SOME CLINICAL FEATURES OF THE PITUITARY CHROMOPHOBE ADENOMATA AND OF THE RATHKÉ POUCH CYSTS

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by
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MUCH HAS BEEN written on the subject of the chromophobe pituitary adenomata. Henderson's (1939) paper describing in detail, and from the point of view of the patient's vision, the results observed in Harvey Cushing's cases will stand for all time as a landmark in the growth of our knowledge of this condition. Adopting a rather different emphasis, I propose to bring before you some facts indicating the frequency and the importance of many of the better known signs which occur in this disease. This is not a rounded clinical presentation of the chromophobe adenomata or of the Rathké pouch cysts, for the general features of these diseases are well known. Emphasis will be laid upon the symptoms of abnormal metabolism which may frequently and for so long precede visual failure and upon the long survival which often follows treatment. The patients and the case records which have been studied are mainly those of the late Professor Sir Hugh Cairns and of Mr. Joe Pennybacker. I am indebted to the foresight of Professor Cairns in insisting on the meticulous recording of clinical data and to Mr. Pennybacker for allowing me access to this wealth of material. (A few cases in the series were under the care of Mr. W. S. Lewin, and I am grateful also to him for permission to include them.)

MATERIAL

The material to be described concerns 131 patients with a pituitary chromophobe adenoma; of these the lesion was histologically verified on 121 occasions. The remaining ten cases are included because there were firm clinical and radiological grounds to sustain the diagnosis and they possessed features of special interest. Of fifty-seven patients with a Rathké pouch cyst, the lesion had been histologically verified in thirty-three, and in the remaining twenty-four the radiographs showed typical suprasellar calcification. Several patients have been rejected from consideration because of insufficiently accurate information about the pathological process. Of those patients included in the study I have personally examined fifty-two with a chromophobe adenoma and eighteen with a Rathké pouch cyst. Information up to April 1956 has been obtained about all but three of these patients, which is equivalent to a satisfactory follow-up obtained in over 98 per cent.

The average age at which patients with a pituitary chromophobe adenoma required surgical treatment was forty-one years for the males

and forty-four years for the females. Some patients with a Rathké pouch cyst did not require surgery at any stage so, in this group, the age at which admission to hospital for full assessment became necessary has been selected to provide a comparable figure. For the males it was twenty-five years and for the females it was twenty-six years.

Patients with a Rathké pouch cyst have been subdivided into those with compression of the visual pathways as the outstanding feature (" visual " group) and those in whom other symptoms were the cause of hospital admission (" non-visual " group). Naturally, there were several differences in the clinical characteristics of these two groups of patients, but they will not be explored here. For the moment attention, with regard to Rathké pouch cysts, must be confined to patients whose symptoms were primarily those of compression of the visual pathways and who, thus, bear comparison with the patients with chromophobe adenomata.

From Figure 1 it can be seen that the age of the patient alone plays a large part in helping to decide whether a given patient harbours a

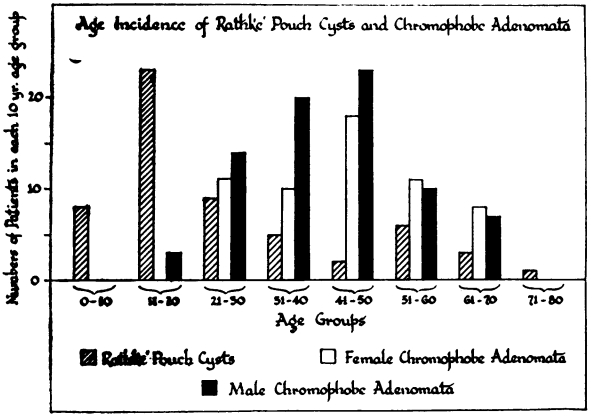

Fig. 1. To show numbers of patients with chromophobe adenomata or Rathké pouch cysts admitted to hospital. Patients divided into ten-year age-groups; chromophobe adenomata subdivided into males and females, Rathké pouch cysts undivided.

chromophobe adenoma or a Rathké pouch cyst. This method of differentiation is most applicable to the young patient (the youngest female patient with a chromophobe adenoma requiring operation was twenty-four years, and the youngest male was eighteen years), but with the older patient it must not be forgotten that a Rathké pouch cyst, although a congenital lesion, may be entirely dormant until, as in one man in this series, the age of seventy is reached.

In half of the male patients with a chromophobe adenoma there was sparseness of the facial hair. Such patients found it necessary to shave less frequently than normal in order to keep themselves presentable, in

addition they may not have found it necessary to begin shaving until later in life than their normal colleagues. Rarely, growth of the beard was normal initially, but as the disease progressed the patients became aware of reduced facial hair. Sometimes, sparse facial hair was associated with a definite lack of body hair in general. It is a most curious thing that when this subnormal " hairiness " occurs in a male patient with a chromophobe adenoma it may precede by as much as forty-five years the development of visual symptoms. One patient (R.I. 6458/46) who was sixty-five when he first noticed visual symptoms, said that all his life he had shaved only twice weekly, and that he had never had any axillary hair. When he came to be admitted, he was noted to have a pale dry skin with a thin beard ; his axillary hair was absent and his pubic hair was of female distribution.

An upset in the menstrual rhythm was the commonest first symptom among the female patients. It was decided that in these patients amenorrhoea occurring before the age of forty-seven and scanty irregular menses occurring before the age of forty-two were probably manifestations of deranged pituitary function. On this basis, disordered menstruation antedated by some years the awareness of a visual disorder in exactly half the patients with a chromophobe adenoma.

Significant changes in body weight (either gains or losses) occurred occasionally at some point during the course of an illness caused by a chromophobe adenoma or by a Rathké pouch cyst. In 6 per cent. of the males and in 12 per cent. of the females, a pronounced disturbance in weight preceded visual failure. However, in the females with a chromophobe adenoma a change in weight only once preceded the onset of disordered menstruation. Because a gain in weight quite frequently follows the naturally occurring menopause, the significance of weight change in the female cannot properly be assessed.

If these prodromal symptoms (i.e., deficient body hair, amenorrhoea) be accepted as relevant, there is a striking difference between the males and the females in the duration of the history (Fig. 2.) It is plain that for the male with a chromophobe adenoma it is so common to find evidence of abnormal body hair commencing in the late teens or early twenties that the duration of history estimated by this criterion increases *pari passu* with the patient's age. For the female, the average length of history is far more closely centred about the mean for the whole group (five and a half years). The numbers of patients with a Rathké pouch cyst involved in the construction of this figure were too small to allow the sexes to be shown separately, but, in the length of their history, there was no pronounced difference between the males and the females. One example of a long prodromal history given by a female with a Rathké pouch cyst is quoted below :

Female (R.I. 130277/50), who although not diagnosed as suffering from a Rathké pouch cyst until the age of forty-seven years, had possessed metabolic

disorders for many years, for she had always been small in build, had never possessed pubic or axillary hair, and she had never menstruated.

As many as 14 per cent. of the female patients with a chromophobe adenoma had prodromal symptoms (e.g., disordered menstruation) dating from the termination of pregnancy. One patient in the series actually developed visual symptoms during the puerperium.

Female, aged 36 (R.I. 18576/41). Three weeks after the birth of her child she was busy answering congratulatory letters from her friends when she became aware of a mistiness in both temporal fields which improved after spectacles had been supplied. The significance of this transient symptom became clear five years later when progressive visual deterioriation led to an operation for pituitary adenoma.

