THE CONFIGURATION AND RELATIONS OF THE PITUITARY GLAND AND FOSSA

A radiological, pathological and clinical study

VOLUME I (Text)

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I, Maurice S. F. McLachlan, certify that this thesis has been composed by myself. The contributions of co-workers are recorded in the preface. The remainder is my own work.

M. S. F. McLachlan

CONTENTS

Preface

The bulk of this work was performed at Hammersmith Hospital and the Royal Postgraduate Medical School, London. I am very happy to acknowledge the contributions of many colleagues there.

In Parts I and II, Dr. E. D. Williams and Dr. R. W. Fortt of the Department of Morbid Anatomy performed the pituitary dissections and the histological studies.

In Part III, Dr. A. D. Wright of the Department of Medicine contributed the clinical details and acted as a "blind" observer. The other "blind" observer was Dr. B. E. Nathan of the Department of Diagnostic Radiology. Miss Susan Russell performed some of the measurements.

In Part IV, Dr. C. R. W. Edwards of the Department of Medicine provided clinical data and helped to assess the side effects of pneumoencephalography. The regime to control these effects was evolved with the help of Dr. M. Heath of the Department of Anaesthetics. Analysis of the pneumoencephalograms was undertaken with Dr. J. P. Lavender of the Department of Diagnostic Radiology. Dr. G. F. Joplin of the Department of Medicine, whose own work on the pituitary provided much valuable source material, attempted to predict suprasellar extension of tumour on the basis of sellar shape.

The other observer who attempted this at my request was Dr. F. H. Doyle of the Department of Diagnostic Radiology. To him I owe a special debt of gratitude, as co-worker, critic and friend throughout this work, particularly in Parts I, II and III. The statistical analyses are his.

Patients studied in Parts III and IV were under the care of Professor T. R. Fraser of the Department of Medicine who provided the stimulus for many aspects of this work. Professor R. E. Steiner of the Department of Diagnostic Radiology provided many facilities and constant encouragement.

The work was completed at Cardiff Royal Infirmary and the Welsh National School of Medicine where Professor K. T. Evans and Dr. A. S. Bligh of the Department of Diagnostic Radiology offered much helpful criticism of the manuscript.

I would also like to thank the Departments of Medical Illustration at the Royal Postgraduate Medical School and the Welsh National School of Medicine for the reproductions and the libraries of both Schools for assiduously tracing references.

Parts I, II and III have been modified from papers published in the British Journal of Radiology (see Appendix : Published papers). Part IV has been adapted from material accepted for publication in Clinical Radiology (Clin. Radiol. 22, 361 - 369, 1971).

Abstract of Thesis

In 50 adult necropsies, measurements of linear dimensions and volume of the normal pituitary gland were correlated with corresponding measurements of the sella turcica obtained from radiographs. Though the female pituitary gland was significantly larger than the male, there was no significant sex difference in sellar size. Dimensions of gland and fossa were correlated separately for each sex. Correlation between gland volume and estimated sellar volume was good. The length of the sella and the width of its floor correlated well with the length and width of the gland, but correlation between measurements of sellar height and gland height was poor, especially in women.

Detailed studies of the radiological anatomy of these glands and fossae showed wide variation in the configuration of the diaphragma sellae, particularly in the position of its central portion relative to bony landmarks. In several a sub-diaphragmatic extension of the subarachnoid space was found. The shape of the gland varied markedly and was frequently distorted by compression by the carotid arteries. Bony configuration was also altered by these arteries which in some cases eroded the lateral margins of the dorsum sellae, undercutting the posterior clinoid processes. Some other variations in sellar contour are illustrated and discussed.

To evaluate radiological criteria of abnormality in the light of such wide normal variation, radiographs of the pituitary fossa of 140 acromegalic patients were assessed. Over half were grossly abnormal, showing marked bony erosion and enlargement. In a quarter, a double sellar contour was present, but, since dimensions of the inner contour were normal or only slightly enlarged, abnormality was often overlooked. The remainder (18%) presented particular diagnostic difficulty. On plain films, commonly accepted criteria of abnormality discriminated poorly between this group and controls. Measurement of sellar dimensions, because of the wide normal range, was also unhelpful. However, tomography of the sella demonstrated significant abnormality in almost all and frequently revealed downward extension of the pituitary tumour unsuspected on plain films. Combined assessment by plain films and tomography showed sellar abnormality in nearly 99% of the 140 patients.

To demonstrate suprasellar anatomy, tomography in two planes was combined with pneumoencephalography in 37 patients suffering from various types of pituitary tumour. Examinations were successful in all but one, showing a wide variation in the position of the superior aspect of the tumour. Suprasellar extensions were not predictable on the basis of bony configuration of the sella and frequently failed to produce visual field defects. Subarachnoid extensions into the sella were also demonstrated. Attention is drawn to the implications of these variations and the importance of their demonstration before therapeutic procedures on the pituitary gland are undertaken.

Review of the Literature

Oppenheim (1901) was, apparently, the first to report radiological abnormality of the sella turcica caused by a pituitary tumour. Others (Zander, 1896; Hrdlička, 1898; Gibson, 1912; Cope, 1916; Camp, 1923) observed in anatomical specimens that even the normal fossa varies widely in size and shape. Similar observations were made on radiographs (Jewett, 1920; Enfield, 1922; Camp, 1924; Haas, 1925; Goldhamer and Schüller, 1926; Pancoast, 1932; Kornblum, 1932), provoking many attempts to define normal sellar dimensions radiologically. Jewett (1920), Enfield (1922), Camp (1924), Pancoast (1932) and Kornblum (1932) made simple linear measurements in a sagittal plane. Their choice of end points varied and only Pancoast and Kornblum considered the importance of radiographic magnification. Further attempts followed, including those of Heublein (1946), Acheson (1956) and Silverman (1957), but, despite improvements in radiographic technique, inconsistencies remained particularly in defining the superior aspect of the fossa. Szondi and Haas (1922) preferred to measure lateral sellar area and were followed in this by Bokelmann (1934), Hurxthal (1947), Hare, Silveus and Smedal (1949) and Mahmoud (1958). Though claimed as an improvement on linear measurements, definition of end points again varied. Furthermore, these estimates too were two-dimensional and confined to the sagittal plane. To obtain a coronal diameter, the width of the dorsum was measured by Haas (1925, 1927) and Kovács (1934) using an angled postero-anterior ("nucho-frontal") projection. Fariñas (1939) apparently unaware of this earlier work, made similar measurements. By multiplying this width by lateral area, Meldolesi and Pansadoro (1937) attempted a volumetric assessment. Others multiplied lateral area by the width of the fossa floor measured from antero-posterior tomograms (Cardillo and Bossi, 1941) or from plain postero-anterior radiographs (Oon, 1963). Though choice of landmarks differed slightly, each of these three-dimensional assessments included corrections for radiographic magnification. Di Chiro and Nelson (1962), seeking greater accuracy, used a formula based on that for an ellipsoid. Clearly defining their end points, they measured length (L) and height (H) from lateral radiographs and floor width (W) from postero-anterior plain films. Their formula, volume = $\frac{1}{2} \times L \times H \times W$, incorporated a factor which corrected for radiographic magnification and "the empirical error found in a small series of 15 cases". Their results differ considerably from those volumetric assessments made by multiplying area by width.

Attempts to estimate in this way the size of the normal hypophysis itself depend for their accuracy on the extent to which the gland occupies the sella. This varies widely (Kovács, 1934; Bokelmann, 1934; Carstens, 1949; Busch, 1951; Di Chiro and Nelson, 1962) and may differ for males and females since, although the female gland is larger (Erdheim and Stumme, 1909; Rasmussen, 1928, 1934), the female fossa is not (Mahmoud, 1958; Joplin, 1965).

Di Chiro and Nelson (1962) found examples of normal glands bulging beyond sellar boundaries. More commonly, gland volume is less than sellar volume. Rasmussen (1924) pointed out that the amount of periglandular connective tissue may be large, dural sheath sometimes constituting as much as 25% of the weight of the gland. He also emphasised that the intercavernous venous sinuses, which lie within the sella, vary in size, a feature previously noted by Knott (1882). Extensions of the subarachnoid space may occupy the upper part of the sella. These were illustrated by Key and Retzius (1875) and described in detail by Sunderland (1945) and Busch (1951). Mahmoud (1958) too illustrated examples, but without comment. Though Bloch and Joplin (1959) showed that the diaphragma sellae runs from the tuberculum to the most anterior point on the convexity of the posterior clinoids, Busch (1951) found that it often curved downwards between its points of attachment. Furthermore, Schaeffer (1924) observed that while it sometimes consisted of a tough fibro-elastic sheet, it was often a much weaker structure and on occasion was reduced to a rim of tissue by a large infundibular foramen. Others have confirmed these findings (Sunderland, 1945; Busch, 1951; Mahmoud, 1958). Compression of the gland between tortuous carotid arteries was described by Simmonds (1914) and Kraus (1926). Bull and Schunk (1962) demonstrated angiographically the variability of the cavernous segment of the carotid arteries. Many of these anatomical variations were confirmed by Bergland, Ray and Torack

(1968) in their study of 225 necropsy specimens. Nonetheless, Oon, Lavender and Joplin (1962) and Di Chiro and Nelson (1962) found good correlation between gland width and the widths of the dorsum and floor, confirming earlier work in smaller series (Bloch and Joplin, 1959; Di Chiro, 1960). Other dimensions were not considered, these authors accepting the statement by Mahmoud (1958) that "the pituitary gland fills most of the sella turcica".

