into a suprasellar extension invading the 3rd ventricle.

N. A., aged 32, was referred by my colleague, Dr. A. H. Holmes, with the diagnosis of pituitary adenoma, August 30, 1934. Two years ago menstruation ceased suddenly; she became irritable,

[6] Henderson classified Cushing's examples into frontal, temporal, Sylvian, and thalamic. I have seen no important Sylvian extension, though I have observed tumour tissue overlying an optic nerve, tissue that was drifting in a Sylvian direction. I doubt whether a true massive Sylvian variety exists as a solitary feature; perhaps once attention has been directed to it a rare example may be found. I prefer " hypothalamic " to " thalamic " as a name for upward and backward protrusion. The posterior fossa extensions, apart from protrusions via Meckel's cave, are newly designated.

chiefly because of violent headaches, usually in the left temporal fossa. She had gained considerably in weight. Recently she had become extremely lethargic and would lie in bed for hours. A week before admission her left eye had squinted inwards. On examination she was an obese woman with hypertrichosis; metabolic functions normal to tests; B.P. 125/85. There was a variable paresis of the left abducens; sometimes it was scarcely noticeable, and it was never seen to be complete, though she stated that it had been so for three or four days recently. The optic nerve heads were only faintly pale, but there was an incongruous right homonymous hemianopia of which she had been unaware. X-rays showed a moderate but definite enlargement of the sella. Cerebrospinal fluid pressure not recorded. Albumin 40 mgm.%. The pre-operative diagnosis was chromophobe pituitary adenoma with a left-sided suprasellar extension. It was assumed that her lethargy was due to endocrine disorders and her peculiarly severe headache to sellar distension. Operation was undertaken by an assistant and proved to be easy but, significantly, only after the right ventricle had been tapped; before that the brain was very tight. A large bluish adenoma was brought into view and easily evacuated with spoon and sucker. It was very

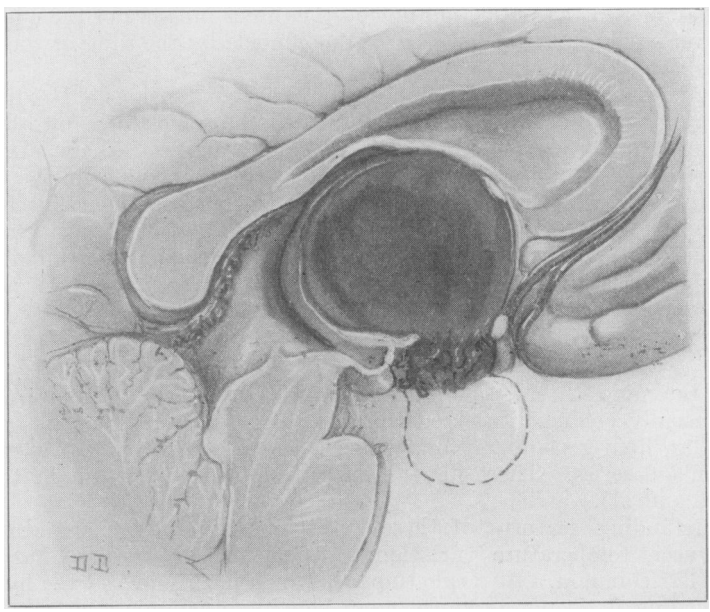


FIG. 3 (Case 1).—Hypothalamic extension of adenoma filled with blood.

vascular. Three hours after operation her temperature rose to 102° F. and in spite of antipyretic measures she died twelve hours after operation in a hyperpyrexial state. Necropsy revealed a large suprasellar extension full of clot filling the cavity of a suprasellar extension rising high into the 3rd ventricle (*see* fig. 3). The specimen resembles some of those of large basal aneurysms but histology supported the operation findings of chromophobe adenoma. The occurrence of violent headache in a patient with a chromophobe adenoma should have aroused greater suspicions, especially with the association of so uncommon a finding as homonymous hemianopia. A transsphenoidal approach could hardly have failed to excite a similar hæmorrhage, and one must write this down as a surgically irremovable lesion. There can be no doubt that the intraventricular cyst was a prefixed adenomatous extension and not a post-operative suprasellar clot which must have a different distribution.

Comment.—A similar death from hyperpyrexia within a few hours of evacuating a pituitary cyst, an operation that had proved very simple, remains unexplained from lack of post-mortem verification. But the very severe headaches that this patient also had suffered, and her entreaties for operation during a long period when she was undergoing X-ray therapy, make one suspect that she also may have had an identical and unrecognized upward extension behind the chiasma.

Frontal Extensions

A pituitary frontal extension (which has not previously been exactly specified) can be defined as a protrusion towards the anterior fossa, in which this protrusion is larger than the intrasellar portion. These extensions bury themselves in the surface of the frontal lobes or of one frontal lobe. Epilepsy is a common sequel, as it is with any frontal tumour. Three cases will be described.

Case 2.—Huge suprasellar extension into the right frontal lobe.

S. B. L., male, aged 54, an electrician, was admitted to the Neuro-Surgical Service of the Manchester Royal Infirmary, December 31, 1936, complaining of failing vision, severe headache,

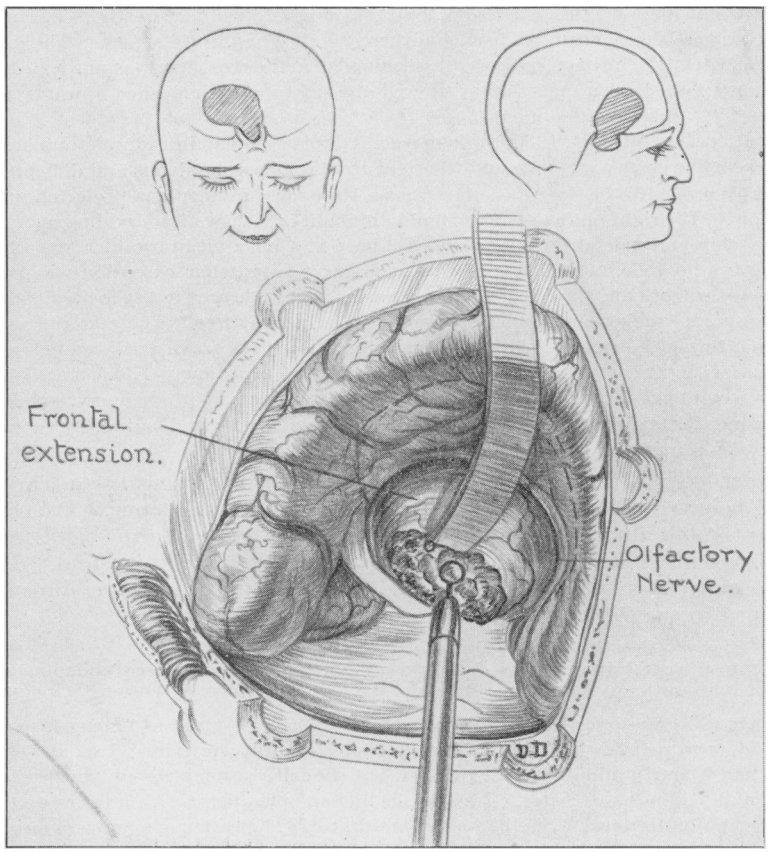


FIG. 4 (Case 2).—Sketch of tumour as seen at operation.

character changes ; later fits. Eighteen months previously his sight had begun to deteriorate. Finally diplopia was a definite feature before the vision in the right eye became too bad for binocular vision. He was finally referred to Mr. G. F. Rowbotham, who diagnosed a pituitary tumour and transferred him to the Manchester Royal Infirmary. His wife had recognized personality changes—irritability, a distaste for company, and loss of ambition. By this time his sight had become so bad that he was having difficulty in getting about ; he had not been able to read newspapers for four months. He became much worse after a severe generalized convulsion. His right eye, in which there had been a central scotoma, was now virtually blind, and he was suffering from continuous headaches often very severe. On examination there were

no neurological signs apart from vision. He was a well-looking man greatly worried by occipital headaches severe enough to make him dizzy. He had lost weight. There was no polyuria or hypersomnia. His memory was good, no behavioural peculiarities were observed ; no anosmia. The pupils measured 3·0 mm. and reacted to light. Ocular movements were normal. The optic nerve heads were very pale with the vessels rather small, no papillœdema. *Visual fields.*—Right eye : hand movements recognized in the nasal field only. Left eye : temporal hemianopia sparing macula. V.A.R. less than $\frac{6}{60}$; V.A.L. $\frac{6}{36}$. X-ray showed the sella a little enlarged, the floor depressed, more so on the left than on the right. The posterior clinoids were slightly eroded but the picture was not characteristic of the ordinary ballooned sella of the adenoma. Optic foramina not enlarged. B.M.R. + 5. Sugar tolerance curve shows slight retention ; fasting level 81 mgm.%. All other laboratory tests negative except the cerebrospinal fluid. Pressure low (80 mm.), proteins 100 mgm.%, globulin marked opalescence (Pandy). It was clear enough that this patient had a chiasmal lesion, but the unusual points were the sellar pattern, the severity of his headaches, his invalidism, and the generalized epileptic attack. The high cerebrospinal fluid protein might have indicated a meningioma, though there was no basal hyperostosis in the radiographs. An encephalogram showed the right ventricle pushed upwards and its floor indented as by a sub-frontal tumour.