Occasionally, in both groups of patients, head injuries or other episodes which might be expected to raise venous pressure within the lesion occurred under circumstances such that the injury appeared related to

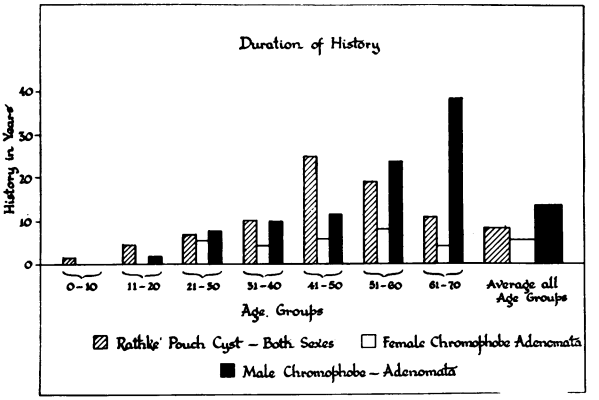

Fig. 2. To indicate duration of illness, dating onset from first "prodromal" symptom (see text). In ten-year age-groups, but with averages for whole series shown in broad columns on right.

the development of symptoms. With the chromophobe adenomata this occurred in 7 per cent. of cases, and with the "visual" group of Rathké pouch cysts in 8 per cent. of cases. How often these events are mere coincidence it is impossible to say, but in view of their frequency it seems likely that at times there is a causal relationship. Two examples will be quoted.

A man aged thirty-three on admission (R.I. 6277/40) had two years earlier struck his vertex severely against a steel girder. There was no scalp wound and no loss of consciousness, but he had severe headaches for three weeks thereafter and dated the onset of a gain in weight of two stones from this time. Six months later regularly intermittent headaches commenced. One month before admission he again struck his head without loss of consciousness, but sufficiently hard to force him to his knees. Intense headaches developed immediately, and these soon led to hospital admission. At operation, 20 ml. of blood-stained fluid were found within a chromophobe adenoma.

A female (R.I. 8045/40) aged thirty-nine had begun to use glasses for sewing four years before admission. Two years before admission her menstruation

ceased. Six months before admission her glasses were renewed because of difficulty with distant vision. Eight days before admission two teeth were extracted under nitrous oxide anaesthesia. She vomited whilst in the dental chair and, on her way home, developed a severe occipital and nuchal ache. Two hours after the extraction her eyesight became dim and this progressed in the space of an hour to near blindness with pupils fixed to light. On admission to the Radcliffe Infirmary, vision was restricted to the upper nasal fields bilaterally and the acuity was J.16 (right) and J.14 (left). At operation, two days later, a pituitary adenoma was encountered. It contained no cyst fluid, but Professor Cairns thought that there might have been a small haemorrhage in its depths.

A search was made for other factors which may have had an adverse effect on an already existing lesion. One such factor occurring in 10 per cent. of patients both with a chromophobe adenoma and with a Rathké pouch cyst was an attack of " influenza."

For example, a doctor of thirty-six (R.I. 20284/43) began to suffer from lack of energy and susceptibility to cold a year before his admission. Four months before admission ten days were spent in bed on account of " nasal catarrh." On resuming normal activities he was aware of bitemporal scotomata which interfered very little with his work. However, a week before admission there was another attack of " influenza," following which vision deteriorated so that an operation became necessary.

In none of these patients has the tissue removed at operation been cultured, and in none of them was a frank " pituitary abscess " encountered. It is known that an upper respiratory infection may spread, probably by the sphenoidal sinus, to the contents of the pituitary fossa. However, in the patients described here there is no means of assessing for certain whether the so-called " influenza " was in reality an infective process or whether it was the symptomatic expression of a vascular accident or of rapid growth within the lesion.

It is interesting that although the prodromal histories were often long, the time for which vision had been affected was for most patients only about two years (Fig. 3). However, the patients over fifty years with a chromophobe adenoma might have observed a disturbance of vision in one eye for four to five years before they came to operation. This may indicate that these tumours grow more slowly in the older patient. The older patient with a Rathké pouch cyst had a shorter history of visual failure than did his counterpart with a chromophobe adenoma, whilst for the younger patients the reverse was true. For the Rathké pouch cysts the variability in the duration of visual failure from patient to patient was rather greater than for the adenomata. Figure 3 also shows the length of time for which the patient had been aware of failure in the subsequently affected eye.

In both groups of patients an initial disturbance of vision may be temporary, and such remissions of symptoms may delay diagnosis by many years.

For the chromophobe adenomata this can be illustrated by a man (R.I. 201495/55), aged thirty-two on admission, who, nine years before, had

suffered from blurred vision of the left eye. After three months this resolved completely, and there were no further symptoms until, eleven months before operation, both eyes began to show visual failure. Once more there was a temporary improvement, but it was shortlived. At operation, the tumour contained a cyst from which 18 ml. of fluid were withdrawn, and the diagnosis of chromophobe adenoma was proved histologically.

A man with a Rathké pouch cyst (R.I. 11651/53), aged fifty-five at the time of operation, had had transient trouble with the left eye three and a half years earlier. This was a scotomatous defect and it resolved at the same time that he gave up smoking, so that the diagnosis of tobacco amblyopia was entertained until further visual failure occurred, which it did six weeks before operation.

Spontaneous remission of symptoms is, however, rare among the adenomata although it forms a relatively common characteristic of several of the symptoms with which the Rathké pouch cysts may present.

In almost exactly half the patients, both with Rathké pouch cysts and with chromophobe adenomata, headaches were a prominent symptom and, in the remainder, the headaches were either trivial or absent altogether. Occasionally the headaches may be curiously localised. For example, a

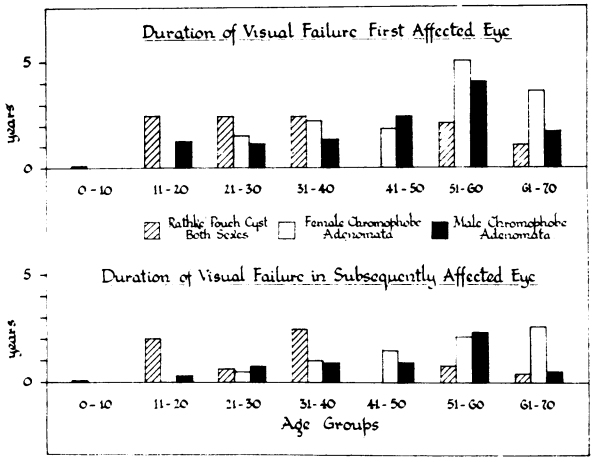

Fig. 3. (*Above*) To show duration of visual failure in first affected eye and (*below*) in subsequently affected eye.

man of fifty-six had complained for eighteen months of a persistently tender area in the left temple. There were no visual symptoms or signs, and it was only when a radiograph of the skull revealed the presence of an intrasellar lesion that the cause of this symptom became apparent. A course of radiotherapy directed to the pituitary fossa gave complete relief of this symptom. Headache associated with these lesions may either result from distortion of dura or blood vessels in relationship to the tumour, or, when there is a large extrasellar extension, from the widespread

distortion of the intracranial contents by the tumour mass, or it may be a manifestation of a secondary suprarenal insufficiency (Jefferson, 1957).

Epilepsy as a preoperative symptom did not occur among the " visual " Rathké pouch cysts. With the chromophobe adenomata it was noted in 5 per cent. of patients, but if doubtful cases, where the symptoms might have been only syncopal, are included this figure is raised to 14 per cent. Occasionally, with either kind of lesion, epilepsy developed post-operatively and, if it did so, it never occurred unless there was either a sizeable extension of the tumour into the brain or else a portion of the frontal lobe had been removed at operation.

With regard to the examination of the patient, the incidence of hypopituitary features at the time of the patients' hospital admission is set out in Figure 4. For the chromophobe adenomata as many as 80 per cent.