Enfield (1922) declared against measurement in the assessment of sellar abnormality stating "that the only definitely and positively abnormal roentgenographic finding is clear evidence of erosion of the bony structure", a view endorsed by du Boulay and El Gammal (1966). The radiological features of an intrasellar tumour as described by Cushing (1914), consisted of sellar enlargement and deformity, thinning and erosion of its bony outline and expansion of tumour into the sphenoid sinus. Camp (1924) and Pancoast (1932) noted that these downward extensions, if uneven, sometimes produced a second contour of the sellar floor. They noted also that erosion of the dorsum occurred first on its anterior surface. Mahmoud (1958) showed that this was greatest at its base. Cushing (1914) considered that the abnormal sella in acromegaly differed from that due to other pituitary tumours, bony thinning and erosion of its outline being less likely in this disease. Pancoast (1932) and Lindgren (1957) agreed. More recent work opposes this view (Tönnis, Friedman and Albrecht, 1957; Mahmoud, 1958; Ross and Greitz, 1966; Cecchini, 1968) but consistently indicates that the sella in acromegaly is normal in about 10% of patients (Steinbach, Feldman and Goldberg, 1959; Lang and Bessler, 1961; Cecchini, 1968). Of these authors only Cecchini described the use of tomography, despite evidence of its effectiveness in revealing sellar abnormality, particularly downward extensions of tumour (Petit-Dutaillis, Fischgold and Metzger, 1954; Šilinková-Málková and Blažek, 1957).

Suprasellar abnormality may be even more difficult to assess. In their joint anatomical studies de Schweinitz (1923) and Schaeffer (1924) emphasised that variations in the position of the optic chiasm and of the circle of Willis and anterior cerebral arteries make analysis of visual fields unreliable in the diagnosis of suprasellar extension of tumour. Steinbach, Feldman and Goldberg (1959) and, more tentatively, Schüller (1918) implied that these extensions produce a characteristic deformity of the fossa, its anterior and posterior walls diverging superiorly. This was not the view of Heuer (1920) or Camp (1924). Lindgren (1957), though suggesting that prediction of upward extension of tumour might be possible from analysis of sellar deformity, concluded that pneumoencephalography was essential. This too has its limitations. Collections of gas in the Sylvian fissures or around the supraclinoid segments of the carotid arteries frequently obscure the suprasellar cistern and anterior end of the third ventricle (Schvarcz, 1959; Lewtas and Jefferson, 1966). The latter, because of its variability

(Bull, 1956) may not reliably reflect the extent of suprasellar abnormality. To improve visualisation in the sagittal plane during pneumoencephalography Ziedses des Plantes (1937, 1950) suggested autotomography, whereby the patient, by rotating his head during the radiographic exposure, produced blurring of images not lying in the midline. The method was successfully employed by Schvarcz (1959) and Schechter and de Gutiérrez-Mahoney (1962). Twining (1938), on the other hand, suggested mechanical tomography in the lateral position. "A five spiral motion" was used by Epstein and Davidoff (1946) who strongly recommended the method. Paleirac, Labauge and Bassède (1953) also clearly demonstrated suprasellar anatomy by tomography during pneumoencephalography but gave few technical details. Later workers (Lindgren and Mattsson, 1965; Lewtas and Jefferson, 1966) also confined their examination to the sagittal plane. Tomography in a coronal plane was added by Metzger, Engel, Bonnemazou and Fischgold (1967) using hypocycloidal movement. Though much illustrative evidence attests to the success of these methods of pneumoencephalography in individual situations, no series has attempted to assess their accuracy.

Introduction

It became apparent from review of the literature that several aspects of sellar and parasellar anatomy required more detailed investigation, much of which could be accomplished by radiological means. This thesis follows four main avenues of investigation. Part I assesses the value of sellar measurement as a reflection of gland size by correlating the dimensions of the normal gland and fossa. Part II studies variations in the shape of the normal gland and fossa and in the contour of the diaphragma sellae and parasellar portions of the carotid arteries. Part III attempts to refine the accuracy of the radiological diagnosis and assessment of pituitary tumours by detailed analysis of sellar appearances on plain films and tomography. Part IV describes and evaluates a pneumoencephalographic method of demonstrating suprasellar anatomy. Many of the details which this thesis discusses and attempts to clarify have become of practical as well as academic interest since the introduction of pituitary ablation by implantation of radioactive seeds, heavy particle therapy, cryotherapy and transethmoidal hypophysectomy.

PART I

ESTIMATION OF PITUITARY GLAND DIMENSIONS FROM RADIOGRAPHS OF THE SELLA

Introduction

In Part I gland volume is correlated with fossa volume estimated from radiographs in a series of 50 necropsy specimens. Linear dimensions of gland and fossa are also correlated.

Material and Methods

Preparations were made from 50 adults who died from non-endocrine diseases and without evidence of raised intracranial pressure. They included 27 women aged 22 to 84 years, with a mean of 59 years, and 23 men aged 36 to 75 years, with a mean of 59 years (Fig. 1). Immediately after removal of the brain at necropsy, a block was cut from the sphenoid to include the intact pituitary gland with the carotid siphon on either side. Antero-posterior and lateral radiographs were taken with the centre of the block held 4 cm from a non-screen film using a focus-film distance of 180 cm. Subsequent measurements were made without correction for magnification (linear magnification = 2%).

In 31 of the specimens the whole preparation was fixed in 15% formol saline immediately after removal (i.e. the pituitary gland was fixed in situ in the sella). After fixation the gland was carefully removed from the sella by fracturing the dorsum. As much as possible of gland coverings was removed. The pituitary stalk was cut off flush with the superior surface of the gland.

The length and width of the gland were measured by calipers and the height by a micrometer screw gauge (Fig. 2). Gland volume was estimated by weighing the towel-dried specimen in air and in normal saline. In the other 19 specimens, the gland was removed from the fossa in the fresh state and the linear measurements and volume measured immediately and again after fixation for one week in 15% formol saline. No differences were apparent between glands fixed in situ and those fixed after dissection (see Figs. 7 - 10). The mean reduction in volume due to fixation was 3.1%. The change in linear dimensions was too small to be measured.

The glands were examined histologically and no major abnormalities likely to lead to a significant alteration in weight were found. Eight glands contained one or more microadenomata, mostly less than 1 mm in diameter, and one gland contained a small deposit of secondary carcinoma at the junction of the stalk and the pars nervosa.

Sellar dimensions on the radiographs were measured independently of gland measurements. The widths of the fossa floor and the dorsum sellae were measured directly from the antero-posterior radiograph to the nearest 0.5 mm. The lateral area was measured by projecting the lateral film on white cardboard (linear magnification x 10). The sellar outline was traced and cut out. The weight of the cut-out was compared with a standard of known area. The length and height of the fossa were also measured from the cut-out. The projection system was found helpful in resolving problems about end-points.

Definitions (Fig. 3)

Lateral sellar outline was considered to run from the tuberculum sellae around the sellar margin to the most anterior point on the convexity of the tip of the dorsum. A straight line was then drawn from here to the tuberculum. This line was considered to represent the usual position of the diaphragma. (This rather over-simplified representation of diaphragma position takes no account of possible convexity or concavity and is considered further in Part II). The area thus enclosed was regarded as the lateral area of the sella.

Length of the sella was defined as the longest dimension of this profile measured parallel to the line of the diaphragma. Where more than one contour was seen on the dorsum the most posterior line was chosen as the posterior limit of the fossa.

Height was defined as the greatest dimension measured at right angles to the line of the diaphragma. Where, on the lateral film, two contours were seen on the sellar floor measurement was made to the mid-point between them. If there were three contours at the sellar floor the middle one was chosen. Here the suggestions of Di Chiro and Nelson (1962) have been adopted.

Width was as defined by Di Chiro (1960), viz. the distance between the highest points of the lateral edges of the plateau of the sellar floor.

Width of the dorsum was that of its "waist" as defined by Bloch and Joplin (1959) viz. the width of the dorsum at the level of maximal narrowing, usually just below the posterior clinoids.

Gland measurements are defined in Fig. 2.

Results and Conclusions

Gland dimensions

A highly significant difference in gland volume exists between the sexes (Fig. 4). Mean female volume is 147 mm^3 greater than that of the males. Mean linear dimensions of the gland in the females are all slightly greater than in the males (Fig. 5).

Sellar dimensions

There is no significant difference in linear sellar dimensions between the sexes (Fig. 6). The product of the three linear dimensions and of lateral area and width showed slightly higher mean values in the females but this was not statistically significant ($0.4 < p < 0.5$).

Correlation of linear measurements of the gland with linear sellar measurements

1. Length of gland : length of sella (Fig. 7)

Males

Correlation between the length of the pituitary gland and the length of the sella is good ($r = 0.73$, $p < 0.001$). Average sellar length is 0.4 mm greater than average gland length.

Females

Again correlation is good ($r = 0.73$, $p < 0.001$). Sellar length equals gland length on average.

2. Height of gland : height of sella (Fig. 8)

Males

Correlation between the height of the gland and sellar height is poor ($r = 0.45$, $p < 0.05$). Average sellar height is 2.5 mm greater than average gland height.

Females

There is no significant correlation ($r = -0.02$). Mean sellar height is 1.5 mm greater than mean gland height.

3. Width of gland : width of sellar floor (Fig. 9)

Males

Correlation between the width of the gland and sellar width as measured from its floor is moderately good ($r = 0.60$, $p < 0.01$). Average floor width is 1.2 mm less than average gland width.

Females

Correlation is again moderately good ($r = 0.53$, $p < 0.01$). Average floor width is 2.2 mm less than average gland width.

4. Width of gland : width of dorsum (Fig. 10)

Males

Gland width correlates less well with the width of the dorsum than with floor width ($r = 0.41$, $0.05 < p < 0.1$). Average width of the dorsum is 0.3 mm greater than average gland width.

Females

By contrast, gland width in the females correlates well with the width of the dorsum ($r = 0.62$, $p < 0.001$). This correlation is better than that between gland width and floor width. Average width of the dorsum is 1.3 mm less than average gland width.

Correlation of three-dimensional sellar estimations with measured gland volume

1. Comparison of length (L) x height (H) x sellar floor width (W) with gland volume (Fig. 11)

Males

A good correlation exists ($r = 0.68$, $p < 0.001$). The best estimate of gland volume is obtained from the regression equation :

$$\text{Volume of gland} = 0.30\,(L \times H \times W) + 131 \text{ mm}^3.$$

Females

Correlation is less satisfactory ($r = 0.49$, $p < 0.01$).