At operation December 24, 1936, through a right Trotter flap an intradural approach was made to the lesion. The cortex was pale and the right frontal lobe voluminous and difficult to elevate. This difficulty proved to be due to the fact that a large mass of adenoma projected upwards into it from below. The right optic nerve was finally brought into view after dividing many adhesions. It was very thin and pale stretched around the base of a huge pituitary adenoma which rose to indent the frontal lobe. A full exposure of this large suprasellar extension was not possible. Its surface was smooth and dark red. After exposing a suitable area it was incised and a quantity of its soft contents sucked and punched away. Bleeding was free. The material removed was typical of a pituitary adenoma. Although the tumour was very greatly reduced in size it was not possible to evacuate it completely, nor to bring the chiasma into view. The operation was broken off and the wound closed with drainage. The patient made a smooth recovery. He returned to work in six months and three years later he was re-examined. He had had an occasional epileptic attack but was continuing his trade as an electrician.

Comment.—**The tumour in this case, although histologically a chromophobe adenoma, behaved like a frontal rather than a pituitary tumour. Its prechiasmal site led to the bitemporal hemianopia but its break through to the right frontal lobe gave him a central scotoma in the right eye and later made it blind. The severe headaches and character changes, the high protein count in the cerebrospinal fluid, all combined to suggest an extrasellar origin for the tumour.**

Case 3.—*Chromophobe pituitary adenoma.*

Seventeen years' amenorrhœa. Four years' history of generalized epileptic fits. Slight pallor of both optic discs. Normal fields. Massive suprasellar extension. Operation.

L. H., aged 37, was referred by Professor Henry Cohen. At age of 22 menstruation ceased suddenly, never to reappear. During the next twelve months she gained 3 st. in weight ; since then there had been a gradual increase to 12 st. but she felt reasonably well, finished her training as a nurse, and held posts as Sister. In 1934 she had an epileptic fit with no aura except a vague and brief feeling of dizziness. She had eight fits that day, but after one or two more during the next week they ceased. From that time on her history was one of occasional epileptic fits which usually ended the tenure of her official post. But she felt perfectly well as soon as the attacks were over. In 1936 encephalograms were made without any abnormality being discovered. In December 1938 Professor Cohen discovered that the pituitary fossa had been completely destroyed. This was difficult to account for, because there never had been, nor were there then, any symptoms or signs to suggest the presence of an intracranial tumour, save a relative hyposmia on the left. The optic nerve heads though pale showed a faint œdema, whilst the fields were full. She was admitted to the Neuro-Surgical Service of the Manchester Royal Infirmary in January 1939. She was an obese, slightly hypopituitary but generally normally active woman. B.P. 150/90. L.P. pressure 100 mm., albumin 55 mgm. Ventriculograms were made. Once again no unmistakable abnormality was discovered. There was no hydrocephalus, no ventricular displacement. Tomograms showed an unusually high 3rd ventricle with the

normal suprachiasmal and infundibular notches. The same technique showed destruction of the upper part of the basisphenoid with destruction of the dorsum sellæ and clinoids. A scooping out of the right parasellar region was also visible. The presumptive diagnosis was arrived at of benign chromophobe adenoma with upward and frontal extension. The high 3rd ventricle with normal inferior contour was not at that time given its correct valuation, which operation later showed an unusual degree of post-fixation of the chiasma. Operation was not at once undertaken because the patient's only disability arose from her epileptic incidents. It seemed uncertain that operation would cure them. However, a transfrontal exploration was carried out, October 29, 1939. There was now no trace of papillœdema, the discs were a trifle pale ; the fields of vision showed a slight temporal upper quadrantic notch in the smallest isopters. A large hard fibrous adenoma was disclosed rising out of the sella, pre-chiasmally, and was seen to be indenting the inferior surfaces of both frontal lobes. The tumour proved to be too hard for radical removal, without first sacrificing the right frontal lobe. Only this step would have allowed of a sufficiently full exposure of the tumour to permit of a proper attack. But since the effect of such a step on her epilepsy was doubtful, nothing more than a partial removal was attempted. Recovery was uneventful, except that for the first few days she was a little disorientated, excitable, and complaining about minor annoyances.

Comment.—This is an admirable example of generalized fits occurring as the leading outspoken symptom of a pituitary adenoma. It is true that the amenorrhœa and obesity must be given pride of place in her history, but it was epilepsy that led to her seeking advice rather than amblyopia. A transient papillœdema was observed, hyposmia on the left, then slight pallor of the discs and a faint disturbance of her temporal visual fields. This adenoma was one of the fibrous, " rubbery ", type so difficult to extirpate. It was lobulated and spread over the right optic nerve. Evidently it was a very slowly growing adenoma with no hint of malignant intention, and may continue to enlarge very slowly for years to come. After some twenty years (supposing it to have antedated the amenorrhœa by a year or two) it is even now no larger than a bantam's egg.

Another case of frontal extension illustrates an important practical point, the manner in which its presence makes exposure so difficult that amputation of a frontal lobe may be necessary to allow of proper visualization of the lesion.

Case 4.—*Chromophobe adenoma.*

Bitemporal hemianopia and failing vision. Lethargy. Excision of right frontal lobe to obtain exposure.

L. P., female, aged 27, was referred by Dr. Horsfall of Leeds. The leading symptom in this case was headache, radiating to the right frontal region, headache which gradually became more and more disabling. Six months later she became conscious of a temporal field defect in her right eye and on admission she had no useful vision on that side, and a temporal hemianopia to the left. There was no anosmia. She occasionally had diplopia during the past two years. She had gained 2 st. in weight, she was very sleepy, no energy, and was not interested in things. She would rather stay at home when the rest of the family went out. She had to give up her work on account of headache rather than defective vision. She volunteered no information and her history had to be got from her by question and answer. Amenorrhœa had been present for two and a half years.

At operation on August 6, 1937, it proved to be impossible to elevate the right frontal lobe sufficiently to bring the tumour into view. This was thought to be due to mucous obstruction of the intratracheal tube and venous congestion, so the operation was suspended. Eight days later under local anæsthesia conditions were found to be no better. The right frontal lobe had to be removed and a not very large extension dealt with summarily, leaving a collapsed capsule Improvement in her mental state was immediate. Two days after operation she was writing letters home.

The importance of this case lies in its illustration of the reason for the difficulties which may arise in exposure. If they are so great that the tumour cannot be seen we may be sure that at least a massive tumour is present, and that there is more

probably an extension. The after-history of this case was that her acuity greatly increased after the lobectomy and that she seemed to her relatives to be much more intelligent than she had been. The reasons for improvement, even though important brain tissue has been sacrificed, were advanced by the writer in 1937. Apart from some glycosuria in 1939 she has remained well.

Temporal Extensions

Adenomatous tissue may escape laterally from the sella below the chiasma and proliferate in the middle fossa. Probably there is no other reason why it should do so except that there may be an unequal proliferative urge in one part of the tumour. In a case of Cushing's the temporal extension crossed the middle fossa and, having eroded the temporal squama, came to infiltrate the muscle. The patient remained well nine years later, showing that the adenoma was not malignant. The next case (5) was very puzzling because there were clear signs of a left temporal tumour and yet there was bilateral optic atrophy. The problem was not solved until necropsy. In Case 6 a more correct pre-operative diagnosis was made. A further example of temporal extension will be found amongst the malignant adenomas (Case 11).

Case 5.

Fits 2½ years. Failing vision 2 years. Weakness right arm and leg 1½ years. Headaches 1 year. Nocturnal incontinence 4 months. Operation. Chromophobe adenoma with left temporal extension.