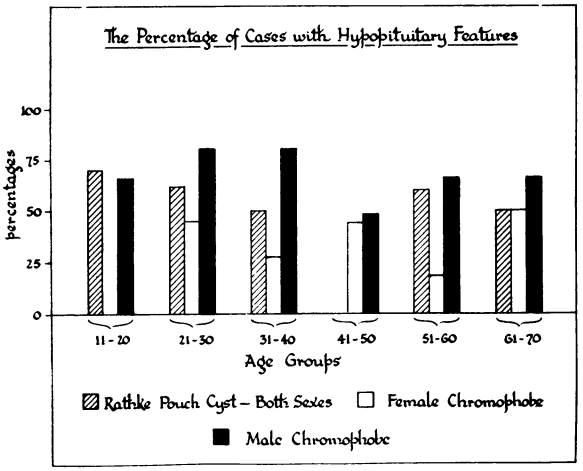

Fig. 4. The percentage of patients in each ten-year age-group who showed hypopituitary features.

of the males under forty years old showed " hypopituitarism." Even though there was a fairly considerable drop in the proportion of hypopituitary males between forty-one to fifty years, the men throughout showed a higher incidence of this feature than did the females. For the Rathké pouch cysts there was no apparent difference in the incidence between the sexes.

This is not the place to refer in detail to the changes in the visual fields or the fundi, but among the rarer changes it should be noted that 5 per cent. of patients with a chromophobe adenoma had an homonymous hemianopia (due in two cases to a mass of tumour in the temporal lobe and in the remainder to optic tract compression). It is also interesting that patients with an homonymous hemianopia made up exactly half the eight

cases (6 per cent.) in whom there was papilloedema. Two further points about the fields of vision must be stressed. First, with chromophobe adenomata very frequently the brunt of the visual failure falls upon one eye. This visual disturbance may be so asymmetrically distributed that only a careful examination of the internal isoptres of the " good " eye reveals that it is affected at all. Secondly, bitemporal scotomata may occur with varying degrees of preserved peripheral vision. At times the sharp vertical meridian of the scotoma may be obscured by a macular defect, and if the internal isoptres alone are examined the true significance of the defect may be lost. These features require emphasis for they sometimes lead to tragic delays in arriving at the diagnosis and it is only in cases where optic atrophy is not far advanced that worthwhile recovery can occur.

Frequently diplopia has occurred as one of the presenting symptoms among the chromophobe adenomata. Rarely, this may be due to an overt disturbance of the ocular motor muscles. If those patients be discounted whose defective eye movements were clearly associated with serious visual loss, there were only five patients who presented with clinically recognisable oculomotor disorders (three with weakness of the external rectus, and two with bilateral and virtually complete ophthalmoplegias). One patient developed a complete third nerve palsy following an arteriogram, and one patient developed a severe third nerve palsy post-operatively. In spite of the infrequency of these frank oculomotor pareses, diplopia was a symptom in 36 per cent. of the patients with chromophobe adenomata about whom information is available. When present, this diplopia was commonly worse for distant objects than for close ones, and it is very likely that it resulted from slight disturbances in the balance of the eye muscles which were revealed as macular vision became involved.

A disturbance of the functions of the trigeminal nerve is rare and when it occurs among the chromophobe adenomata it frequently indicates invasive changes in the tumour (Geoffrey Jefferson, 1955). It has been noted five times in this series, and in three of these patients there were histological features compatible with malignancy. However, it is necessary to say that different pathologists might easily hold different histological criteria of malignancy in these tumours. In one patient with a malignant adenoma the trigeminal disorder which was unmistakable preoperatively resolved following a very limited operation and radiotherapy. Another patient with a histologically unverified lesion but with unmistakable and very extensive radiological changes had trigeminal paraesthesiae with altered sensation for thirteen years before she died.

Regarding lateralised weakness of the face or limbs, this occurred in 10 per cent. of the chromophobe adenomata. The incidence of hemiparesis was rather higher (18 per cent.) among the " visual " Rathké pouch cysts (in parenthesis it may be noted that 50 per cent. of the patients

with a " non-visual " Rathké pouch cyst had evidence of lateralised motor weakness).

At lumbar puncture there were no outstanding features. Except for the few cases already mentioned with papilloedema the pressure relationships were normal. For the patients with a chromophobe adenoma, the mean protein content in the males was 78 mg./100 ml., and in the females it was 56 mg./100 ml. There was an occasional cellular reaction in the C.S.F., for 13 per cent. of the patients had a white cell count greater than 5/cu.mm. (examples where the fluid was contaminated with red blood cells have been excluded from consideration). The greatest number of white cells encountered were 37/cu.mm. With the Rathké pouch cysts, the average protein content (males and females) was 63 mg./100 ml. and 7 per cent. of these patients had more than five white blood cells per cu.mm. of C.S.F.

The radiological appearances of these cases are well known. However, some points of especial importance require emphasis. First, although a chromophobe adenoma can very rarely occur with a small pituitary fossa (Fig. 5), the fossa is usually considerably enlarged. The area enclosed

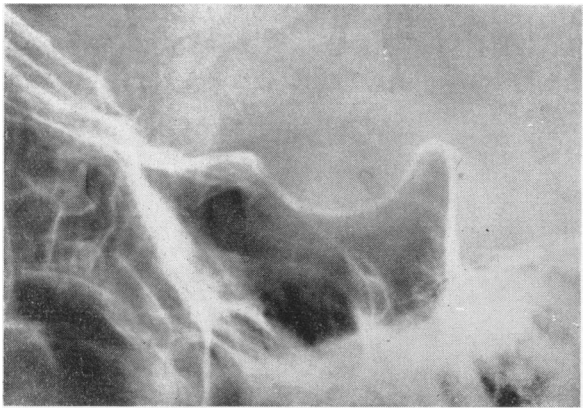

Fig. 5. Deceptively small and shallow pituitary fossa containing a surgically verified chromophobe adenoma. (Area enclosed within pituitary fossa in original radiograph was 1·4 sq. cm.—see text.)

within the sella turcica beneath a line joining the tuberculum sellae to the estimated tip of the dorsum sellae has been measured in fifty normal patients with no intracranial space occupying lesion. The average area was 0·9 sq. cm. For the chromophobe adenomata the average area was 3·6 sq. cm., and for the " visual " group of Rathké pouch cysts (only patients of seventeen years or more have been included), it was 1·7 sq. cm. It is clear that the average patient with a Rathké pouch cyst has a very much less expanded sella turcica than does one with a chromophobe

adenoma. With the chromophobe adenomata, the older patients had, on average, a smaller sella turcica than did the younger ones (Table I), and taken overall the female patients had a smaller sella (3·2 sq. cm.) than did the males (3·9 sq. cm.).

TABLE I

CHROMOPHOBE ADENOMATA. AREA ENCLOSED WITHIN SELLA TURCICA AS SEEN IN AS LATERAL RADIOGRAPH

	Mean area (sq. cm.) patients up to 40 years	Mean area (sq. cm.) patients over 41 years
Females ..	3·7	2·8
Males	4·4	3·5

Note that the males have a more expanded sella turcica than the females; the younger patients have a more expanded sella than the older patients.