The best estimate of gland volume is obtained from :

Volume of gland = 0.24 (LxHxW) + 333 mm^3.

2. Comparison of lateral sellar area (A) x sellar floor width (W) with gland volume (Fig. 12)

Males

Correlation is not significantly better than that obtained by using the product LxHxW ($r = 0.69$, $p < 0.001$). The best estimate of gland volume can be derived from the regression equation :

Volume of gland = 0.36 (AxW) + 121 mm^3.

Females

Correlation is significantly better than that obtained using LxHxW ($r = 0.65$, $p < 0.001$). The best estimate of gland volume is obtained from :

Volume of gland = 0.39 (AxW) + 226 mm^3.

DISCUSSION

In a random post-mortem sample, the pituitary gland is larger in women than in men. Of the many authors who have estimated sellar size from radiographs, only Bokelmann (1934) has emphasised this fact. In the present series, mean gland weight is 685 mg in females and 533 mg in males. These results correspond to those of Rasmussen (1928, 1934), who, as in the present study, removed as much as possible of the meningeal covering and cut off the stalk flush with the upper surface of the gland. He found a mean gland weight of 620 mg in 33 women and 499 mg in 47 men aged over 50 years. The figures of Erdheim and Stumme (1909) obtained from routine necropsy studies, suggest that increased gland size in females is mainly due to past pregnancies. They quote a mean gland weight of 669 mg in 14 nullipara aged 20 to 49 years, and 629 mg in 59 males of the same age, a difference which is insignificant ($0.2 < p < 0.3$). Their post-mortem measurements show that the female pituitary gland enlarges throughout pregnancy, reaching a maximum at 40 weeks and within one week post-partum. In 22 multipara dying at term or within one week of delivery, mean gland weight was 1070 mg. Thereafter the gland diminishes in weight. In 13 multipara dying one to seven weeks post-partum, mean gland weight was 788 mg. In ten multipara dying three and a half months to 18 years after pregnancy, mean gland weight was 735 mg. These figures suggest that reduction in gland weight after pregnancy is rapid but incomplete. In the present series, the female population is a mixture of multipara and nullipara. Numbers are insufficient for separate analysis of the effects of parity on gland size.

Although the pituitary gland is larger in females, this study has confirmed other work (Mahmoud, 1958; Joplin, 1965) that there is no sex difference in radiographic sellar dimensions. Haas (1954) found an insignificant sex difference in lateral sellar area. In the present series, the sex difference in lateral sellar area was also insignificant ($0.3 < p < 0.4$). Thus, derivation of pituitary gland dimensions from fossa dimensions should be separate for males and females. The results of Erdheim and Stumme (1909) quoted above suggest that, to be rigorous, separate analyses should be done for parous and nulliparous women.

No attempt was made to measure actual sellar volume. Removal of the intact gland by fracturing the dorsum precluded this. Mahmoud (1958) claimed that "the pituitary gland fills most of the sella turcica". Di Chiro and Nelson (1962) measured the volume of the sella after removal of its contents. They found that, on average, the gland occupied 79% of measured sellar volume, but quote a range from the German literature of 50 to 85% (Kovács, 1934; Carstens, 1949; Dill, 1952). Volume measurement of a space bounded superiorly and laterally by soft tissue structures is obviously open to considerable error. Moreover, the pituitary gland can clearly enlarge by displacement of soft tissue structures without altering the bony contours of the sella.

Oon (1963), estimating sellar volume radiologically, found a range of 466 - 1306 mm^3 (mean = 860 mm^3) in 250 normal adults. Di Chiro and Nelson (1962) quote a range of 240 - 1092 mm^3 (mean = 595 mm^3) in 173 normal adults. This discrepancy arises from different assumptions about the shape of the sella. Di Chiro and Nelson considered that this could be regarded as ellipsoid. Oon, like Meldolesi and Pansadoro (1937) and Cardillo and Bossi (1941), assumed that the volume of the sella could be derived by multiplying its lateral area by its width. The only estimates of fossa dimensions that can be made from radiographs are the length (L), height (H) and area (A) from lateral films and the floor width (W) or width of dorsum from antero-posterior or postero-anterior films. Except for height, there is a reasonable correlation between the linear dimensions of gland and fossa. In the present study, the product of three linear sellar dimensions (LxHxW) and the product of (AxW) have been related to gland volume, using regression analysis and making no assumptions about sellar shape. A good linear correlation between gland volume and the products (LxHxW) and (AxW) has been shown. In women, though not in men, the product (AxW) correlates slightly better with gland volume than the product (LxHxW). From the regression equations a "best estimate" of gland volume can be made from fossa measurements of length, height and floor width, or of lateral area and floor width.

The end-points used for sellar measurements in this study in general follow the recommendations of Di Chiro and Nelson (1962). A slightly different posterior limit of the diaphragma has been chosen, namely the most anterior part of the convexity of the tip of the dorsum rather than the highest point. This is a compromise reached after consideration of other published views (Silverman, 1957; Mahmoud, 1958; Joplin and Fraser, 1960; Di Chiro, 1960). It is supported by observations considered in Part II.

The closest correlation in linear measurements is that between gland and sellar length (r = 0.73 in men and women). Sellar length is easier to estimate than width and height. Width is measured from bony landmarks which do not themselves define the lateral limits of the sella. Nevertheless, gland and floor width correlate reasonably well. This confirms observations by Di Chiro and Nelson (1962) and by Oon, Lavender and Joplin (1962). In the present series, the width of the dorsum provides a better estimate of gland width than floor width in women but not in men. Gland and sellar height correlate poorly in men and not at all in women. Since gland height was measured from the centre of the concavity on the upper surface of the gland, it is reasonable that, on average, sellar height should exceed gland height. To measure sellar height, a constant position of the diaphragma was assumed. This takes no account of a diaphragma pushed upwards by a bulky gland, or of a gland the upper surface of which lies some distance below the line of the diaphragma as defined here. The lack of correlation between gland and fossa height in females may be related to the fact that the data of parous and nulliparous women were not separated.

The "best estimate" of pituitary gland volume from pituitary fossa measurements requires the use of regression analysis. A simpler though less precise estimate of gland volume can be made by assuming that the relationships between gland volume and the products (LxHxW) and (AxW) are linear and start from the mathematical origin. These approximate formulae in men are :-

$$V = 0.40\ (L \times H \times W)\ ;\ V = 0.48\ (A \times W).$$

In women they are :

$$V = 0.50\ (L \times H \times W)\ ;\ V = 0.59\ (A \times W).$$

These formulae were derived ignoring the 3% gland shrinkage produced by formol-fixation. If used in life, correction factors for radiographic magnification would have to be applied. The formula quoted by Di Chiro and Nelson (1962), $V = 0.50\ (L \times H \times W)$, already incorporates a correction for geometrical magnification and does not discriminate between males and females.

This part of the study has been concerned to estimate dimensions of normal pituitary glands from radiographs of the sella turcica. Techniques of pituitary ablation other than surgical excision require an accurate knowledge of the relationships between gland and fossa dimensions. As others (Enfield, 1922; du Boulay and El Gammal, 1966) suggest, sellar dimensions provide an insensitive indicator of pathological enlargement of the pituitary gland. In clinical practice, alterations in sellar contour and localised resorption or thinning of bone are probably better guides to the presence of an intra-sellar tumour. This is considered further in Part III.

SUMMARY OF PART I

Measurements of length, height, width and volume of the pituitary gland have been correlated with radiological measurements of corresponding dimensions of the sella turcica in 23 male and 27 female necropsies. The pituitary gland is significantly larger in women than in men. The pituitary fossa is not significantly different in size in men and women. Gland and fossa dimensions were correlated separately for each sex. Sellar length and floor width correlate well with gland length and width. Sellar height correlates poorly with gland height, especially in women. Sellar volume, derived from the product of length, height and floor width or from the product of lateral area and floor width, correlates well with gland volume.

PART II

CONFIGURATION OF SOFT TISSUE BOUNDARIES OF THE SELLA

Introduction

The relationship between the dimensions of the pituitary gland and radiological estimations of fossa size was considered in Part I. In Part II variations in the soft tissue boundaries of the fossa have been studied together with some variations in sellar configuration. These are of importance in planning dosimetry and operative procedures on the pituitary gland and may explain some failures of ablation and some complications.

Material and Methods

The material consisted of the 50 post-mortem preparations referred to in Part I. The block cut from the sphenoid was radiographed in antero-posterior, lateral and supero-inferior projections. Powdered bismuth was dusted on the diaphragma and antero-posterior and lateral radiographs repeated. The carotid siphons were then insufflated with bismuth powder and further antero-posterior, lateral and supero-inferior radiographs were taken. Measurements were again made from the films without correction for magnification (linear magnification = 2%).

The gland was removed intact from the sella and was then radiographed in antero-posterior, lateral and supero-inferior projections to provide a permanent record of gland shape.

Measurements and Results

1. Lateral wall of fossa

The anatomy is illustrated in Fig. 13. The carotid siphons lie nearest to one another posteriorly and here may be separated from the gland only by the medial wall of the cavernous sinus. Tortuous carotid arteries had made impressions on the lateral aspects of 14 of the glands and in a few had resulted in actual narrowing (Fig. 14). This narrowing is obviously most likely to occur posteriorly, and the gland can follow carotid configuration to a remarkable degree (Fig. 15). In an attempt to quantify this, measurements of maximum gland width were related to minimum intercarotid distance (Fig. 16). This is defined as the distance between the medial aspects of the carotid siphons at the point of maximum convergence. The measurement was made on supero-inferior and antero-posterior radiographs in which the carotid siphons had been opacified. In the very few specimens where the point of maximum convergence was posterior to the fossa, the distance was measured immediately anterior to the dorsum. In two preparations carotid filling was too poor to allow measurement. Intercarotid distance varied from 8.5 to 22 mm with no significant sex difference. There was a significant correlation with gland width ($p < 0.001$ in females and < 0.01 in males). In 13 out of 25 females, but only in three out of 23 males, maximum gland width exceeded minimum intercarotid distance.