A. S., male, aged 41, was admitted to the Manchester Royal Infirmary January 19, 1935, under Dr. T. H. Oliver, who made the diagnosis of cerebral tumour. He gave a history of generalized epileptic fits which had commenced two and a half years ago, at a time when he had considered himself to be in excellent health. He had six attacks the first day and for some time after might have eight or ten in one day though without loss of consciousness. The attacks always commenced with a foul taste in the mouth and a bad smell associated with a feeling of dizziness. He became accustomed to these attacks, would stand still for two or three minutes until they were over. He was able to continue with his work until a few months ago, when he gave it up for a different reason, failing eyesight and difficulty in walking. For a year past he had observed a very slowly increasing weakness of the right arm and leg. Two years ago vision in the left eye had begun to fail and since then very slowly worsened. He was aware, in the end, that not only could he not see well with the left eye, but that he could not see to the right-hand side with either eye. Two years ago he had diplopia for a time and it had occasionally troubled him since. For a year past he had had severe headache, lasting for an hour, on rising in the morning. The ache was in the left temporal region and had improved lately. For one year also he had difficulty in walking, first the right leg was the worse, later the left, but at the same time the right hand had become weak as well. For four months he had been apt to wet the bed during sleep and was worried and distressed on this account. Mentally he was said to have become different, liable to short periods of depression and emotional instability. For some time past he had been sexually apathetic. On account of these mental changes, incontinence, and optic atrophy, he was thought to be a neurosyphilitic until serological studies negatived this diagnosis. On examination the most important findings were: Bilateral optic atrophy with normal vessels and nothing to suggest œdema or consecutive atrophy. V.A.R. $\frac{6}{18}$, V.A.L. $\frac{6}{36}$. Visual fields, right homonymous hemianopia, fairly congruous in size and shape. No anosmia in either nostril. No oculomotor palsies in spite of the history of diplopia. Pupils reacted sluggishly to light. No trigeminal pain or anæsthesia. He had right-sided pyramidal signs including a positive Babinski reflex. In spite of his complaint of weakness in the left leg also, allegedly worse recently than the right, there were no signs of pyramidal tract involvement on that side. Nor were there any sensory disturbances, only the history of gustatory and olfactory auræ. Lumbar puncture: The cerebrospinal fluid was yellow, contained 200 mgm.% of albumin, and gave a positive reaction for globulin. Wassermann reaction negative in blood and cerebrospinal fluid.

Radiographs of the skull showed enlargement of the sella, the dorsum sellæ could not be seen. Unfortunately he had an unusually pneumatized temporal bone, basal zygomatic air cells, obscuring the sella. Ventriculography gave definite evidence of the presence of a left temporal tumour.

A diagnosis of left temporal fossa (probably sphenoidal wing) meningioma was made, but the bilateral optic atrophy without a trace of œdema remained unexplained, and some uneasiness was expressed as to the correctness of the diagnosis.

Operation.—Through a left fronto-temporal Trotter flap the left temporal lobe was exposed. After a short search a curiously lobulated and smooth-walled tumour was located in the anterior end of the middle cranial fossa. The tumour was " uncapped " by excising an oval piece of the temporal lobe, 6·0 × 4·0 cm. A good view of the tumour was thus obtained ; it was dark red in colour with thin-walled vessels running in the depressions of its irregular surface. On commencing to loop the tumour out with the endothermy small cystic spaces were come upon here and there which made the nature of the tumour even more difficult to recognize. Its relations precluded the possibility of its being a glioma. Owing to brisk hæmorrhage progress was slow, and after four hours all hope of the total removal of the tumour was abandoned, for it seemed to be firmly attached to the sella or cavernous sinus on the outer side of the chiasma ; the carotid

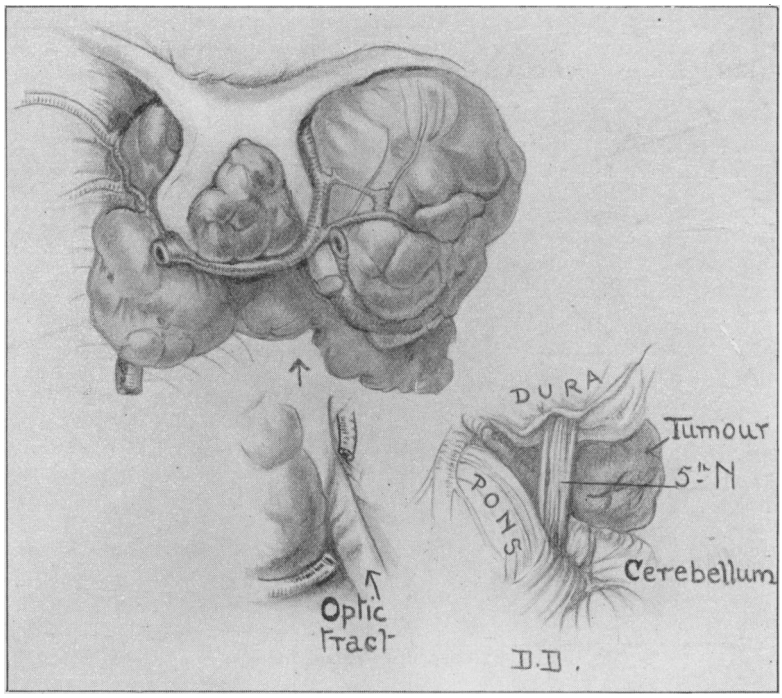


FIG. 5 (Case 5).—Drawing of lobulated chromophobe adenoma of pituitary.

artery was not to be seen. The whole of the floor of the temporal fossa was empty. Muscle grafts were placed over a bleeding point on the sheath of the Gasserian ganglion. The flap was replaced but the wound was reopened twenty-four hours later as he had not regained consciousness. The already weak right side was weaker still. No clot was found. The cause of the clinical state was acute cerebral œdema.

Post-mortem examination gave the answer to the various anomalies which had already introduced difficulties into the clinical and operation picture. The tumour was a pituitary adenoma which had entangled the visual apparatus bilaterally and had, apparently by chance, grown out under the optic chiasma to form the large tumour in the temporal fossa which had been removed two days before (*see* fig. 5).

The tumour was, of course, essentially inoperable. Even if the removal of the temporal extension had been successful, it seems unlikely that a second operation directed at the pituitary from the front would have achieved a really worth-while improvement in vision or length of life.

The tumour was mainly retro-chiasmal. Possibly a considerable amount could have been recovered if the left optic nerve had been sacrificed, but there was a formidable attachment of the carotid artery to the tumour.

A further example of temporal extension has recently (1940) come under the writer's care referred by Professor Henry Cohen.

Case 6.—J. D., male, aged 38, suddenly lost visual acuity eighteen months ago, so that he could not read, but after two weeks his vision returned. The left eye has been the worse ever since. Six months ago he began to experience sudden attacks of dizziness with a curious sensation creeping up the left side of his body, associated with a very curious smell that he could not identify (uncinate attacks). They lasted for a period of three months and then ceased. For one month he had had exceedingly severe right-sided headache of a paroxysmal nature and for three weeks he had vomited. On examination he was an obese man with depressed libido for many years. Bilateral optic atrophy, no anosmia. *Visual fields.*—Very incongruous. Left eye: Vision was lost except for a crescent which ran across the superior temporal and nasal quadrants. Macula vision was lost. Right eye: A clear-cut temporal hemianopia sparing the macula (fig. 6).

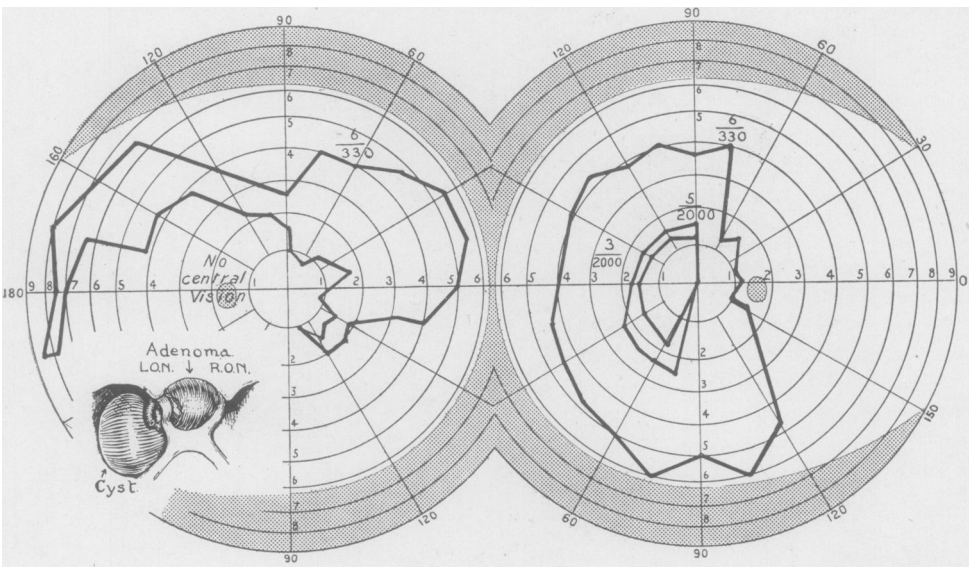


FIG. 6 (Case 6).—Visual fields.