The findings at operation in these patients is of considerable interest for, according to Schaeffer's diagram (1924), in 17 per cent. of cases access to the pituitary fossa should be very limited and only in 4 per cent. of cases is the chiasm post-fixed. If this were true of patients with a pituitary adenoma, it would make an adequate operation very difficult indeed. The data available in the cases here reported is at variance with Schaeffer's findings for the " normal." Table II shows that, especially with the

TABLE II

THE INCIDENCE OF PATTERNS OF CHIASMAL " FIXATION "

	Prefixed	Normal	Postfixed
Schaeffer's " normals "	17%	79%	4%
Present series, Rathké pouch cysts	25%	50%	25%
Present series, Pituitary adenomata	25%	—	75%

Notice the high incidence of postfixation.

chromophobe adenomata there is a very much higher incidence of " post-fixation." It may well be that in the presence of a " tumour " the optic nerves have been subjected to considerable degrees of stretch, if not to local distortion. It is common in the larger tumours to find that the optic nerves do not run gently upwards and backwards, but are sharply angulated so that to the surgeon they appear to ascend at right angles to the floor of the anterior fossa. Not infrequently, the operation notes referred to the distortion of the nerve; for example, in one case Professor Cairns noted that the chiasm was very post-fixed (3·0 cms. from the tuberculum sellae) and that the right optic nerve was flattened and ribbon-like " being about 1 cm. wide." This patient had a bitemporal hemianopia with a visual acuity on the right of 6/36, J.16. This is a good example of stretch and distortion affecting the *whole* optic nerve whilst

the patient experiences a *selective* disturbance in the field of vision. I would suggest that the capacity to withstand distortion may differ in the nerve fibres innervating the two halves of the retina. Certainly, it has been shown in cats that the crossed and the uncrossed visual fibres have different speeds of conduction, and presumably other different properties (Bishop, Jeremy and Lance, 1953).

There is probably not complete agreement among neuro-surgeons as to the side on which operation should be performed. Some claim that since they find a right-sided approach technically easier than a left-sided one, the operation is better performed from the right, whilst others advance arguments in favour of operating on the side of the better or of the worse eye. The visual acuities of the patients in this series have been arbitrarily divided into six different grades. The acuity immediately before operation has been compared with the best post-operative acuity (regardless of whether radiotherapy was also given), and the cases have been divided into those where the visual defect pre-operatively affected both eyes nearly equally and those where the acuity of the better eye differed by at least two divisions of the arbitrary scale from that of the worse eye. The sum of the figures representing visual acuity has been calculated for both eyes pre- and post-operatively. The sum obtained post-operatively has been expressed as a percentage of the sum recorded pre-operatively (Table III). (Similar results were seen when the calculations were repeated utilising a different arbitrary grading of the visual acuities.) It can be seen that when there is asymmetrical involvement of the eyes the better results follow from an operation conducted from the side of the less affected eye. When the eyes are nearly evenly affected the results are less clear cut, but there is still a suggestion that the better results follow an operation upon the better eye.

The figures designating visual acuity of right and left eyes were summed and were compared with the measurements of the sella turcica already mentioned (see Table IV). It may be seen that the larger sellae turcicae (viz. > 3·6 sq. cm.) were, on average, associated with the more extensive loss of vision.

Ninety per cent. of the Rathké pouch cysts were cystic and on the average 17 ml. of fluid was withdrawn from them. For the chromophobe adenomata the corresponding figures were 40 per cent. cystic lesions with an average of 8 ml. withdrawn.

Two patients with a chromophobe adenoma showed post-operative C.S.F. rhinorrhoea. In one patient this was present five and a half years after the operation, and in another six years after operation. No particular inconvenience to the patient was caused in either case, and there had been no episodes suggestive of meningitis. Apart from the rhinorrhoea there were no unusual clinical, operative or radiographic features of these patients.

The effect of treatment upon vision will not be discussed in detail, it is

enough to say that when the examination of the fundus has shown little or no evidence of optic atrophy there is a good chance of abolishing the pre-operative field defect. There have also been a few cases which have re-emphasised the importance of the point made by Henderson (1939) that at times the eye which appears much the more severely damaged may, in the long run, prove to be the more serviceable. Two factors which are not generally acknowledged to influence the visual performance in cases of chiasmal compression require attention. The first of these is the level of the haemoglobin in the circulating blood.

TABLE III

POSTOPERATIVE VISUAL ACUITY EXPRESSED NUMERICALLY AS A PERCENTAGE OF PREOPERATIVE VISUAL ACUITY

Side of Operation	Both eyes nearly evenly affected		Eyes asymmetrically affected	
	Less affected eye	More affected eye	Less affected eye	More affected eye
Operation from side of less affected eye	+30%	+30%	+11%	+77%
Operation from side of more affected eye	+34%	+20%	+11%	+20%

Read from left to right. Upper line—when operation is from the side of the " better " eye—shows more improvement than lower.

Numerical expression of visual acuity was as follows:

Grade 1. Absence of light perception → appreciation of hand movements.
Grade 2. Finger counting → Jaeger Type 16 (J. 16) → Snellen 6/36.
Grade 3. J.16 → J.10 or 6/36 → 6/18, but if involvement of macular vision could be demonstrated on Bjerrum screen grade reduced to 2.
Grade 4. J.10 → J.6 or 6/24 → 6/12, but if nasal field involved grade reduced to 3.
Grade 5. J.6 → J.4 or 6/18 → 6/9, but if nasal field involved grade reduced to 4.
Grade 6. J.2 → J.1 or 6/12 → 6/6, but if definite defect in temporal field grade reduced to 5.

Note that many of the grades overlap slightly, so that in awarding the grades account could be taken of the character and the severity of the field defect.

TABLE IV

VISION FOR BOTH EYES EXPRESSED IN ARBITRARY UNITS AND SUMMED. (NORMAL VISION = 12 UNITS)

Area of sella turcica as seen on lateral radiograph	MALES		FEMALES	
	Preoperative vision	Postoperative vision	Preoperative vision	Postoperative vision
< 3·6 sq. c.m.	7·9 units	9·6 units	7·4 units	8·5 units
> 3·6 sq. cm.	5·4 units	7·7 units	5·6 units	7·5 units

Note that in both sexes the larger sellae turcicae (i.e., those greater than 3·6 sq. cm.) are associated with poorer vision.

This point is illustrated by a forty-eight-year-old female (R.I. 175220/53), whose visual performance and whose haemoglobin levels are set out in Table V. Although the ability to read Snellen type fluctuated as the haemoglobin level rose, there was a steady improvement in the ability to read Jaeger test types, and although the visual fields did not change in form they became less constricted.

The other factor that may be of importance is lack of cortisone in severely hypopituitary patients. The most striking illustration of this which I have seen concerned a patient who is not in this series because the chiasmal compression was due to a suprasellar meningioma. Because she collapsed when an anaesthetic was attempted, she did not come to operation. Later, when she had received treatment with cortisone, her visual fields expanded very considerably (Fig. 6). It is reasonable to suppose that this sequence of events might sometimes occur in the presence of a Chromophobe adenoma or of a Rathké pouch cyst.

TABLE V

Date	Left eye		Right eye		Haemoglobin
28.5.53 Three pints of packed cells given 4.6.53	6/9	J.6	6/36	J.20	40 per cent.
7.6.53 Three pints of packed cells given 10.6.53	6/12	J.4	6/18	J.16	75 per cent.
12.6.53 Operation for chromophobe adenoma 13.6.53	6/12	J.2	6/24	J.12	93 per cent.

Chromophobe adenoma before operation. To show increasing Jaeger acuities when severe anaemia was relieved by blood transfusion.

Many papers on chromophobe adenomata or Rathké pouch cysts have been concerned with particular features of the disease or with the effects of treatment upon vision. I have been unable to trace any large series giving a clear idea of the prognosis as regards life. The following figures (Figs. 7 to 9) provide a panoramic view of the duration of symptoms and of the course of events after treatment for the chromophobe adenomata. The shaded line on the left indicates the duration of the prodromal symptoms, the vertical line indicates the moment of operation. Radiation therapy is indicated by the letter " R " and any further operations by the letter " O." The general impression gained is of the benignity of these lesions as regards life itself. Figure 10 charts the course of the small selected group of chromophobe adenomata who never required an operation. Again the long survival rate is impressive. Now the Rathké pouch cysts (Fig. 11) show a less consistent picture and the high mortality among the young female patients is particularly obvious. (In parenthesis, I should say that the " non-visual " group of Rathké pouch cysts have a still less favourable prognosis.)