Tortuous carotid arteries may not only compress the pituitary gland; they may erode the dorsum sellae. In 38 out of 48 cases the arteries were so tortuous that they came into contact with the upper half of the dorsum. In the more extreme cases the posterior clinoids were undercut, with erosion of the lateral margins of the dorsum (Figs. 17 and 18). The apparent thickness of the dorsum sellae in lateral radiographs is due in part to the curving forward of its lateral margins (Fig. 19). This thickness is diminished by erosion of the curved lateral margins. Increased carotid tortuosity in old age may therefore help to account for senile "thinning" of the dorsum. The curve of the dorsum is also responsible for the multiple contours of the dorsum commonly seen on lateral radiographs. A further variant of these contour lines is shown in Fig. 20 in which an example of a "fossetta pituitaria" (Cardillo and Bossi, 1941) is illustrated.

2. Roof of fossa

(a) Attachments of diaphragma

Lateral radiographs of all specimens demonstrated that the diaphragma was attached anteriorly to the tuberculum and postero-laterally to the most anterior point of the posterior clinoids. This confirms the findings of Bloch and Joplin (1959). The midline attachment to the dorsum was also considered. In 45 of the present series the diaphragma was attached to the most anterior point of the convexity of the tip of the dorsum. In the others, it was attached to the most superior point.

The tuberculum may be difficult to define. It usually lies 5 - 8 mm behind the limbus sphenoidale (Joplin, 1965), which is normally quite easily identified but may be absent. The configuration of the sulcus chiasmaticus varies (Zander, 1896). It may lie horizontally or at various degrees of angulation and may be almost vertical (Fig. 21a). According to Schaeffer (1924) this latter configuration is unusual and is due to failure of development of the post-sphenoid. In this situation the tuberculum may not be obvious, and there is a danger that on radiographs a point on the limbus sphenoidale may be taken for the tuberculum. Sometimes a gently curving sulcus is present and the tuberculum may be no more than an insignificant projection (Fig. 21b). Radiological interpretation may be further confused by the presence of middle clinoid processes (Figs. 21c; 21d and 22). In the present series, 14 examples were found, their position on lateral radiographs being 3 - 4 mm below the tuberculum. Occasionally these form prominent projections on the lateral part of the anterior wall and may fuse with the anterior clinoids to form the carotico-clinoid foramina through which pass the carotid arteries (Fig. 22).

This latter situation is most likely to occur in the "bridged fossa" where anterior and posterior clinoids are also joined. These bridges do not form a roof for the fossa but are placed more laterally. Diaphragmatic position on lateral radiographs can be assessed, as in more normal sellar configurations, by defining the tuberculum and the most anterior point of the convexity of the tip of the dorsum (Fig. 23).

(b) Diaphragmatic contour

Since, on lateral radiographs, the diaphragma is generally regarded as a straight line, the frequency with which actual diaphragma position varied from this was checked. The lateral film in which the diaphragma had been outlined by bismuth was chosen. A straight line was drawn on the film from the tuberculum to the most anterior point on the convexity of the tip of the dorsum, this over-simplified representation of diaphragma position (the "diaphragmatic line") being a compromise of other published views (Silverman, 1957; Mahmoud, 1958; Joplin and Fraser, 1960; Di Chiro, 1960). The distance of the central part of the actual diaphragma above or below this line was measured, and a considerable variation found (Fig. 24). In 14 of the 27 women the centre of the diaphragma deviated from its predicted position by 1 mm or more (either above or below the "diaphragmatic line") and in seven of these the deviation was 2 mm or more. The extremes of variations are illustrated (Fig. 25) and a further example of a large intrasellar extension of the subarachnoid space (not in the consecutive series) is shown in Fig. 26. In 15 of the 23 males the central part of the diaphragma was 1 mm or more below the predicted position. None was above. In ten males the deviation was 2 mm or more. In a total of eight cases from both sexes the central part of the diaphragma lay 3 mm or more below its predicted position.

The diameter of the infundibular foramen, through which the stalk passes, is known to vary considerably (Schaeffer, 1924; Sunderland, 1945; Busch, 1951; Mahmoud, 1958; Bergland, Ray and Torack, 1968). Though this variation was not measured, one unusually large infundibular foramen was noted (Fig. 14) and a fenestrated diaphragma, another recognised variant, is also illustrated (Fig. 26). Subarachnoid extensions into the sella are known to occur (Key and Retzius, 1875; Sunderland, 1945; Busch, 1951). All glands were examined microscopically in horizontal section and small collections of bismuth in minute spaces lying between the anterior and posterior pituitary lobes were found in eight instances (Fig. 27). Serial sections demonstrated that these spaces were of subarachnoid origin and in one instance, the tubular subarachnoid extension was followed for nearly 1 mm before it merged with the gland surface.

DISCUSSION

Compression of the lateral surfaces of the pituitary gland by carotid arteries has been described by previous writers. Simmonds (1914) comments on this, and Kraus (1926) illustrates a good example of pituitary compression by "sclerotic" carotid arteries. Bull and Schunk (1962) measured the distance between the carotid siphon and the midline in a series of control patients and patients with pituitary and other intracranial tumours. In the patients without tumours this distance (approximately half the distance measured in the present study) varied from 5 to 11 mm, a range which is in good agreement with present measurements of intercarotid distance (range 8.5 to 22 mm). These show how closely the posterior parts of the carotid siphons can approach each other. An example of carotid siphons lying only 4 mm apart is illustrated by Bergland, Ray and Torack (1968). The pituitary gland is often much narrower posteriorly than anteriorly. In pituitary implantation, posteriorly placed seeds are more likely to lie near the carotid siphons. The potential danger is underlined by the death of a patient from a subarachnoid haemorrhage a few days after pituitary implantation for metastatic breast cancer. The haemorrhage occurred from an aneurysm of the left carotid siphon unrecognised before implant (Fig. 28). This complication is rare but the danger is obviously greater in older patients who are likely to have tortuous carotid arteries.

In this series, the carotid siphons came into contact with the upper half of the dorsum in 38 out of 48 cases. This figure probably reflects the high average age of the subjects since both Mahmoud (1958) and Joplin (1965) found that the carotid arteries in their series were related to the lower half of the dorsum. Undercutting of the posterior clinoids should be looked for, particularly in elderly patients; if present, carotid angiography should be considered before operative or implantation procedures. A seed giving uniform radiation throughout its length should not be implanted too far posteriorly in these patients. This consideration may be more important in women since 13 out of 25 females but only three out of 23 males had a minimum intercarotid distance which was less than maximum gland width.

Carotid tortuosity and the wide variation in intercarotid distance limit the value of carotid angiography in the assessment of gland width. As an alternative method of investigation Weidner, Rosen and Hanafee (1965) have suggested venography of the cavernous sinuses and Dutou and Colon (1964) have injected iodised oil into the sella at the time of pituitary implant. Neither method has been widely adopted.

The variation that was found between the actual position of the diaphragma and the position deduced from bony landmarks is also considerable in terms of the size of the gland. Busch (1951) and Bergland, Ray and Torack (1968) made similar observations.

It is obviously very difficult in any routine way to identify actual diaphragma position from bony landmarks. Present measurements show that the mean actual diaphragmatic position in women does not differ significantly from the predicted position though the range is wide. In men, the mean actual position is 1.5 mm below the "diaphragmatic line" and the range of variation is less. This difference is measured at the centre of the upper surface of the gland; it is probable that the mean difference over the whole upper surface of the gland is about half this. Allowance for this should be made in calculating gland height from plain radiographs.

A serious complication of pituitary implantation is the development of cerebrospinal fluid leakage. This complication may be manifest shortly after implant or it may occur many days or even weeks later. An accepted explanation of this occurrence is excessive radiation damage to the diaphragma sellae. In eight out of 50 necropsies the central part of the diaphragma has been shown to be 3 mm or more below the "diaphragmatic line". Mean fossa height estimated from radiographs was found in Part I to be 8 mm. The anatomical variations that have been documented here are likely to contribute significantly to the incidence of cerebrospinal fluid leaks. A radioactive rod placed centrally in the fossa as judged radiologically would have been within 1 mm of the true position of the diaphragma in eight of the 50 cases. A minor variation in the position of the rod could obviously lead to an immediate drip. The risk of a delayed drip from radiation effects would in any event be high with a β -emitting rod only 1 mm from the diaphragma. A prolongation of subarachnoid space between the anterior and posterior lobes, found in eight out of 50 necropsies, is a further possible cause of leakage of cerebrospinal fluid immediately after implantation. It is likely that anatomical variations in the diaphragma and subarachnoid space account for the majority of cases of cerebrospinal fluid drip after pituitary implantation. Busch (1951) found intrasellar extensions of the subarachnoid space as large as those illustrated here (Figs. 25a and 26) in 5.5% of 788 anatomical specimens. Their fortuitous demonstration by pneumoencephalography, frequently in patients without evidence of endocrine disease, is well documented (Engels, 1958; Friedmann and Marguth, 1961; Kaufman, 1968; Zatz, Janon and Newton, 1969; Caplan and Dobben, 1969). The term "empty sella" has been applied by some of these authors. In a gland showing such extreme variation from normal it would obviously be impossible to produce satisfactory pituitary ablation by implantation techniques based on bony landmarks alone without placing a seed virtually in contact with the subarachnoid space. Demonstration of the position of the superior aspect of the gland by pneumoencephalography is considered in Part IV.