Complete destruction of the sella turcica and of the left anterior clinoid. Cerebrospinal fluid protein 120 mgm., fluid xanthochromic at first puncture. No pyramidal signs. Subjectively a slight impairment of memory for proper names for a long time past. He was inclined to be somnolent. There was no sign of involvement of the nerves in the cavernous sinuses. This was evidently a massive pituitary adenoma with a left temporal extension. Ventriculography did not show the 3rd ventricle very clearly in the lateral view but in the antero-posterior the 3rd ventricle was shortened and pushed to the right.

A left osteoplastic flap was turned down which disclosed a rubbery asymmetrical pituitary adenoma under the left optic nerve, with a large cystic extension in the left temporal lobe. Recovery.

Protusion into the Cavernous Sinus

It must have struck all observers of pituitary tumours as curious that there are not more often signs of pressure on the cavernous sinuses and the nerves within them. There is something unexpected in the way in which a pituitary adenoma burrows into

the bone of the sellar bed and so rarely gives evidence of extending laterally where the boundaries are membranous. The fact is that the tumours do, actually, press heavily laterally, but that the structures there are sufficiently elastic to adapt themselves. Were it not so, oculomotor palsies and trigeminal anæsthesia would be as common a result of pituitary tumour as of cavernous aneurysm. In the latter the nerves are enclosed in the same sheath as the artery, and cannot escape. But there are often minor signs of involvement of the oculomotor fibres in the form of transient or persistent diplopia (e.g. Cases 7, 10); a frank paralysis of one or other nerve is rare. Trigeminal anæsthesia has, in my own series, been a definite sign that the adenoma has broken through into the cavernous sinus, and is important and grave evidence. Sensory changes in all three trigeminal divisions is a sign of invasion of Meckel's cave and perhaps of the sensory root (*see* Case 9). Although the nerves and vessels are never eroded by the tumour cells, a definite break-through into the cavernous sinus is, in my view, the certain criterion of malignancy. A prognostic distinction must be drawn, therefore, between the signs of protrusion of an encapsulated adenoma on the sinus, and those of actual invasion. An oculomotor palsy or paresis, as opposed to trigeminal anæsthesia, is not necessarily a bad sign. Case 7 illustrates this fact.

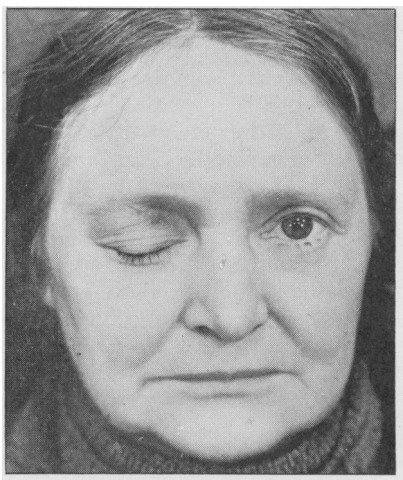


FIG. 7 (Case 7).—Chromophobe adenoma. Paralysis of right third nerve.

Case 7.—Chromophobe pituitary adenoma.

Bitemporal hemianopia. Right 3rd nerve palsy. Operation. Recovery of oculomotor paralysis.

E. N., female, married, aged 55, was admitted July 16, 1932, referred by Mr. Sumner of Preston. She complained of failure of vision and drooping of the right upper eyelid. Menstruation had ceased six years previously. For the last two years her eyesight had been failing, and three months ago the right eyelid had slowly closed after a short period of diplopia. She had had considerable headache, bitemporal and right frontal in distribution.

On examination she was a woman of medium build, right-sided ptosis being a striking feature (*see* fig. 7). There were no gross endocrinal disturbances except glycosuria which had been known to be present for the past three years and was accompanied by polyuria and polydipsia. She had bilateral optic pallor with a bitemporal field defect, scotomatous on the right side. There was complete paralysis of the right 3rd and 4th cranial nerves but not of the 6th. There was no anæsthesia in the distribution of trigeminus, the corneal reflexes being brisk. She had, however, suffered considerably from pain in the right forehead and cheek, with occasional neuralgic pains

in the right upper gum. This, together with the oculomotor paralysis, was suggestive of a saccular aneurysm of the right internal carotid artery in the cavernous sinus. There was no bruit. Radiographs of the skull showed considerable enlargement of the sella (2·7 cm. antero-posteriorly by 2·0 cm. deep); in addition the anterior clinoid processes were ill-defined and there were small areas of calcification below the level of the pituitary diaphragm. The sphenoidal fissure was not enlarged; it is apt to be so when an aneurysm rather than a pituitary tumour is present. Laboratory tests: Basal metabolic rate plus 8. High fasting blood-sugar, 117 mgm.%. Retention of sugar on oral administration of 50 grm. of glucose—260 mgm. after one hour, 246 mgm. at the end of the second. Urine loaded with sugar after two and a half hours. Ordinarily her urine contained sugar.

Comment.—Diagnosis was by no means easy. The glycosuria was more suggestive of a pituitary adenoma than of an aneurysm, but it might have been unrelated to her present condition. The bitemporal hemianopia indicated, as it always does, chiasmal compression without in any way certifying the nature of the lesion producing the visual disturbance. Pain in the forehead and teeth is much rarer with pituitary adenomas than with aneurysms. The one really certain point was the enlargement of the pituitary fossa, but here again there were flakes of calcification that might have been in the carotid wall. The precise nature of the tumour remained uncertain until the actual operation, when a large non-pulsatile swelling was seen between the optic nerves. On puncture with a needle clear yellow fluid was withdrawn demonstrating that she had a pituitary cyst. The capsule was incised and its contents rapidly evacuated by the sucker after some soft tissue had been punched out for microscopy. The tumour proved to be a cystic chromophobe adenoma.

Within three months of the operation the ptosis of the right lid and the oculomotor palsy in general had completely recovered. Eight years later she continues in good health with good vision, and without glycosuria.

The prolonged survival of this patient shows very clearly that the adenoma could have been in no way malignant. The most likely explanation of the oculomotor palsy is that there was a localized " nubbin " of tumour indenting the right cavernous sinus but without actual infiltration (i.e. that it was still encapsulated).

In a further case a similar recovery occurred, this time spontaneously, and the patient again remains well ten years later. In this patient the tumour must have very little intrinsic growth urge.

Case 8.—The writer was called to see a doctor, aged 25, who had during the night suddenly awakened with a severe pain in the head and had rapidly become stuporous. He had been in failing health for a year or more.

On examination he was seen to be a heavy-featured young man turning restlessly in bed in a darkened room. There was an oculomotor palsy on the right side. Lumbar puncture disclosed heavily blood-stained cerebrospinal fluid. No very detailed examination was possible.

A diagnosis of presumed aneurysmal subarachnoid hæmorrhage was made. He was not seen again for some months. In the meanwhile he had made a good spontaneous recovery and had been under the care of Dr. Gordon Holmes, who diagnosed acromegaly with hæmorrhage into the tumour breaking through into the cranial cavity.

Comment.—There is no doubt that this diagnosis was correct. X-rays taken later showed a gross enlargement of the sella turcica, and his features were those of an acromegalic, but not a very pronounced one. This was the first time that an important hæmorrhage into an adenoma had been seen, and it provided a very salutary clinical lesson. So vascular are many adenomas that the wonder is that hæmorrhages are not more common.

Voss (1938) has published an excellent photograph of a pituitary adenoma full of recent blood. This had caused a severe subarachnoid hæmorrhage. In another case again (Olivecrona's, described by Hanke, 1939) there was a subdural hæmatoma surrounding a pituitary adenoma. My own, together with these two cases, are the only ones known to me in which bleeding has led to clear-cut signs.

I am enabled by the courtesy of Dr. Susman to illustrate another intact pituitary tumour with a suprasellar extension (fig. 10). This shows well the break-through of adenomatous tissue (here the chiasma is post-fixed), again compressing the 3rd nerve. This adenoma is no doubt malignant because the cavernous sinus is invaded. (This question is further discussed below.) Fig. 11 illustrates the cutting into the dorsal surface of the chiasma by the anterior cerebral arteries—that, in the writer's view, so important cause of visual loss in the inferior fields of vision in old-standing cases. Herniation of tumour tissue beneath an optic nerve itself has been already shown (fig. 6), but fig. 11 shows something further, not previously described, compression of the outer fibres of a splayed-out optic nerve by a trans-capsular sprout of adenoma. The patient was blind in that eye.