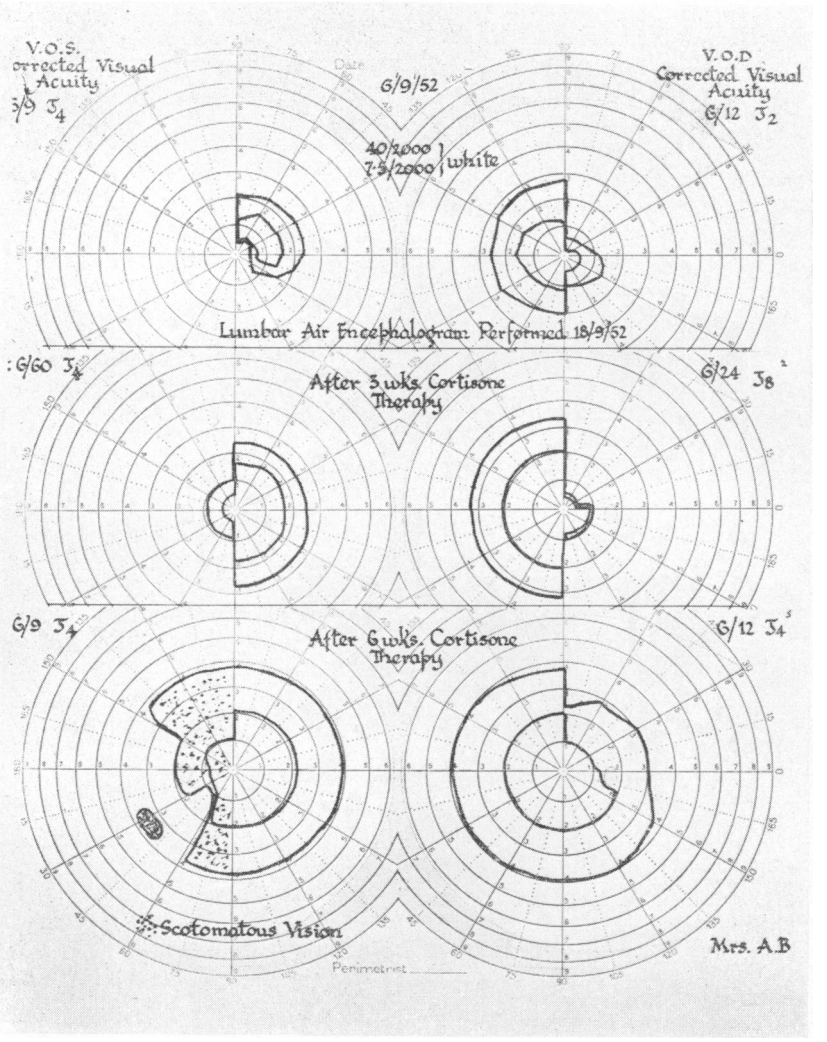

Fig. 6. To show the influence of Cortisone (12·5mg., eight-hourly) on the visual acuity and the visual fields of a severely "hypopituitary" patient with chiasmal compression.

It will be observed that many of the chromophobe adenomata were treated with radiotherapy. There has been a certain reluctance to use radiotherapy in the past because of the likelihood that hypopituitary features would be exacerbated by the destruction of actively functioning anterior pituitary tissue. With the advent of cortisone, the dangers of this

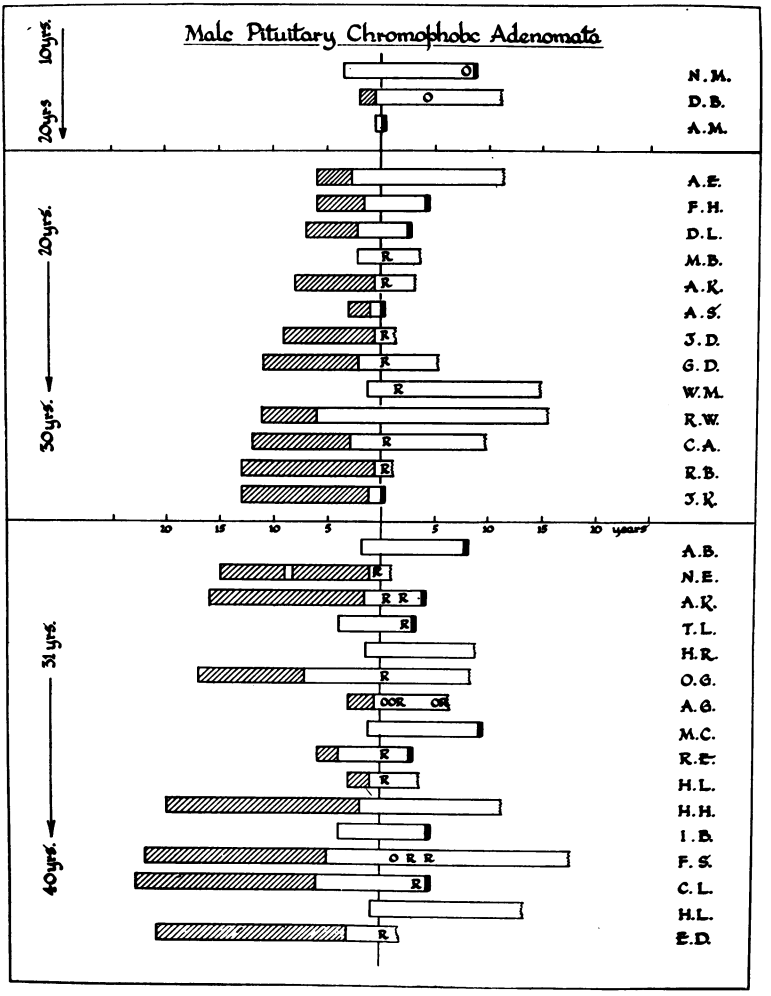

Fig. 7. To show the course of the disease in the male patients up to forty years with a chromophobe adenoma. Patients arranged in increasing age from above downwards. Central vertical line indicates the moment of operation. Shaded area indicates presence of prodromal symptoms only (e.g. subnormal hairiness). Unshaded area before operation indicates presence of symptoms directly ascribable to the lesion (e.g. visual failure, headache, etc.). Unshaded area after the operation indicates duration of life. Heavy vertical line at right of any oblong indicates death of that patient; broken line shows continued survival. R = Radiation treatment; O = a second or subsequent operation. Time scale in five-year increments.

development have been removed, and, although statistical proof of the effectiveness of radiotherapy is difficult to obtain, improvement in vision after such treatment occurs frequently enough to leave a favourable impression upon those responsible for the care of these cases. Figure 12 is a microphotograph of the pituitary contents taken from a patient who died at the age of fifty-seven, fifteen years after radiotherapy had caused a permanent arrest of her visual failure. At post mortem the tumour was small and the outstanding feature of the histological material was that of fibrosis (Fig. 12). Very clearly the growth of this tumour had been arrested.