SUMMARY OF PART II

The radiological anatomy of the 50 pituitary glands and fossae considered in Part I has been studied in detail. Particular attention was paid to variations in the position of the diaphragma sellae relative to bony landmarks of the sella and to the relationship of the carotid siphons to the gland. Marked variations in the shape of the gland and in the level of the centre of the diaphragma sellae were observed. The carotid arteries have a more intimate relationship with the gland than standard anatomical texts imply and in several of the specimens studied, appeared to compress the gland and to undercut the posterior clinoids. Erosion of the curved lateral margins of the dorsum sellae by tortuous internal carotid arteries may explain senile "thinning" of the dorsum. All glands were studied microscopically, and in eight of the 50, an intrasellar extension of the subarachnoid space was observed. Other anomalies of the diaphragma and variations in the bony contour of the fossa are commented upon and illustrated. Attention is drawn to the implications of these observations for operative procedures on the pituitary gland.

PART III

ASSESSMENT OF RADIOLOGICAL CRITERIA OF SELLAR ABNORMALITY ON PLAIN FILMS AND TOMOGRAPHY

Introduction

Variations in size and shape of the normal sella were discussed in Parts I and II. In Part III the frequency and extent of sellar abnormality have been assessed radiologically in a series of 140 acromegalic patients. An attempt has been made to evaluate criteria of abnormality when changes in sellar configuration are sufficiently subtle to cause difficulty in diagnosis and to assess the value of tomography.

Material and Methods

One hundred and forty patients aged 22 to 74 years (mean 50 years) were studied. All had obvious clinical features of acromegaly. Seventy one were female, 69 male. One hundred and nineteen patients had no previous local treatment to the pituitary gland. Twenty one patients had radiotherapy to the pituitary 4 months to 28 years before (mean $6\frac{1}{2}$ years). Postero-anterior and lateral films of the skull were available in all, and coned films of the sella in most patients. Patients were first classified, on the basis of sellar appearances, into three groups : A, B and C. In Group A (77 patients; 55%) the sella was grossly abnormal (Fig. 29), with obvious deformity, enlargement and erosion of its outline. In Group B (38 patients; 27%) sellar abnormality was shown on lateral films by a double contour. However the area bounded by the inner contour was normal or only slightly enlarged (Fig. 30).

Abnormality was confirmed by central or lateral depression of the sellar floor where this was visible on the postero-anterior films. It was considered that an observer with experience of pituitary tumours would have little difficulty in recognising this type of sellar abnormality. In Group C (25 patients; 18%) plain film abnormality was minimal or indefinite or was detectable only after the most careful analysis.

Group C provided particular diagnostic difficulty and was therefore subjected to detailed study as follows :-

1. Lateral plain films were analysed and compared with those from control patients according to five commonly accepted criteria (see below).

2. Lateral tomograms were analysed to assess their value vis-à-vis plain films.

3. Sellar measurements from frontal and lateral plain films were compared with those from the 50 post-mortem specimens considered in Parts I and II.

The preliminary classification was made by the author and another radiologist with considerable experience in the assessment of pituitary fossae. Our assumptions were tested by presenting randomly mixed examples of plain films from Groups A, B and C and controls to two further observers from whom clinical details were withheld.

1. Lateral plain films

The lateral plain films from all patients in Group C were carefully analysed by the author and the other radiologist and compared with lateral skull films of 24 patients without clinical evidence of pituitary disease. Twelve were diabetic and 12 had been referred for skull examination because of minor head injury (Table I). Five criteria of abnormality, viz: sellar enlargement (assessed subjectively), abnormality of sellar shape, pathological double contour, reduction in thickness of the cortical bone forming the sellar outline (the "lamina dura") and erosion of this cortical bone were separately analysed and scored as follows. For each criterion, a score of 2 was given if the fossa was abnormal, a score of 1 if the abnormality was indefinite, and a score of 0 if the fossa showed no abnormality. The scores for each fossa were then summated and the control group compared with Group C.

2. Lateral tomography

Lateral tomography of the sella was available in 24 patients from Group C. This was linear in four and hypocycloidal in 20. The same five features were scored. The tomographic equivalent of double contour was an excessive change in fossa size or contour on adjacent tomographic cuts. Major tumour extensions, unsuspected on the plain films, were sometimes revealed by tomography. An additional score of two was then given. Plain films and tomographic scores were compared. (Lateral tomography of

TABLE I

Group C patients and controls

	No. of patients	Age range (years)	Mean age (years)	Males	Females
Group C patients	25	29 - 69	52	9	16
Controls	24	19 - 59	42	19	5

the sellae of patients in the control group was considered not to be ethically justified and was not performed).

3. Sellar measurements

From lateral plain films of patients in Group C, sellar height, length and lateral area were measured. When the floor could be identified on postero-anterior films, its width was measured. Central or lateral depression of the floor was quantified by measuring on postero-anterior films the vertical distance between its highest and lowest points. Measurements were corrected for magnification and compared with similar measurements from the 50 post-mortem specimens considered previously.

"Blind" assessment

Postero-anterior and lateral plain films of the control group were mixed with eight examples from Group A, five from Group B and twenty three from Group C. Clinical details and tomograms were withheld and films were masked to an area 6 cm in diameter so that only the sella was visible. They were viewed by an endocrinologist and by a third radiologist without special experience of the radiology of the sella. These observers were asked to categorise sellar appearances as abnormal, normal or doubtful.

Results and Conclusions

Seventy seven patients (55%) were allocated to Group A, 32 (27%) to Group B and 25 (18%) to Group C (Fig. 31). Analysis of patients in Group C is now considered in greater detail.

Plain film scores in controls and patients in Group C

These are summarised in Fig. 32. There is a considerable overlap between the two groups. The two control fossae with scores of five are considered to be unequivocally abnormal (see discussion). If the normal range is represented by scores of 0 to 3, then only 11 of the 25 fossae can be regarded as abnormal on critical assessment of plain films. The scores for each of the five features separately assessed are shown in Fig. 33. Fossa shape and reduction of cortical thickness (thinning of the "lamina dura") discriminate poorly between control fossae and fossae in Group C. Subjective assessment of sellar enlargement, the presence of an abnormal double contour and bone erosion discriminate only slightly better.

Comparison of plain films and tomogram scores in Group C

Results are summarised in Fig. 34. In nine of the 24 patients an unexpected major extension of the pituitary tumour into the sphenoid was revealed by tomography. Tomogram scores exceeded plain film scores in 23 of the 24 patients in whom tomography was carried out. Mean increase, including scores for downward extensions, was four points (range 0 to 7). In one patient plain film and tomogram scores were identical. Tomogram score was never less than plain film score. If the normal range for tomogram scores is taken as 0 to 3 points, then all but one of the 24 patients in Group C in whom tomography was available would be classified as having an abnormal fossa. (One patient in Group C did not have tomography; his plain film score was 3.) Scores for each feature separately assessed are shown in Fig. 35. Abnormalities, except for abnormality of shape, were twice as frequent in the tomograms as in the plain films. Bone erosion, thinning of cortex or a pathological double contour were each evident in at least two thirds of the tomographed sellae.

Sellar measurements

Measurements of length, height, width and lateral area are summarised in Fig. 36. Length and floor width are of no value in distinguishing between the fossae in the necropsy series and in Group C patients. Fossa height is a slightly better discriminant. In five Group C patients, fossa height exceeded 10.8 mm. Lateral area in four Group C patients exceeded 128 sq.mm. The figures quoted refer to the upper limits established in the necropsy series. Two fossae showing excess height had a normal lateral area.

Fig. 37 summarises measurement of central or lateral depression of the fossa floor. Central depression of up to 2 mm was observed in the necropsy specimens. In two Group C patients, this was exceeded by 0.5 mm. Maximum lateral depression in the necropsy series was 1 mm. This was exceeded in four Group C patients. In two of these abnormality of the floor was not apparent on lateral radiographs.

"Blind" Assessment (Table II)

Group A : All eight fossae shown to both observers were called abnormal.

Group B : Of the five fossae assessed in this group, one was classified as normal and only one as abnormal by both observers.

Group C : Only two of 23 fossae were classified as abnormal by both observers. Four were called normal by both observers.

Controls : Seventeen of the 24 fossae were classified as normal and none as abnormal by both observers.

"Blind" assessment and plain film scores are compared in Fig. 38.

TABLE II

"Blind" assessment by two observers

	Total	N/N	N/D	N/A	D/D	D/A	A/A
Group A	8	0	0	0	0	0	8
Group B	5	1	1	0	0	2	1
Group C	23	4	7	1	3	6	2
Controls	24	17	4	1	0	2	0

N/N : both observers called the fossa normal.
N/D : one observer called it normal, the other doubtful.
N/A : one called it normal, the other abnormal.
D/D : both called it doubtful.
D/A : one called it doubtful, the other abnormal.
A/A : both called it abnormal.

DISCUSSION

Previously published series suggest that the pituitary fossa is abnormal in about 90% of patients with acromegaly; 89% of 27 patients (Steinbach, Feldman and Goldberg, 1959), 93.5% of 31 patients (Lang and Bessler, 1961) and 87% of 35 patients (Cecchini, 1968). Of these authors only Cecchini refers to the use of tomography. The present figures suggest that 55% of pituitary fossae in acromegaly will show gross abnormality obvious on lateral radiographs. In a further 27% abnormality will be apparent on lateral radiographs as a double sellar contour, the inner one being of normal or near-normal dimensions and frequently intact. Postero-anterior radiographs will confirm abnormality in many. However, the difficulty that may be encountered in this group was under-estimated and only one of the five fossae from Group B presented "blind" to two observers was consistently called abnormal. One was called normal by both observers (Fig. 39). Since this type of abnormality occurred in over a quarter of patients the importance of recognising this radiological presentation is obvious.

Particular difficulty was encountered in 25 patients (18%). Only two fossae in this group were called abnormal by both "blind" observers. Even a system of itemised analysis and scoring failed to distinguish 14 Group C patients from controls, i.e. 10% of the whole series of 140. Thus it appears that even the most rigorous plain film assessment will reveal pathology in only 90% of acromegalic fossae.