We may well wonder how far these herniations of tumour tissue are malignant. They are evidences of considerable tension and proliferative strength within the adenoma, but Case 7 has proved that even if there is such a protuberance of tumour within the cavernous sinus the patient may survive for years. When, however, the adenoma cells actually break into the cavernous sinus we should be justified in regarding the tumour as locally malignant, and call it a malignant adenoma.

The Malignant Adenoma

Reference has earlier been made to the nature of the pituitary adenoma, and emphasis laid on the probability of hormonal stimulation as the basic causal factor. It was pointed out that the early title of " strumous adenoma " had the advantage of suggesting an origin different from that of true blastomas. Yet once formed it seems probable that the adenomas pursue an independent existence (like blastomas). The reason why some grow slowly, some reach a certain size and then stop, whilst others grow increasingly, may never be known. Variability must depend on fundamental cell growth urgencies, the fact of which we may record but for which there is no particular reason. Any attempt to explain the reasons for growth must fail because the search brings us back to the nature of cell vitality itself, back, that is, to the final fact of growth behind which is nothing else, no further reason (what philosophy calls " the final irrelevance "). If we were able to prove that extra-pituitary influences of a hormonal or biochemical nature (the influences, in a word, of total bodily activity in which the pituitary, or what of it is undamaged, plays a part) were continuous in some cases and not in others we should still know no more of the actual *nature* of the growth process though we might be more satisfied to think that we had a *reason* for it. So far as we know such influences are not continuous and the adenoma is the by-product of a glandular activation which is over. In the eosinophilic tumours of acromegaly the parallelism between the toxicity of the adenoma and that of the thyroid in Graves' disease forces itself upon us, even to the point of inconsistencies in the size of gland and the severity of the toxic effects. In neither disease can we pretend to have a deep understanding of the principles by which the disorder of cell function has come about. What can be said is this, that as a result of stimulation to activity the endocrine glands of some persons may be driven to completely disordered action, and that such anarchical behaviour as regards the welfare of the organism as a whole is an inherent potentiality of these glands; beyond this fact search of the gland itself can reveal nothing. We must always be wrong if we study one organ alone for causality without regard to its relationship in total bodily economics.

It has been clearly shown by the cases already presented that some pituitary tumours come to burst their envelopes and to form smaller or larger sprouts through them. Often these are very small, and, unless they happen to press upon one optic nerve, locally on the chiasma, or to bulge into one of the cavernous sinuses, they do nothing to denote their presence. We should scarcely be justified in classifying such protrusions as signs of malignancy, for they give the impression of being mechanical

in origin, in the sense that they have developed as mere herniations because of the unequal density of the tissues which form the pituitary capsule. Yet there are two points that must not be overlooked; first, the fact that the capsule has been broken fulfils one of the conditions by which we classify malignant tumours, and secondly, the very fact that such breaches of the capsule have occurred indicate that the growth pressure inside the tumour must be high. It is true that cyst formation might raise the internal pressure, as might hæmorrhage, but the latter at least indicates a vessel structure which is tending to malignant type.

As for local infiltration of neighbouring tissue as a sign of malignancy, there are special difficulties. The pituitary is surrounded by structures which do not easily lend themselves to invasion. Superiorly the chiasma and the brain-mass are remarkably resistant to infiltration except by a tumour derived from their own proper tissues (cp. Trotter on the insulatory powers of the nervous parenchyma). Hence extension into the cavernous sinus and Meckel's cave are the only sign by which we can say that an adenoma shows malignancy ("malignant adenoma"). Such invasion envelops nerves and vessels without breaking through their sheaths. Malignancy is a term which must be given a different valency in different situations within the body. The ultimate death of the patient cannot be used as a standard, for within the skull a perfectly benign growth can be fatal. It is possible to trace through my own series of adenomas all degrees of growth tendency from the least to the most severe. Four of the most extravagant examples were Cases 9-12. In the background of this discussion lurks the question of pituitary carcinoma, and its relationship to the malignant adenoma. Some principles for definition must be laid down because these are, so far, lacking; the following are suggested :—

(1) The malignant adenoma is a tumour which has by its florid growth broken through its envelopes and is malignant only in the sense that tumour cells have entered into situations where they could not be if the capsule were intact. Malignant adenomas still retain a cell type which is similar to that in the smaller tumours. Invasion of the cavernous sinus would not kill, but its presence is highly significant of a continuous growth pressure or urge which probably eventually will do so. An adenoma may need years to produce such an extension. The term "malignant adenoma" is, in my view, somewhat artificial, but no more accurate designation suggests itself. This brings up very cogently the point raised earlier in this paper, that some adenomas stop growing after reaching a variable size. These are clearly non-malignant. A distinguishing line must therefore have a validity. Clinical signs alone do not always give evidence of invasion of the cavernous sinus (compare Cases 7 and 8).

(2) Pituitary carcinoma. This is a rare disease of which there is no example in this series. The diagnosis can only be made from the total effects of the tumour: (*a*) short history, (*b*) presence of extension, and especially of invasion of the cavernous sinus, (*c*) the presence of metastases[7] carried either from the cavernous sinuses into the blood-stream (e.g. Cushing's, Dudde's cases) or in the spinal fluid and subdural spaces (e.g. Cagnetto's, Cushing's cases), (*d*) from the cell type. There is no doubt that, as regards cell type, the Rathke pouch tumour is much the more easily recognized as having strong malignant tendencies. Erdheim himself classified these "hypophysenganggeschwülste" as existing in two forms, benign and malignant. The anterior-lobe carcinomas are more difficult to describe with a precision that can be clearly appreciated. This emerges very definitely from the attempts that have so far been made. A hard nodular cancer like that of the thyroid has not yet been met. It might exist. Pituitary cancer is said to be distinguished by the lack of pattern

[7] As for bone metastasis, I have operated upon one case, a woman aged 57, with a short history of paraplegia, and found a tumour invading the 6th thoracic vertebra that was returned histologically as a pituitary adenoma. She had no ocular or cerebral manifestations and necropsy was not obtained. Because of the uncertainty of present-day opinion as regards the possible pictures of malignant bone tumours, no certain conclusions can be drawn from this case. It is mentioned tentatively now.

in its cells, irregularity in cell grouping, highly chromatic nuclei, mitosis, and scant cell protoplasm. The more ordinary adenoma itself shows such great variations, as the work of Erdheim, Dott and Bailey, E. J. Kraus, and Berblinger clearly shows, that this description lacks a distinguishing crispness. In the long run metastasis must remain the most certain sign of malignancy ; no argument is possible about cases of this sort. The limitations of the site of the metastasis possibly to a pituitary carcinoma have been indicated above. The malignant adenoma, on the other hand, marks the extreme of activity possible to an adenoma, short of actual metastasis, but includes the possibility of extension into the cavernous sinus.

Having accepted extension into the cavernous sinus as the most certain definition of a malignant adenoma, might not metastasis easily follow from the entrance of cells into the veins ? If that were so then the boundary line between the malignant adenoma and pituitary carcinoma would disappear. It is the fact, however, that

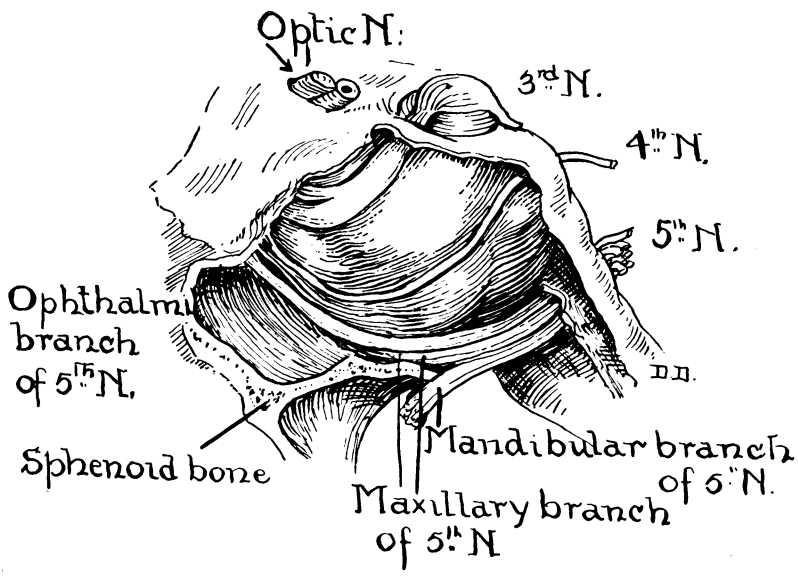


FIG. 8 (Case 9).—Dissection of cavernous sinus to illustrate compression of the nerves by an adenoma.

adenomas do not erode the venous sinuses ; furthermore, in order that a metastasis should survive the cells must retain very great vitality. There is little doubt that for every metastasis that forms many must be destroyed by local reaction. The distinction here made between the types seems to be well founded. Pituitary malignancy is, therefore, of a type peculiar to the organ of its origin, and does not obey the general rules which we apply to carcinoma and sarcoma elsewhere. It illustrates something that is, in my submission, a most important and generally unrecognized fact—that all malignant tumours are specific to their sites and have life-histories and behaviours dependent on that origin. The pathologist tends to a simplification which does not exist in nature when he draws up rules which, he says, malignant tumours obey. To impose such a view is to imagine an abstraction separated from the actual facts of observation.