Of a total of thirty known deaths among the male chromophobe adenomata there were fifteen occasions where the death was in whole or in considerable part the result of endocrine failure. For the females the figures are sixteen deaths, of which seven were associated with endocrine

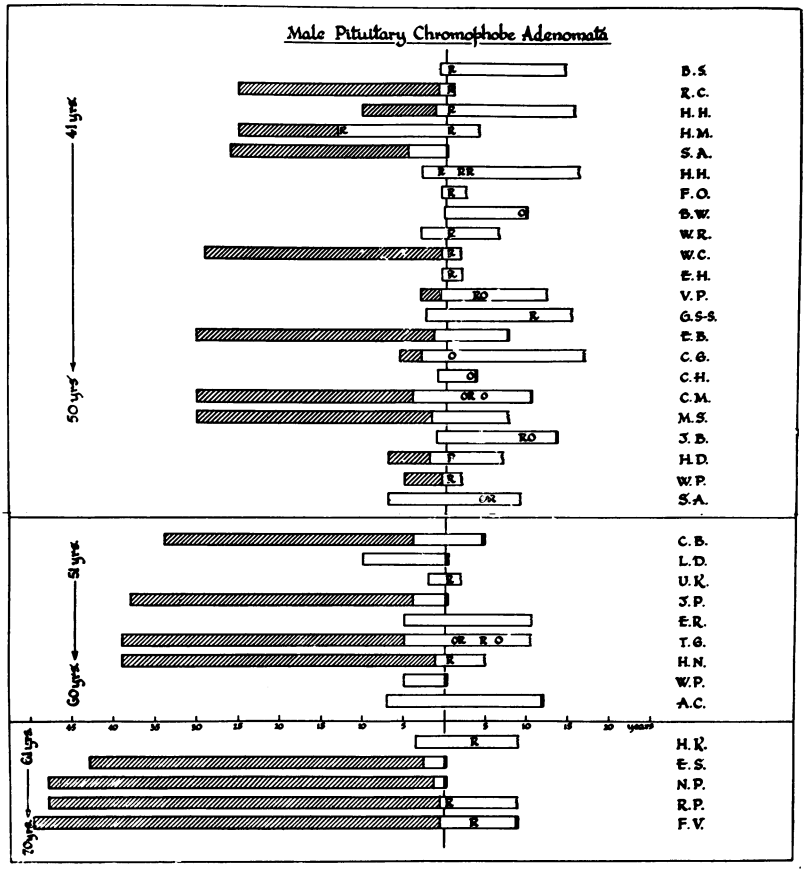

Fig. 8. Males aged forty-one to seventy with a chromophobe adenoma.

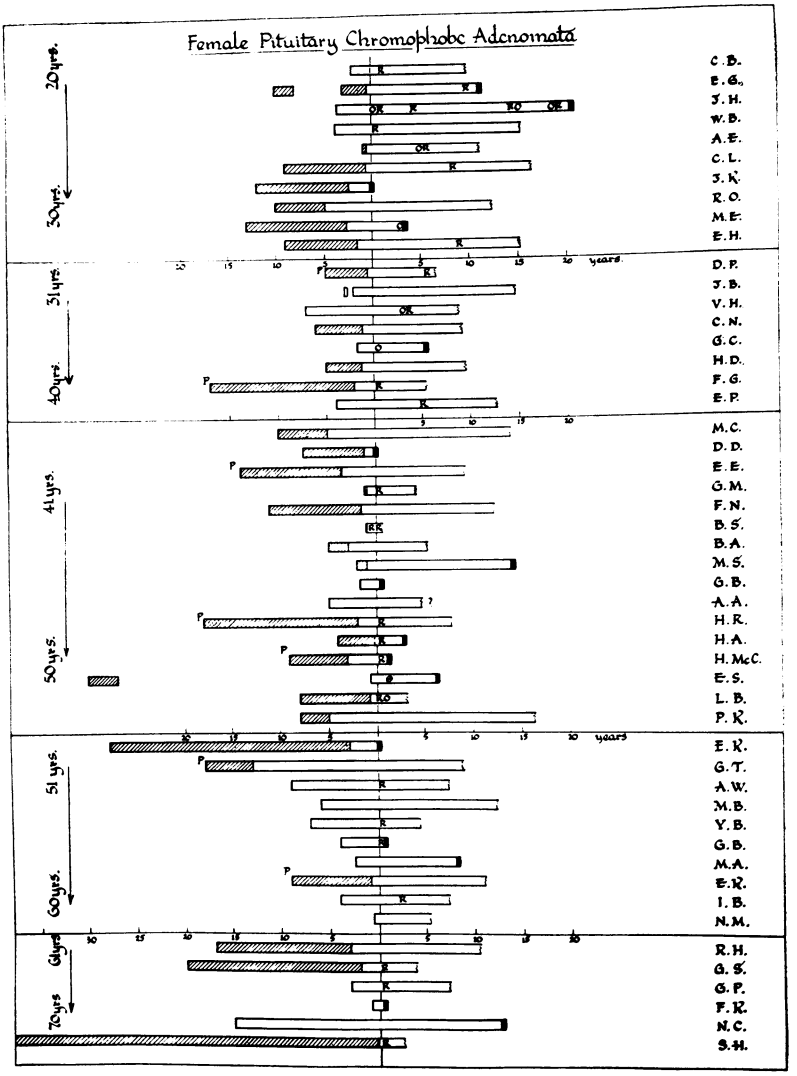

Fig. 9. Females aged twenty to seventy years with a chromophobe adenoma. Shaded area indicates presence of prodromal symptoms only (e.g., amenorrhoea). P = the end of a pregnancy. In other particulars as for Figure 7.

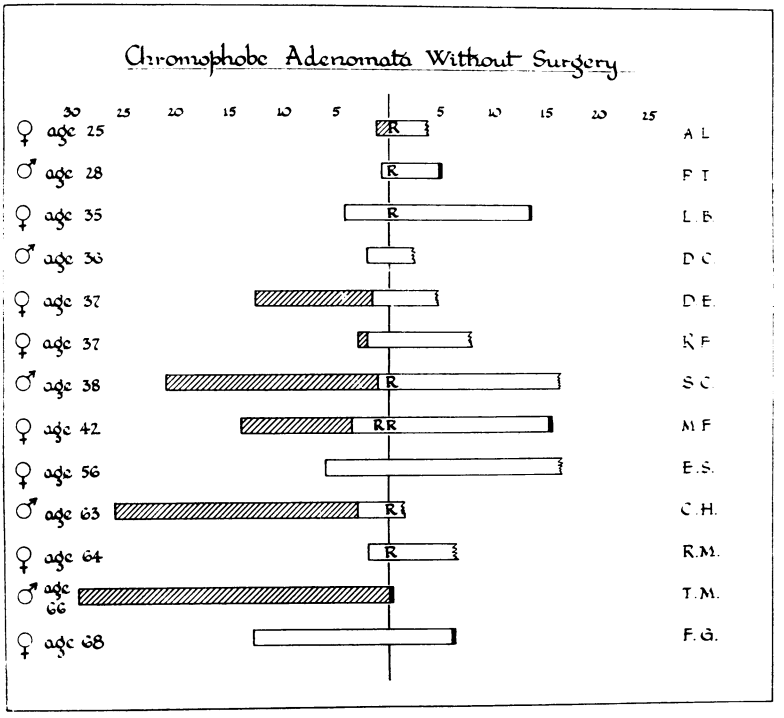

Fig. 10. Small selected group of chromophobe adenomata not treated by surgery. Vertical central line indicates moment of admission to neurosurgical department for full assessment. In other respects as for Figure 7. Sex and age of patients indicated on the left. Time scale in five-year increments.

failure, and for the Rathké pouch cysts twelve deaths with six of them associated with an endocrine disturbance. Total numbers of deaths which have occurred so far are expressed in Table VI as a percentage of the numbers of cases involved. From this data it seems clear that the male patient with a chromophobe adenoma and the females with a Rathké pouch cyst are likely in the future to benefit most from the availability of

TABLE VI

DEATHS ASCRIBABLE TO "HYPOPITUITARISM" EXPRESSED FOR EACH GROUP AS A PERCENTAGE OF TOTAL DEATHS IN THAT GROUP

Male Chromophobe Adenomata 40 per cent.	Male Rathké Pouch Cysts 31 per cent.
Femal Chromophobe Adenomata 28 per cent.	Female Rathké Pouch Cysts 50 per cent.