Minimal sellar abnormality is difficult to detect. Individually, the five criteria of abnormality chosen here are only moderately helpful in plain film analysis. Sellar shape is a poor discriminant. Normal variations make assessment of generalised contour abnormality difficult. Local variations like the fossetta pituitaria (Cardillo and Bossi, 1941) compound the problem. Reduction of cortical thickness also discriminates poorly and bony erosion is only slightly better. However no attempt was made to use the extremely meticulous radiographic methods of Fry and du Boulay (1965) who emphasised the importance of erosion as a diagnostic feature. Subjective assessment of fossa size in the doubtful fossa is of little value and the presence of a double contour discriminates no better. (Distinction is made between the obvious double contour of Group B fossae and the lesser degrees found in Group C and controls). The outline of the normal fossa is frequently double or even treble (Bokelmann, 1934; Di Chiro and Nelson, 1962; Rådberg, 1963). In addition, imperfect radiographic positioning may lead to a false impression of abnormality. Though no one feature discriminates well, itemised analysis compels attention to detail and allows better discrimination when all criteria are considered together. Nonetheless, 14 of the 25 Group C fossae (56%) were in the normal range. This number would have been greater if the fossae of two diabetic patients had not been judged to be abnormal. Both were included as controls since they were originally passed as normal on routine radiological reporting, partly, it is felt, because carotid calcification obscured detail (Fig. 40).

As others have suggested (Enfield, 1922; du Boulay and El Gammal, 1966), sellar measurement in the diagnosis of pituitary tumours is of limited value. Lateral sellar area exceeded the upper limit of the normal range established in Part I (128 sq. mm) in only four of the 25 patients in Group C. Sellar height was increased in five patients, sellar length in none. Di Chiro (1960) claimed that increased width may be a valuable sign of a pituitary tumour. Measurements of sellar width in Group C patients were all within the wide normal range established in the necropsy data.

The value of postero-anterior films in the assessment of diagnostically difficult fossae is limited on two further counts. First, the floor may not be visible because of bone thinning and erosion, large nasal turbinates, poorly pneumatised sphenoid sinuses and perhaps inappropriate tube angulation (Rådberg, 1963). In 11 of the 25 Group C patients (44%) postero-anterior films did not demonstrate the floor. Secondly, central or lateral depression of the sellar floor occurs in the normal. Postero-anterior films showed abnormal depression of the floor in six Group C patients but in only two was this abnormality not evident on lateral radiographs.

Thus in only two of the 25 patients did postero-anterior films make a positive contribution to the diagnosis of sellar abnormality.

Tomograms provide a much more detailed and accurate assessment of the morphology of the sella (Petit-Dutaillis, Fischgold and Metzger, 1954; Šilinková-Málková and Blažek, 1957). Even in Group A patients in whom the sella is grossly abnormal on plain films (Fig. 41) tomography provides a much better estimate of tumour size and extension. The fossae in Group B caused the "blind" observers great difficulty in diagnosis. In this group, tomography will demonstrate dramatically the abnormality of the sella (Fig. 42). In Group C fossae in which no abnormality may be demonstrable on plain films, major downward extension may be shown on tomography. Such an extension was shown in over one third of Group C patients (Fig. 43). In addition, other abnormalities were found over twice as frequently on tomograms as on plain films. A pathological double contour, bony erosion or reduction in cortical thickness were revealed in at least two thirds of these fossae. Even if major downward extensions were ignored, total tomographic scores were abnormal in 23 patients, more than double the number with abnormal plain film scores. Including scores for these extensions, mean increase in score on tomography was four points. Plain film and tomogram scores averaged 3 and 7 respectively. The increase in score was less on linear tomography than on hypocycloidal tomography. However, since linear cuts were made 5 mm apart and hypocycloidal cuts 3 mm apart, the difference may be partly due to the smaller number of films available for assessment on linear tomography. Only one patient had a tomographic score within the normal range. When one adds to this the one patient in whom tomography was not performed 138 of the 140 fossae were abnormal on a combination of plain film and tomographic assessment.

Thus, 90% of acromegalic fossae are abnormal on critical analysis of plain films; 98.6% are abnormal when tomographic assessment is included. Patients with clinical or biochemical evidence of abnormality of pituitary function should be investigated by tomography of the sella, even when plain films are within normal limits.

SUMMARY OF PART III

Radiographs of the pituitary fossa of 140 acromegalic patients have been studied. Patients were divided into three groups on the basis of plain film appearances. Group A (55%) showed gross abnormality. In Group B (27%) a double contour was present, the dimensions of the inner contour being normal or only slightly enlarged. Findings suggest that abnormality is easily missed in this group. Group C (18%) provided particular diagnostic difficulty and was studied in greater detail. Commonly accepted criteria of abnormality on plain films and measurement of fossa dimensions discriminated poorly between control and Group C fossae. Tomography showed significant abnormalities in the majority of Group C fossae, and major downward extensions unsuspected on plain films in more than a third. Combined assessment by plain films and tomography showed abnormalities in 138 of the 140 patients. Tomography of the sella is indicated in patients with clinical or biochemical evidence of abnormality of pituitary function even when plain films appear normal.

PART IV

DEMONSTRATION OF PARASELLAR ANATOMY BY PNEUMOENCEPHALOGRAPHY COMBINED WITH TOMOGRAPHY

Introduction

The difficulty of predicting the position of the superior aspect of the pituitary gland from bony landmarks was commented on in Parts I and II. The value of tomography in the assessment of sellar abnormality was discussed in Part III. In this part, to demonstrate suprasellar anatomy, pneumoencephalograms performed on patients with pituitary tumours were combined with circular tomography using the Philips Polytome in sagittal and coronal planes. Adverse reactions, to which patients with pituitary insufficiency undergoing pneumoencephalography are prone (Taveras and Wood, 1964), were reduced as far as possible by drug control before, during and after the procedure (see appendix to Part IV).

Applied Anatomy

The suprasellar cistern lies between the postero-inferior aspects of the frontal lobes and the pons. On each side it is limited by the medial surfaces of the temporal lobes. Its roof is formed by the anterior part of the floor of the third ventricle and consists mainly of the tuber cinereum. Its floor is the diaphragma sellae. The most important contents are shown in Fig. 44. In addition, an arachnoid membrane crosses between the oculomotor nerves and occasionally obstructs the passage of gas into the suprasellar cistern (Liliequist, 1959).

Material and Methods

Forty examinations were performed in 37 patients of whom 20 were female, 17 male. Mean age was 45 years (range 16 - 69 years). Plain radiographs showed an expanded pituitary fossa in all. Twenty nine patients suffered from acromegaly, three from Cushing's syndrome, four had a chromophobe adenoma and one a craniopharyngioma. (Intrasellar components of this craniopharyngioma were demonstrated on pituitary biopsy). Intrasellar implantation of radioactive seeds had been performed before examination in six patients.

Each examination was begun with the Philips Polytome erect. The seated patient was positioned with his head resting against the table-top, sagittal plane parallel to the radiographic film. A harness was used to help control the position of the head (Fig. 45). A trial midline tomographic cut centred on the pituitary fossa was made. Routine fractional pneumoencephalography by the lumbar route was begun. Approximately 10 - 15 ml of air or oxygen were introduced into the ventricles and a further 20 - 25 ml into the basal cisterns with the patient's head extended. Single midline tomographic cuts were used to assess progress. When delineation of suprasellar anatomy was judged to be satisfactory, circular tomographic cuts 3 mm apart were made in the sagittal plane. To show the entire suprasellar area, both anterior clinoids were included in the region examined. After removal of the lumbar puncture needle the patient was tilted into the supine position. The examination was then continued in the coronal plane. Circular tomographic cuts 5 mm apart were made, the examination extending from the dorsum sellae to the chiasmatic sulcus. (All the above radiographs were obtained without grids. A lead diaphragm 3 cm in diameter was used to limit the area of the X-ray beam). The patient was then transferred to a Schonander skull table where hanging-head lateral autotomograms (Ziedses des Plantes, 1950; Schechter and de Gutiérrez-Mahoney, 1962) were obtained to show the anterior end of the third ventricle.

Cases were divided into three groups according to whether the investigation showed normal suprasellar anatomy (group N), a suprasellar tumour (group S) or intrasellar extension of the subarachnoid space (group I).

Suprasellar tumours were classified as small, moderate or large depending on whether vertical extent of the tumour above the "diaphragmatic line" (see Parts I and II) was less than 6 mm, 6 - 11 mm or over 11 mm respectively, figures being corrected for radiographic magnification.

To assess the completeness of the examination, a note was made of the frequency with which the following structures were demonstrated : the superior aspect of the pituitary gland; the optic chiasm and pituitary stalk; and the parasellar arteries.

Demonstration of suprasellar anatomy by hanging-head autotomography was assessed separately.

Visual fields of all patients were carefully examined using Bjerrum charts to assess the value of perimetry in the diagnosis of suprasellar tumour.

To see if suprasellar extension was predictable on the basis of sellar configuration, plain films and, where available, tomograms of the pituitary fossae of all patients were presented to an endocrinologist and a radiologist, both highly experienced in interpretation of sellar radiographs. Clinical details were withheld. Analysis was attempted in terms of eversion of the dorsum and elevation of the tuberculum where this was undercut. In this context, small suprasellar tumours were ignored.

Results

One examination failed, gas being stopped at the level of the oculomotor nerves as described by Liliequist (1959). Thirty nine successful examinations were made in 36 patients (Table III).

Twenty examinations (in 20 patients) showing normal suprasellar anatomy were assigned to group N (Figs. 46 and 47).

Sixteen examinations (in 14 patients) were allotted to group S (Figs. 48 and 49). The suprasellar component was

TABLE III

Successful examinations *		Examinations showing normal suprasellar anatomy		Examinations showing suprasellar component of pituitary tumour		Examinations showing intrasellar extension of subarachnoid space	
No. of Examinations	No. of Patients	No. of Examinations	No. of Patients	No. of Examinations	No. of Patients	No. of Examinations	No. of Patients
39	36	20	20 †	16	14	3	3 †

* One of the 40 examinations failed, gas being stopped at the level of the oculomotor nerves (see text).

† One patient, examined twice, appears in both groups.

large in four patients, moderate in six and small in four. Re-examination in two of these patients after pituitary implant showed no change in one and marked reduction of the upward extension in the other (Fig. 50).