In Case 9 opportunity arose for dissection of the cavernous sinus and for verification of the relationship of the nerves in the cavernous sinus to the tumour. Although the history of amenorrhœa for twenty-four years would indicate that the adenoma had long been present, at post-mortem it was found to be of malignant type. This case, together with the remaining three malignant adenomas, will be described in brief.

Case 9.—E. G., female, single, aged 44, was admitted complaining of amenorrhœa and failing vision. Menstruation started at the age of 14 but was always scanty and irregular until it ceased at the age of 20. Failing vision. Bitemporal hemianopia. X-ray indicated a large chromophobe adenoma. No oculomotor palsy. Trans-sphenoidal decompression. Primary recovery. Death from sudden meningitis seven weeks later. Post-mortem: Adenoma found to infiltrate the left cavernous sinus. Fig. 8 shows the cavernous sinus dissected with the adenoma pressing heavily on the nerves contained in its walls. It may easily be imagined that diplopia should be a common event given an adenoma of any size.

Case 10.—N. R., female, aged 24, with an acromegalic appearance, was admitted to the Neuro-Surgical Service of the Manchester Royal Infirmary on October 3, 1931, complaining of failing vision and headache. She dated her illness back to five years ago when her menstruation ceased, diplopia developed, and she became extremely thirsty, passing large quantities of pale urine. Webet's syndrome. Left trigeminal anæsthesia. Glycosuria. Death. Necropsy: Hugé suprasellar extension (retro-chiasmal) of a chromophil adenoma. Infiltration of left cavernous sinus and Meckel's cave into trigeminal root (*see* fig. 9).

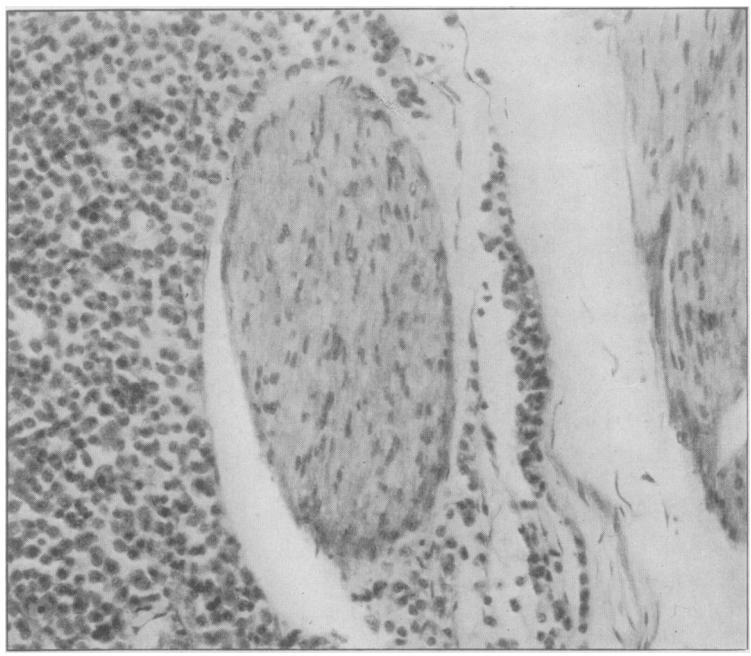


FIG. 9.—Malignant adenoma surrounding nerves in cavernous sinus.

Case 11.—Mrs. G., aged 29, was admitted to the Queen's Park Hospital, Blackburn, November 12, 1937, as a case of acromegaly. She was in very poor general condition and died a month later. She showed evidence of acromegaly and had failing vision, with spasmodic pains in the face. Death. Necropsy: Huge intracranial extension extending into posterior fossa. Infiltration of right cavernous sinus and cavum Meckelii.

Case 12.—R. G., aged 19, male, was referred by Dr. McKibbin of Liverpool on account of severe headaches and bilateral optic atrophy. Some eighteen months previously he had been admitted to a hospital on account of ophthalmoplegia of the left eye and defective vision. Malignant pituitary adenoma. Bilateral 3rd nerve paresis. Bilateral optic atrophy. Involvement of the left trigeminal nerve. Trans-sphenoidal verification. Deep X-ray therapy. Death from tuberculous pneumonia. Adenoma infiltrating both cavernous sinuses and spreading in the dura of the left middle fossa and over clivus into posterior fossa.

Ventriculography in Cases of Pituitary Adenoma

By the careful radiographic study of sellar shape and sellar size a very accurate measurement of the basal or intrasellar part of the tumour can be made. Its extrasellar extension can be gauged with approximate accuracy from (1) the visual acuity, (2) the visual fields. When acuity is bad and the field pattern either bizarre or difficult to interpret, and, in general, when there is anxiety as to the size of the tumour, pneumography is of great value. I have used it in 15% of the pituitary adenomas and tend to use it now more often still (especially by cisternal encephalography). It is only thus that a clear conception of tumour size can be arrived at. Two clear indications for its use can be laid down. First, when the visual symptoms are recent and yet the size of the sella suggests a very large tumour. Second, when the sella is not deeply excavated and yet the symptoms and signs indicate a chiasmal lesion of considerable size. Fig. 12 shows the latter point so well that further comment is unnecessary, save to add that great size is a strong discouragement to operation, especially when it discloses a massive tumour rather than a narrow-necked extension. Cairns (1932) has very properly pointed out the dangers of operating on long-standing tumours with poor vision and advanced optic atrophy, for improvement is unlikely and there is a strong prospect of fatality. With this view I am in complete agreement. Not only may the tumour be of parenchymatous type and difficult to remove, but even should it be soft the capsule fills with clot and a very stormy convalescence can, at best, be expected.[8]

Influence of Extension on Clinical Picture

The chief purpose of this paper has been to focus interest on the growth pattern of the adenomas. It would overburden any message that it contains if a long analysis of clinical variants were added; the most important symptoms and signs have been given at length in the 12 illustrative cases. A brief commentary should suffice.

Endocrinal changes.—These are no different from those in the smaller tumours. In some of the patients with extensions or with massive tumours and long histories the somatic and skeletal alterations are more pronounced because the endocrinal factors have had longer time in which to act. Glycosuria, for example, has been more common. Whether this will prove to hold true when more cases have been collected remains to be seen, for it is a little surprising that it was so. It might have been thought to have been due more to the acuteness of the endocrinal upset than to its duration, and that may be true even with the present cases.

The visual fields.—The importance of post-fixation of the chiasma on the visual field pattern was shown by Case 3, where it was normal in spite of the presence of a large tumour. Papilloedema was present in this case at one time. Wagener, Woltmann, N. N., and Love (1939) have recorded a similar case, also with post-fixation. Except in cases such as these, prefixation is difficult to establish except by the ventriculographic method, which has an important, and hitherto unsuspected, usefulness, in this respect.