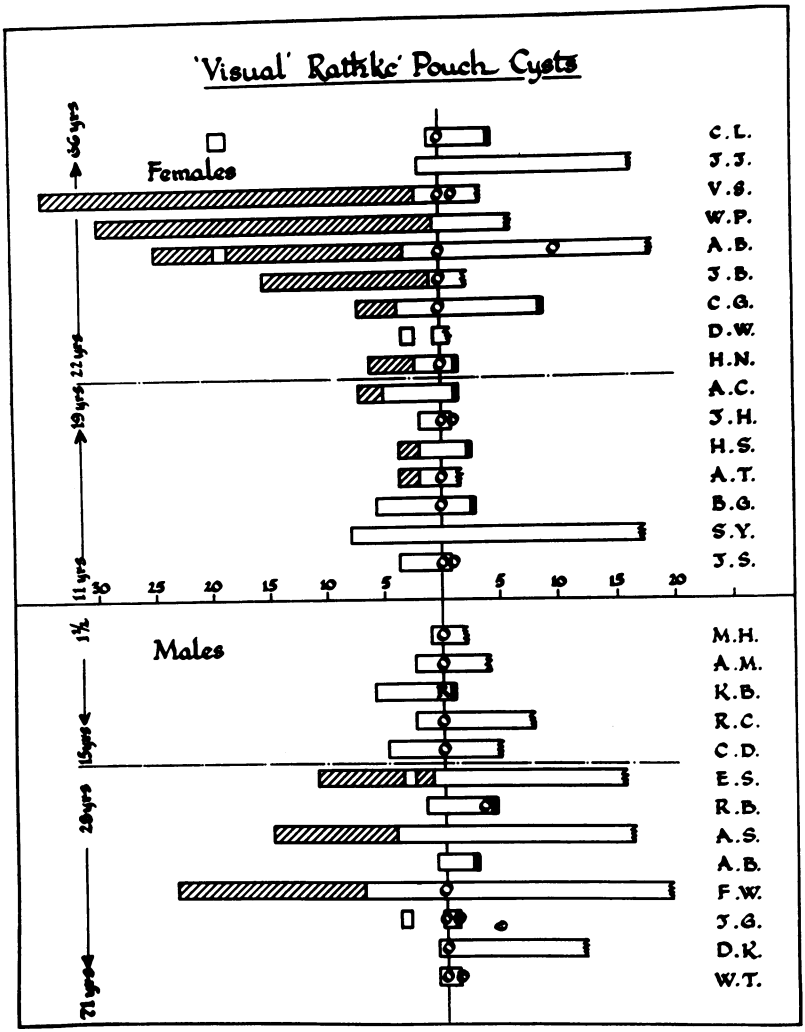

Fig. 11. "Visual" group of Rathké pouch cysts. From horizontal heavy line upwards, females in order of increasing age; from horizontal heavy line downwards, males in order of increasing age. Central vertical line indicates moment of admission to hospital for full assessment or, when indicated by an O, for first operation. Other details as in Figure 7.

cortisone. (From other information it appears that the teenage female with a Rathké pouch cyst is often severely affected by endocrine deficiency.)

From Figures 7 to 9 it will be recalled that a fair proportion of patients with chromophobe adenomata suffered a recurrence of their tumours and it may be useful to discuss some of the means by which satisfactory or incomplete treatment may be recognised. In the small tumours where there is no technical operative problem, the improvement in the visual fields tells its own story. The problem is usually most acute in patients with large tumours where there is already a considerable degree of visual loss and where the tumour is so large that it has not been possible to

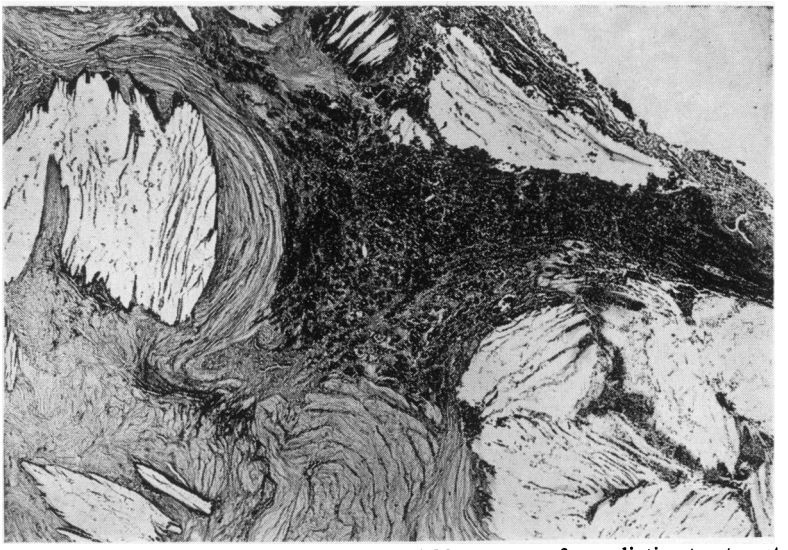

Fig. 12. Microphotograph of pituitary gland fifteen years after radiation treatment of a chromophobe adenoma. Note small island of glandular tissue in mainly fibrosed gland.

attain the surgical ideal in which the remnants of the capsule together with the remaining normal portions of the gland may be packed down at the close of the operation into the floor of the sella turcica. In these cases recurrence may be signalled not so much by detectable changes in vision but by headache or pain centred around the affected eye. Lachrymation is also a symptom which in these circumstances indicates recurrence. It is advisable to follow these cases with serial radiographs at intervals of nine to twelve months. Figure 13 demonstrates the reconstruction of the sella turcica which occurred in the eleven months that succeeded operation for a moderate sized chromophobe adenoma. (Radiotherapy was also given post-operatively.) In the second radiograph not only have the posterior clinoids become more evident, but the dorsum sellae has regrown its cortex. In contrast, when further growth is taking place in a