Group I comprised three examinations (in three patients). In two patients intrasellar extension of the subarachnoid space followed pituitary implant (Fig. 51). In the third patient there had been no previous local treatment of the pituitary tumour or any history to suggest pituitary infarction (Fig. 52).

Completeness of examination

The entire upper surface of the gland was shown in 27 examinations, 21 times in the sagittal plane and 21 times in the coronal plane. It was shown in 14 examinations in group N, 11 in group S and two in group I. Initial examination in the ten patients with moderate or large suprasellar tumours showed the anterior aspect of that component in eight.

The optic chiasm and pituitary stalk were demonstrated in 33 examinations but were separable from one another in only 11, usually in the coronal plane when individual optic nerves could sometimes be identified (Fig. 46b). Chiasm and stalk were demonstrated in all 20 examinations in group N, ten in group S and all three in group I. They were separable from one another in ten examinations in group N, none in group S and one in group I.

The supraclinoid parts of the internal carotid arteries were recognised in 31 examinations, more frequently in the coronal plane when their relationship to any suprasellar extension could be assessed (Fig. 48b). The proximal part of one or other anterior cerebral artery was frequently seen near the midline and was a potential source of confusion with the optic chiasm or nerve on lateral films (Figs. 47, 49 a and b, 51 b and c, 52). The terminal segment of the basilar artery was identified in 35 examinations and in many cases could be seen dividing into posterior cerebral arteries. Here too anatomical relationships to any tumour were apparent.

Assessment of autotomography

Of the 20 patients in group N, hanging-head autotomograms were unequivocally normal in nine. In a further eight varying degrees of doubt existed while in the other three no valid comment was possible.

In group S, all patients with large or moderate suprasellar tumours showed indentation of the anterior end of the third ventricle. Autotomography in those with small suprasellar extensions was normal.

Intrasellar gas was convincingly shown by autotomography in only one of the three patients in group I.

In the one patient in whom there was no delineation of the suprasellar cistern autotomography showed a normal third ventricle.

Visual Fields (see Table IV)

Three of the four patients with large suprasellar tumours had bitemporal hemianopia. The fourth, with normal visual fields, developed a severe field defect immediately after pituitary implant. (This gradually improved on high doses of systemic corticosteroids.) Of the six patients with a moderate suprasellar extension no field defect was present in four, one of whom (Fig. 49) developed blindness in one eye and a temporal hemianopia in the other soon after implant. (The hemianopia recovered completely with large doses of corticosteroids but vision in the other eye showed no improvement.) Normal visual fields were present in the four patients with small extensions and in patients in groups N and I.

Prediction of suprasellar extension from analysis of sellar shape

On the basis of sellar configuration, one observer correctly concluded that a large or moderate extension was present in nine cases, but wrongly predicted upward extension in a further nine. The other observer correctly suggested such an extension in four cases but was wrong almost as frequently, predicting

TABLE IV

Patients with a suprasellar component of the pituitary tumour

	Large (over 11 mm *)	Moderate (6 - 11 mm *)	Small (Under 6 mm *)
Total	4	6	4
Number without visual field defects	1	4	4

* Figures, corrected for magnification, refer to greatest extent of tumour vertically above the "diaphragmatic line" (see Parts I and II).

upward extensions in three others where none existed. Each observer concluded that upward extension was present in the patient D.R. (Fig. 52) in whom the superior aspect of the gland was sunken within the fossa. In general however, suprasellar extension tended to be present more frequently in patients with large fossae.

DISCUSSION

Interest in the use of tomography during pneumoencephalography has been stimulated by recent advances in radiographic machinery. The Mimer was used with linear movement to show suprasellar anatomy by Lindgren and Mattsson (1965) and Hanafee, Bilodeau, Alberti and Wilson (1967). Metzger, Engel, Bonnemazou and Fischgold (1967) preferred hypocycloidal tomography using the Philips Polytome, though aware of its shortcomings. Its design does not allow supine sagittal (transaxial) tomography nor the use of a standard encephalographic chair for support when sagittal cuts are made erect. This position is less likely to allow gas to dissect anteriorly in the suprasellar cistern. In the present study this was not found to be a problem, partly because of the routine use of coronal tomography which is readily performed supine on the Polytome. The entire superior aspect of the pituitary gland was shown in two-thirds of patients and of the ten patients with moderate or large suprasellar extensions, the anterior aspect was shown in eight. This compares very favourably with the figure of 10% quoted by Lewtas and Jefferson (1966) who, with the patient supine, used tomography in only the sagittal plane. Though coronal tomography is illustrated by Lewtas (1966) and mentioned briefly by Hanafee, Bilodeau, Alberti and Wilson (1967) only Metzger, Engel, Bonnemazou and Fischgold (1967) have made extensive use of tomography in planes other than sagittal. Unlike this previous work, the present study used circular tomography. Hypocycloidal movement, with its longer period of tube swing, increases the difficulty of immobilisation of the patient. Linear tomography tends to produce confusing artefacts, especially in the coronal plane where tomography has most to offer (Liliequist, 1959).

As carefully performed by Schechter and de Gutiérrez-Mahoney (1962) hanging-head autotomography is valuable, albeit in only the sagittal plane, if mechanical tomography is unavailable. However present results suggest that in a number of cases uncertainty will remain. Rarely entry of gas into the suprasellar cistern is obstructed by an arachnoid membrane as described by Liliequist (1959) or by post-operative adhesions and in this situation demonstration of the anterior end of the third ventricle by hanging-head films may help to exclude from consideration a large suprasellar tumour. The present study, like that of Camp (1924), found that this conclusion could not be made from an analysis of sellar configuration despite the suggestion of Steinbach, Feldman and Goldberg (1959) that increase in "the distance between the anterior and posterior clinoid processes" indicates suprasellar extension.

Precise anatomical demonstration is especially important where gland shrinkage has led to intrasellar extension of the subarachnoid space. This must be convincingly demonstrated before surgery or pituitary implant if leakage of cerebro-spinal fluid is to be avoided. Lewtas (1966) describes a particularly gross example in which after radiotherapy of the pituitary the third ventricle extended into the sella. If either hypophysectomy or pituitary implant is contemplated, it is essential to show that the optic chiasm or nerves have not also sunk into an intrasellar position. This development, with visual deterioration, has been noted after pituitary implant (Hartog, Doyle, Fraser and Joplin, 1965) and after radiotherapy (Lee and Adams, 1968) and clinically may be confused with further extension of tumour.

On the other hand, visual field defects were not detected in five out of ten patients in whom moderate or large suprasellar tumours were shown. This is not surprising in view of the variation in position of the optic chiasm demonstrated anatomically by Schaeffer (1924) who found that it may lie as much as 10 mm above the diaphragma. Bull (1956) confirmed these observations radiologically. The anterior cerebral artery may also participate in compressing the optic nerve (Bartels, 1906; de Schweinitz and Holloway, 1912; Schaeffer, 1924) and this study frequently demonstrated the juxtaposition of these two structures. When pituitary implant is performed in patients with visual field defects it is important to administer cortico-steriods in high dosage to reduce local oedema (Fraser, 1970). This was not done in the two patients with suprasellar extension who developed field defects only after implant. Had steroids been used on the basis of the anatomical findings this complication might have been avoided. These cases provide a powerful argument for accurate pneumoencephalography before treatment of any pituitary tumour. In view of the variation in position of the superior aspect of the normal gland documented in Part II this argument can be applied with equal force to any patient undergoing therapeutic procedures on the pituitary gland.

APPENDIX TO PART IV

Control of adverse reactions during Pneumoencephalography

Since the procedure usually involved a fairly long period of sitting upright, it was necessary to have an effective regime to control side effects, many patients being pituitary deficient. The following regime was evolved in close co-operation with the Department of Anaesthetics at the Royal Postgraduate Medical School (Heath, 1969). Premedication consisted of cortisol hemisuccinate 100 mg, atropine 0.6 mg, haloperidol 5 - 10 mg and phenoperidine 1 - 2 mg, all given intramuscularly 45 minutes before the procedure. At the same time crepe bandages were tightly applied from the toes to mid thigh, to avoid pooling of blood in the lower limbs. During the procedure, any headache was treated with intravenous phenoperidine. Since this drug is a respiratory depressant, the patient's breathing was carefully observed. Hypoventilation could frequently be corrected by asking the patient to increase the rate and depth of respiration, but if this failed, nalorphine 5 mg was given intravenously. Blood pressure was monitored and any hypotension was treated with intravenous mephentermine. For the first 48 hours after the procedure the patient received prednisone, oral perphenazine and dihydrocodeine. On the third and fourth days perphenazine and dihydrocodeine were given as required.

In 20 patients randomly selected, a careful record was kept of headache, vomiting and fainting. The blood pressure was monitored. Headache, the commonest side effect did not occur in 40% and of those who did develop headache 40% required no further analgesia. There was marked increase in frequency and intensity of headache in those patients given more than 35 ml of gas and when the procedure took longer than 2 hours. Vomiting did not occur in 70% of patients and in the remainder was only slight. There were no significant falls in blood pressure and, though two patients felt faint, none fainted.

Taveras and Wood (1964) comment on the reluctance of many workers to investigate patients with pituitary tumours by pneumoencephalography but suggest that the use of replacement hormones and small amounts of gas will prevent adverse reactions. However, the detailed examinations made in the present study demanded a degree of co-operation and freedom from side effects not available until recently. The above regime is founded on the use, in combination, of the analgesic phenoperidine and the sedative haloperidol. Used in this way they have been widely discussed in the anaesthetic literature (Robertson, 1967; Holmes and Gibbs, 1967). Together they provide a high level of tolerance to pain yet leave the patient sufficiently alert to co-operate. Complete abolition of headache is possible despite fairly large quantities of gas in the basal cisterns, though it was found that the introduction of a total of more than 35 ml of gas was an indication for further phenoperidine. Respiratory depression was not a major problem. The anti-emetic properties of haloperidol effectively controlled nausea and vomiting. Hypotension was successfully avoided by bandagi ng the legs.