The effects of prefixation have been mentioned. Balado (1937) pointed out that macular sparing was the rule with the average bitemporal hemianopia of pituitary enlargement. He agreed with Cushing (1930) that the macular fibres decussate in the posterior part of the chiasma. The converse effect of bilateral macular scotomas should mean that the tumour was either behind the chiasma or that it extended well back beneath it. Cushing had come to much the same opinion as a matter of

[8] The reason why these old-standing cases are so unpropitious can be summarized as (*a*) because the tumour is very likely to possess an extension and (*b*) for reasons remarked earlier the main tumour mass is likely to be retro-chiasmal. Even if there is no extension in its anatomical sense the tumour will usually be massive and irreparable damage to the optic nerves and chiasma will have been occasioned on the one hand by tumour pressure, on the other by the cutting into the chiasma of the anterior cerebral and communicating arteries.

observation at operation, an idea supported by Henderson's later study of the same material. My own cases confirm this view, though it must be admitted that the intrachiasmal course of the macular fibres is not yet known with complete certainty. The possibility of a large tumour forming behind a pre-fixed chiasma has been alluded to, as well as the possibility of tract, rather than chiasmal compression occurring in such cases with a resulting homonymous defect. Fig. 5 shows that prefixation is not an absolute necessity to homonymous defects; this specimen is a valuable corrective to speculative reasoning. No example of hemianopia due to indentations of the temporal lobe has occurred in this series. Study of this figure suggests something more. Since the lesion as it passes into the temporal lobe must always compress the optic tract, distinction between the two types would seem to be invalid. When the chiasma is more normally placed an extension or a massive tumour leads to the deep cutting of the anterior cerebral arteries into the dorsal surface of the

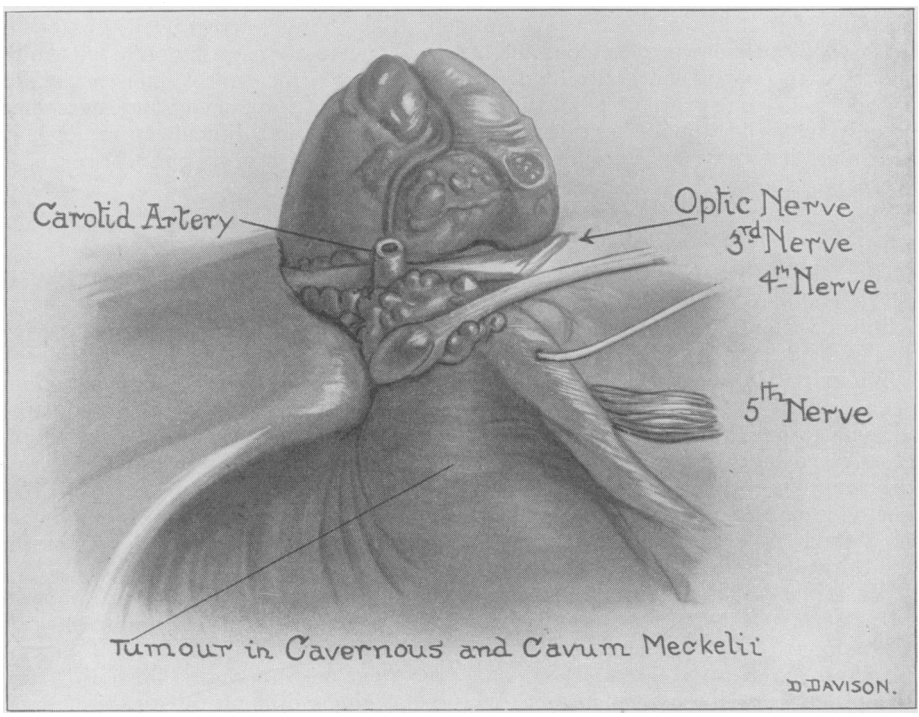


FIG. 10.—Malignant adenoma invading cavernous sinus and surrounding carotid artery. Compression left third nerve.

chiasma (*see* fig. 11). This has always seemed to me to be a much more probable reason for the cutting off of the fields of vision inferiorly than a supposed kinking of the optic nerves against the upper margins of the optic foramina. Indeed, what with the tumour below and these arteries constricting the chiasma above, it is remarkable that the chiasma is not earlier completely blocked to light impulses. The importance of local protrusion in producing a unilateral central scotoma has been mentioned.

Diplopia.—Diplopia is not an indication of extension. It is a common symptom. It is due to pressure on the medial walls of the cavernous sinuses, much thinner than the outer. Pressure on the oculomotor nerves leads to that slight inco-ordination

of ocular movements which is sufficient to cause diplopia without there being any easily discernible lack of parallelism of the eyes.

Oculomotor palsy.—This is generally, but not invariably (cp. Case 7), a sign of invasion of the cavernous sinus, a sign that is, in the classification suggested above, of the " malignant adenoma ". The 3rd and 4th nerves suffer much more often than the 6th, which is protected from pressure by the carotid artery, on the outer side of which it lies. Cases besides the three here have been reported by Strumpell, Borchard, Castiglione, and others (*see* Atkinson, 1932), and by Sjöquist, 1936. As in Case 10 it may be associated with hemiparesis as Weber's syndrome.

Trigeminal anæsthesia.—Three beautiful examples have been given of infiltration of the trigeminal root by malignant adenomas. No purely benign adenoma ever produces it. The importance of trigeminal hypoæsthesia as an indication of the nature of the tumour cannot be over-estimated.

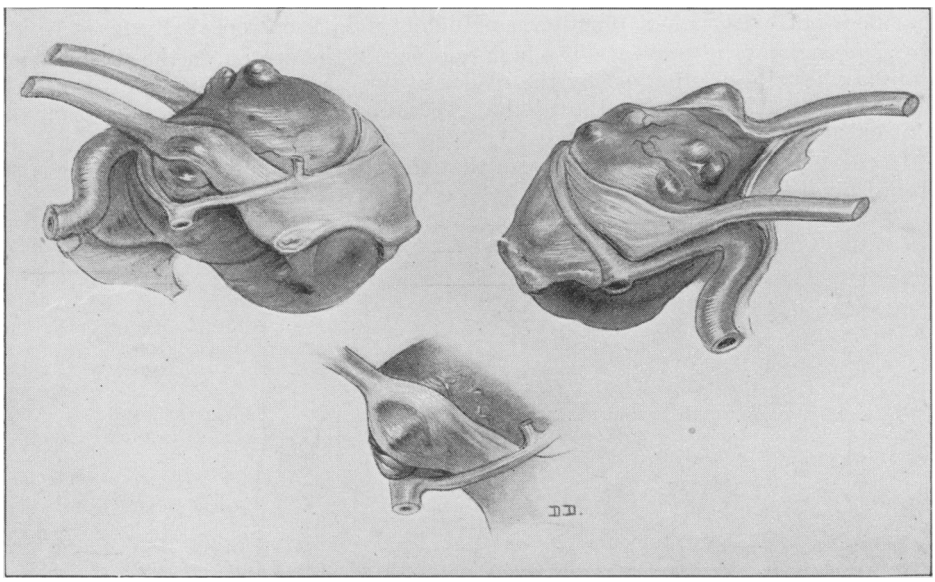


FIG. 11.—Chromophobe adenoma, herniation of adenoma compressing the outer fibres of left optic nerve (left eye blind). Compression by anterior cerebral arteries on dorsum chiasmatis.

Epilepsy and mental changes.—Fits would be expected in at least half the cases with frontal and temporal extensions. With temporal extension a lesion situated in the sella and passing outwards is ideally situated to impress the uncus. It is significant that uncinate fits were an early feature in the two cases with temporal extensions in this series. The frontal fits were of the usual pre-frontal type, without aura or with dizziness only, and the convulsions were generalized.

Hypothalamic signs.—The lethargy and mental hebetude described by so many writers as characteristic of pituitary tumours are, in the writer's opinion, overdue for correction. It is by no means a constant or even a common feature with small adenomas, whatever their type. It cannot therefore be due to the endocrinal disorder itself, except in a minor form. When it becomes a feature of the patient's state it is due either (*a*) to extension upwards into the cranial chamber, or (*b*) to loss of visual perception. In the former case the retardation is due to neural or circulatory

abnormalities produced by the tumour mass, in the latter to that general slowing down which is so characteristic of severe visual impairment. The effects of loss of vision in animals on total bodily activity have been investigated in recent years and found to be of great importance. Such contribution to the state as is made by the endocrinal disturbance of hypopituitarism must be of the same order, for lack of the normal hormones clearly has general effects and cannot be thought of in pituitary terms alone. It may be urged that hypersomnia as distinct from lassitude and a general preference for idleness predicates a lesion of the hypothalamic sleep centre (*see*, for example, Globus 1940). To differentiate between hypersomnia and general hebetude is artificial. They must all be part of one general process. In Case 1 where hypersomnia was a feature, there was a localized hypothalamic extension (fig. 3), but also pressure was very high within the skull. It is not intended to deny that there is an area in the hypothalamus the destruction of which leads to hypersomnia, for the fact that lesions there have led to somnolence is well attested. One thing is certain, that the areas destroyed cannot have been the sleep centre, since what does not exist cannot function, as Hughlings Jackson repeatedly insisted.