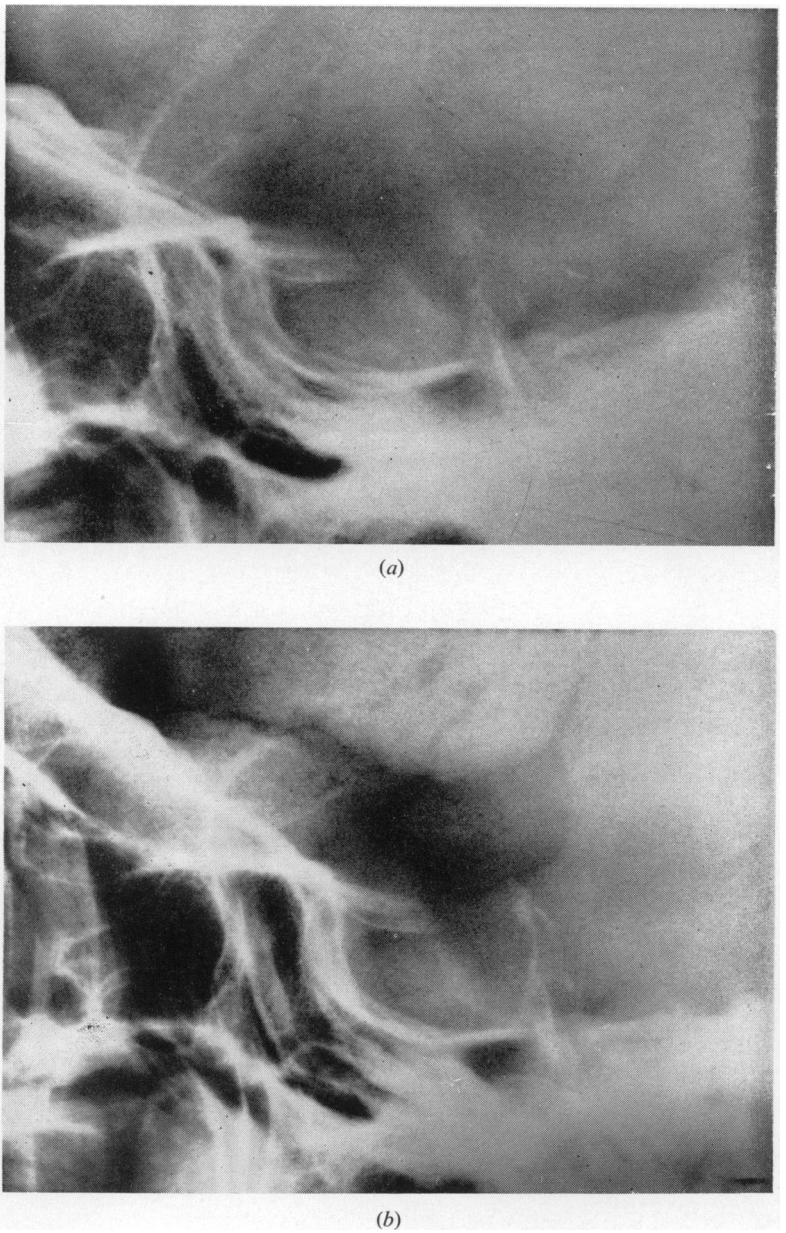

Fig. 13. Male aged forty-nine with chromophobe adenoma. (*a*) Lateral radiograph of sella turcica immediately before operation. Notice porosity of the dorsum with loss of cortex. (*b*) Eleven months after operation. Dorsum has been reconstructed.

tumour which has already caused an extensive visual loss, certainty that the tumour is expanding may be derived from films such as are shown in Figure 14 which are from a female aged thirty at the time of her operation. She then had lost light perception in the left eye and since the left optic nerve was found to be exceedingly thin at operation it was divided. Vision in the right eye was scarcely affected. Figure 14a shows the appearance at that time. After some years she slowly began to lose vision in the right temporal field of vision, but the normal acuities were preserved and the patient made light of the loss of vision. However, the erosion of the dorsum sellae confirmed (Fig. 14b, taken seven and a half years later) that the tumour had expanded. Radiotherapy was given with the improvement in the visual fields. Subsequently, after a further seven and a half years, although the patient's visual acuity remained unchanged, a radiograph (Fig. 14c) showed complete disappearance of the dorsum sellae. The tumour was clearly still expanding. However, it should not be concluded that tumour growth cannot occur without further recognisable enlargement of the sella turcica. It may indeed do so. This may happen when the growth is mainly suprasellar in position and an upward extension which obstructs the third ventricle may prove to be exceedingly dangerous.

Similar radiographic changes occur with the Rathké pouch cysts, but here they have less significance, for so often the main body of a Rathké pouch cyst lies above the sella and the most striking radiographic change with the passage of time is an increase in the amount of suprasellar calcification. It is a commonplace that the extent of the calcification very seldom indicates the full extent of the tumour, so it follows that the tumour may not in fact have grown ; rather the subsequent increase in calcification may give a truer picture of its dimensions.

Before concluding, I should like to stress again that the chromophobe adenomata as a whole form a " worthwhile " group of patients, so that we should all keep alert and alive to the problems of their diagnosis. He who detects the presence of such a lesion and directs the patient into the appropriate channels for treatment is performing a real service to the patient. As always diagnosis may be achieved from a careful history and examination, but special features have to be considered. The most important of these are detailed examination of the fields of vision and radiographs. The E.E.G. should not be omitted in the study of these patients (see Boselli and Jefferson, 1957) for it may provide evidence of a large extrasellar extension, or suggest the presence of endocrine disorder. Before the treatment can be planned or safely executed, the " endocrine status " of the patient must be assessed, with particular reference to the functions of the adrenal cortex (see Jefferson, 1957). Only by paying attention to the associated endocrine disorders can the mortality be kept to the minimum and the largest number of patients be restored to a sense of well-being and to an active life.

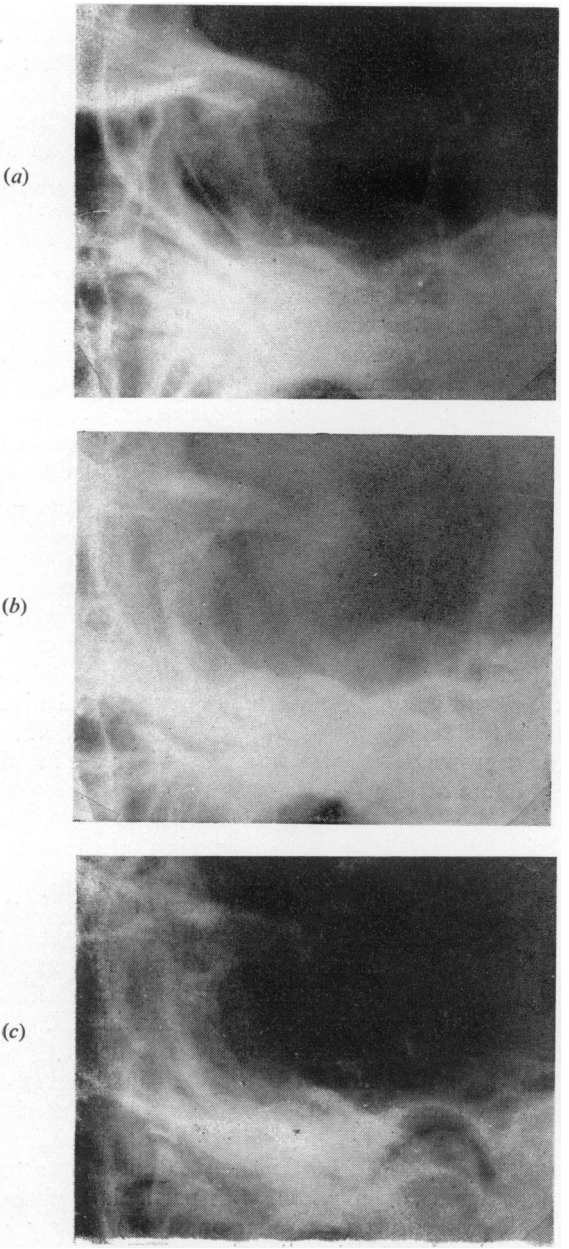

Fig. 14. Female, aged thirty, with chromophobe adenoma. (*a*) At the time of operation. (*b*) Seven and a half years later. Dorsum now present only as a thin line. (*c*) After a further seven and a half years. Tumour has grown further and the dorsum can no longer be recognised.

Finally, I should like to end on a provocative note. Much of the natural history of the chromophobe adenomata could be explained if they are regarded not as " tumours " in the sense of a body of cells multiplying in numbers for no apparent reason, but as a group of cells which have multiplied in an effort to compensate for some metabolic abnormality. If the prodromal symptoms mentioned at the beginning of this talk be admitted as valid evidence, they surely show that many of these patients have had an hormonal abnormality, sometimes existing for several years, which preceded the development of an expanding tumour. The chromophobe cells contain, as far as we know, no active hormones. It would seem that they are chromophobic because they cannot manufacture their appropriate hormone. It may very well be that if the hormonal environment is restored to normal by the administration, when appropriate, of cortisone, thyroid and the sex hormones, one of the stimuli which causes these cells to divide will be removed. We have it on record that John Hunter regarded resort to surgery as an admission of failure (*The Works of John Hunter,* 1835, ed. Palmer, Vol. 1, p. 210). If these " medical " means of treatment should in time be shown not only to prolong the life and wellbeing of many of these patients, but also to contribute to the limitation of tumour growth, we may be sure that it would be an event which would delight the soul of Hunter.

ACKNOWLEDGMENTS

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