Cerebrospinal fluid protein.—The high quotient of the protein in the cerebrospinal fluid may have been observed by the reader in two of the cases quoted. It will be worth while to give some of the results, especially because no information on this point exists.

In the following table it will be seen that the larger the tumour the higher is the cerebrospinal fluid protein.

LUMBAR C.S.F. PROTEIN ESTIMATION.

	Sex	Age	Proteins mgm.%
Acromegalics	F.	47	45
	M.	50	50
	F.	42	100
	F.	35	20
Chromophobe adenomas			
A. Small tumours ..	M.	60	45
	F.	48	35
	M.	29	25
	F.	52	30
	M.	42	65
	F.	39	25
B. Large tumours ..	M.	57	140
	M.	54	100
	M.	60	70
	F.	46	95
	F.	55	160
	M.	34	150
	M.	41	200

There is a protein rise whenever a tumour has access to the cerebrospinal fluid, whenever it has the opportunity of excreting its metabolites into it, whenever capillary oozing may be contributed to it. Surface area must play a considerable part, and a small tumour with a high protein cerebrospinal fluid count is probably a very active one.

Effect of extension on operative mortality.—In most cases with a large extension operation is a course of doubtful wisdom. In a series of 128 adenomas, the writer's own mortality was 2·0% for the small adenomas (one death from extradural post-operative hæmatoma, one presumably from avertin) for 98 cases. In those with extensions the mortality was 33%, 4 out of 12 cases operated upon. The other cases with extension were left alone. The operation on the small pituitary adenoma is so gentle a procedure that theoretically there should be no mortality; actually

the mortality is slight. The danger of delaying operation whilst prolonged X-ray therapy is tried in an early and favourable case is clear. If the adenoma grows and forms extensions the risk of operation increases. Finally, operation on old-standing and massive tumours is not often profitable to the patient. The severe changes in the chiasma brought about by prolonged and increasing compression are irremediable. The study of some of the illustrations shows the hopelessness of their problem.

It is impossible to give an accurate percentage figure of incidence of extrasellar extension; Henderson states that there were 51 in Cushing's 365 adenomas (about 1 in 7). There were 18 cases in the present series (of which 12 were described), the only truly verified examples in 128 cases, a similar incidence. I should estimate it therefore as occurring in some 14% of adenomas, a fairly high ratio.

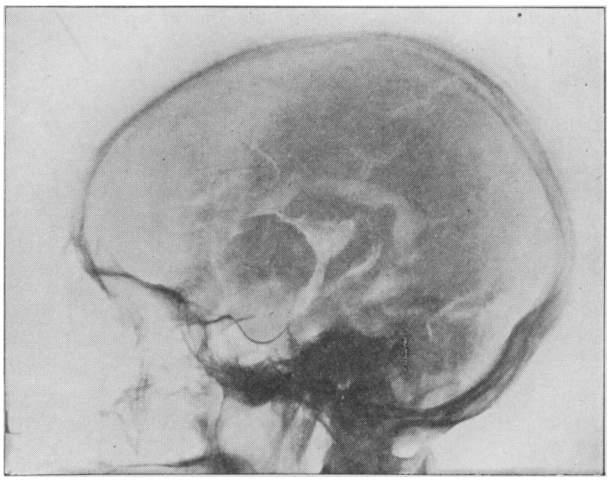


FIG. 12.—Encephalogram of suprasellar extension. No depression of sellar floor.

CONCLUSIONS

The foregoing account has been an attempt to broaden the conventional description and to correct too didactic a formulation of the nature of the pituitary adenoma, to account for variations in symptomatology, and to give reasons why operation is sometimes, though rarely, attended by ill-success. Detailed information on all the relevant points does not yet exist in sufficient volume to allow of an infallible interpretation of the biological history of these tumours. None the less, even in the malignant cases, the histories tend to be so long that the adenomas remain a thoroughly worth-while field of surgery. All writers hitherto have shown a disinclination to define exactly the criteria of pituitary malignancy. So far as reliance is placed on differentiation by cell structure alone ambiguity would have remained. An attempt has been made here to designate malignancy with more precision. It has been shown that the growth tendency of the adenomatous cells is highly variable, and it might be concluded that such tumours as tended to produce massive intracranial extensions were all essentially malignant, that "extension" is but an alias for "malignancy". This is not necessarily true, for size is not an index and unless there is either invasion or metastasis a tumour, whatever its size or ramifications, or whatever its cellular structure, must be considered to be benign.

REFERENCES

ATKINSON, F. R. B., " Acromegaly ". London, 1932.
BALADO, M., and FRANKE, E., " Das Corpus Geniculatum Externum ". Berlin, 1937.
BENDA, C. (1900), Beitrage z. normalen u. patholog. Histologie d. menschlichen Hypophysis cerebri, *Berl. klin. Wchnschr.*, **37**, 1205.
BERBLINGER, W. (1936), Die Adenome d. Hypophyse, *Nervenarzt*, **9**, 329.
CAGNETTO, G. (1904), Alterazione del midollo spinale in an caso di acromegalia, *Riv. sper. di freniat.*, **30**, 267.
CAIRNS, H. W. B. (1932), The Prognosis of Pituitary Tumours, *Lancet* (ii), 1310–1363.
CASTIGLIONE, G., quoted by Atkinson.
CROOKE, A. C. (1935), Change in Basophil Cells of Pituitary Gland Common to Conditions which Exhibit the Syndrome Attributed to Basophil Adenoma, *J. Path. & Bact.*, **41**, 339.
CUSHING, H., " The Pituitary Body ". Philadelphia, 1912.
Id. (1930), The Chiasmal Syndrome, *Arch. Ophth.*, N.S. **3**, 505, 704.
DOTT, N., and BAILEY, P. (1925), Hypophysial Adenomata, *Brit. J. Surg.*, **13**, 314.
ERDHEIM, J. (1925–26), Pathol. d. Hypophysengeschwülste, *Ergebn. d. allg. Path.*, **21**, 482; see also *Beitr. z. path. Anat. u. z. allg. Path.*, 1903, **33**, 158, and again 1904, **35**, 366.
FLESCH, M., " Tagebl. auf d. 57 Deutscher Naturforscher u. Aerzte ". Magdeburg, 1884, p. 195.
GLOBUS (1940), Probable Topographic Relations of the Sleep-regulating Centre. *Arch. Neurol. & Psychiat.*, **43**, 125.
HANKE, H. (1939), Das subdurale Haematom, *Ergebn. d. Chir. u. Orthop.*, **32**, 1.
HENDERSON, W. R. (1939), The Pituitary Adenomata, *Brit. J. Surg.*, **26**, 811.
JEFFERSON, G. (1937), Removal of Right or Left Frontal Lobes in Man, *Brit. M. J.* (ii), 199.
KRAUS, E. J. (1926), Die Hypophyse, *Handb. d. spez. path. Anat. u. Histol.*, Hanke and Lubarsch, Vol. 8.
LOEWENSTEIN, C. (1907), Die Entwicklung d. Hypophysisadenoma, *Virchows Arch.*, **188**, 44.
MCCONNELL, A. A., and MOONEY, A. J. (1938), On Normal Discs in Patients with Chiasmal Lesions, *Brain*, **61**, 415.
RASMUSSEN, A. T. (1933), The Percentage of the Different Types of Cells in the Anterior Lobe of the Hypophysis in the Adult Human Female, *Am. J. Path.*, **9**, 459.
Id., " The Pituitary Gland ". Baltimore, 1938, p. 118.
DE SCHWEINIIZ, G. E. (1923), The Bowman Lecture, *Tr. Ophth. Soc.*, **43**, 12.
SCHOENEMANN, A. (1892), Hypophysis u. Thyroidea, *Virchows Arch.*, **129**, 319.
SEVERINGHAUS, A. E. (1933), A Cytological Study of the Anterior Pituitary of the Rat, &c., *Anat. Rec.*, **57**, 149.
Id., " The Pituitary Gland ". Baltimore, 1938, p. 69.
SJÖQUIST, O. (1936), Ueber intrakranielle Aneurysma d. Arteria carotis, &c., *Nervenarzt*, **9**, 233.
TROTTER, W. (1926), The Insulation of the Nervous System, *Brit. M. J.* (ii), 103.
VOSS, O. (1938), Beitrag z. Hirnblutung an d. Schädelbasis, *Deutsche Ztschr. f. Chir.*, **250**, 727.
WAGENER, H. P., WOLTMANN, H. W., and LOVE, J. G. (1939), Pituitary Tumour associated with Choked Disc and Normal Peripheral Fields of Vision, *Proc. Staff Meet., Mayo Clin.*, **14**, 417.