SUMMARY OF PART IV

Thirty seven patients suffering from various types of pituitary tumours have been examined by pneumoencephalography combined with tomography using the Philips Polytome. The technique described uses careful premedication by phenoperidine and haloperidol. Circular tomography in sagittal and coronal planes showed suprasellar anatomy in 39 out of 40 examinations. Hanging-head autotomography was much less informative. Fourteen patients had suprasellar extensions of tumour. In three patients the subarachnoid space extended into the sella. Suprasellar anatomy in the others was normal. The therapeutic implications of accurate anatomical assessment are discussed. Suprasellar extensions of tumour could not be reliably diagnosed by analysis of sellar configuration and frequently produced no detectable visual field defect.

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<u>APPENDIX TO THESIS</u>

<u>Published Papers</u>

Estimation of pituitary gland dimensions from radiographs of the sella turcica

A post-mortem study

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In two recent papers (Di Chiro and Nelson, 1962; Oon, 1963) attempts were made to estimate the volume of the sella turcica from radiographs. The formula of Di Chiro and Nelson, which was based on that for an ellipsoid, used the length (L) and height (H) of the pituitary fossa measured on a lateral skull radiograph and the width of the floor (W) measured from a postero–anterior projection. It incorporated a factor which corrected for geometrical magnification and what the authors called "the empirical error found in a small series of 15 cases". Using this formula, Volume $=0{\cdot}5(L\times H\times W)$, Di Chiro and Nelson (1962) found that the sellar volume ranged from 240 to 1,092 mm^3 (mean $=595$ mm^3) in 173 normal adults (p. 1001 of their publication quotes a range of 233–1,092 mm^3 but on p. 1006 the range is 240–1,092 mm^3). Oon (1963) multiplied the lateral area of the pituitary fossa by the width of its floor and, after correction for magnification, found that the volume of the fossa ranged from 466 to 1,306 mm^3 (mean $=860$ mm^3) in 250 normal adults.

du Boulay and El Gammal (1966), noting the disagreement between these authors and the wide range of normal measurements, judged sellar enlargement subjectively. They considered that quotation of the actual dimensions of the sella in their own series "would impart a spurious appearance of exactitude".

In the present study gland volume is correlated with fossa volume estimated from radiographs in a series of 50 necropsy specimens. Linear dimensions of gland and fossa are also correlated.

MATERIAL AND METHODS

Preparations were made from 50 adults who died from non-endocrine diseases and without evidence of raised intracranial pressure. They included 27 women aged 22–84 years and 23 men aged 36–75 years (Fig. 1). After removal of the brain at necropsy, a block was cut from the sphenoid to include the intact pituitary gland with the carotid syphon on either side. Antero–posterior and lateral radiographs were taken with the centre of the block held 4 cm from a non-screen film using a focus-film distance of 180 cm. Subsequent measurements were made without correction for magnification (linear magnification $=2$ per cent).

In 31 of the specimens the whole preparation was fixed in 15 per cent formol saline immediately after removal (*i.e.* the pituitary gland was fixed *in situ* in the sella). After fixation the gland was carefully removed from the sella by fracturing the dorsum. As much as possible of gland coverings was removed. The pituitary stalk was cut off flush with the superior surface of the gland. The length and width of the gland were measured by calipers and the height by a micrometer screw gauge (Fig. 2). Gland volume was estimated by weighing the towel-dried specimen in air and in normal saline. In the other 19 specimens, the gland was removed from the fossa in the fresh state and the linear measurements and volume measured immediately and again after fixation for one week in 15 per cent formol saline. No differences were apparent between glands fixed *in situ* and those fixed after dissection (see Figs. 7–10). The mean reduction in volume due to fixation was 3.1 per cent. The change in linear dimensions was too small to be measured.

The glands were examined histologicaly and no major abnormalities likely to lead to a significant alteration in weight were found. Eight glands contained one or more microadenomata, mostly less than 1 mm in diameter, and one gland contained a small deposit of secondary carcinoma at the junction of the stalk and the pars nervosa.

Sellar dimensions on the radiographs were measured independently of gland measurements. The widths of the fossa floor and the dorsum sellae were measured directly from the antero–posterior radiograph to the nearest 0·5 mm. The lateral area was measured by projecting the lateral film on white cardboard (linear magnification $\times 10$). The sellar outline was traced and cut out. The weight of the

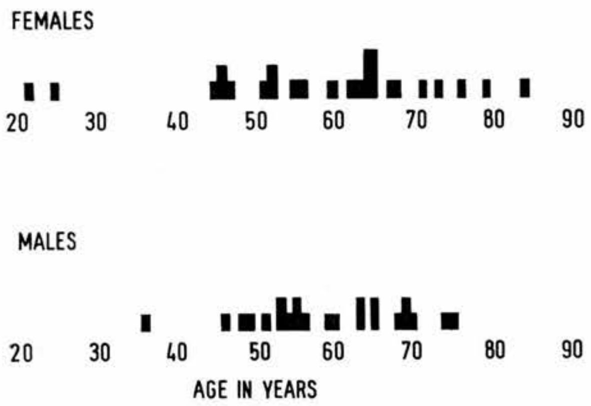


FIG. 1.

Age distribution in males and females in the series.

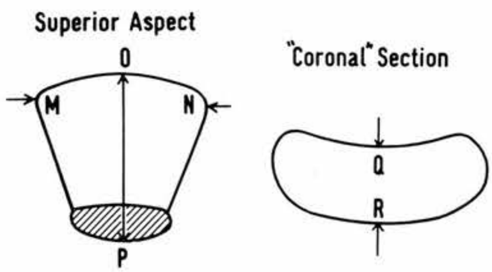


FIG. 2.

Diagram of the pituitary gland. A considerable variation in gland shape exists. The most common shape is shown. The pars posterior is shown shaded The greatest width (MN) and length (OP) were measured. Height (QR) was measured from the centre of the concavity that usually forms the superior surface of the gland. Where no concavity existed we measured the greatest supero–inferior dimension. In each case the pituitary stalk had been removed.

cut-out was compared with a standard of known area. The length and height of the fossa were also measured from the cut-out. The projection system was found helpful in resolving problems about end-points.

Definitions (Fig. 3)

Sellar outline was considered to run from the tuberculum sellae around the sellar margin to the most anterior point on the convexity of the tip of the dorsum. A straight line was then drawn from here to the tuberculum. We considered this line to represent the usual position of the diaphragma. (This is a rather over-simplified representation of diaphragma position and takes no account of possible convexity or concavity.) The area thus enclosed was regarded as the lateral area of the sella.

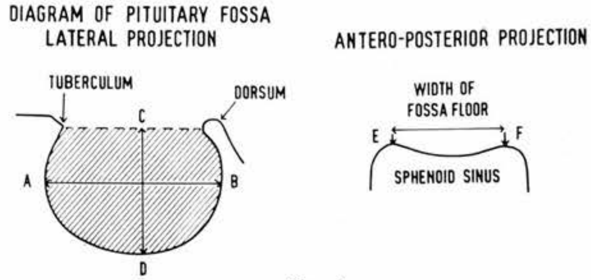


FIG. 3.

The line of the diaphragma (as defined by us) runs from the tuberculum to the most anterior point on the convexity of the tip of the dorsum.
Dotted line = diaphragma.
Shaded area = lateral sellar area.
Horizontal dimension (AB) = length.
Vertical dimension (CD) = height.
Length (AB) and height (CD) are, respectively, the greatest dimensions measured parallel to and at right angles to the diaphragma. Width (EF) is measured between the highest points of the lateral edges of the plateau of the fossa floor.

Length of the sella was defined as the longest dimension of this profile measured parallel to the line of the diaphragma. Where more than one contour was seen on the dorsum the most posterior line was chosen as the posterior limit of the fossa.

Height was defined as the greatest dimension measured at right angles to the line of the diaphragma. Where, on the lateral film, two contours were seen on the sellar floor we measured to the mid-point between them. If there were three contours at the sellar floor we chose the middle one. Here we have followed Di Chiro and Nelson (1962).

Width was as defined by Di Chiro (1960), *viz.* the distance between the highest points of the lateral edges of the plateau of the sellar floor.

Width of the dorsum was that of its "waist" as defined by Bloch and Joplin (1959), *viz.* the width of the dorsum at the level of maximal narrowing, usually just below the posterior clinoids.

Gland measurements are defined in Fig. 2.

RESULTS AND CONCLUSIONS

Gland dimensions

A highly significant difference in gland volume exists between the sexes (Fig. 4). Mean female volume is 147 mm^3 greater than that of the males. Mean linear dimensions of the gland in the females are all slightly greater than in the males (Fig. 5).

Sellar dimensions

There is no significant difference in linear sellar dimensions between the sexes (Fig. 6). The product of the three linear dimensions and of lateral area

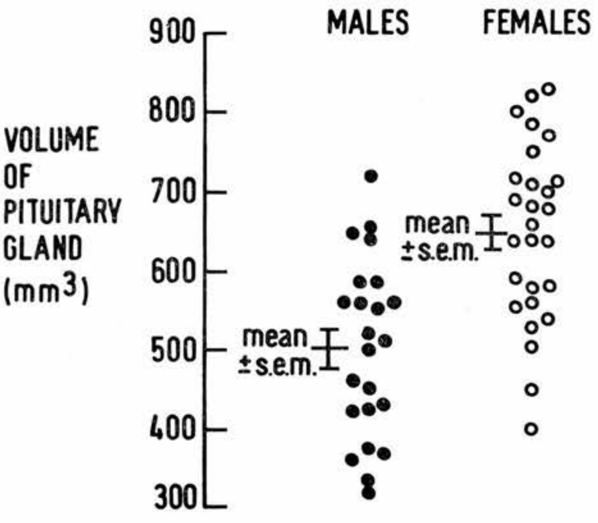


FIG. 4.

Pituitary gland volume plotted separately for males and females. Mean volume in females (range 399–827 mm³) is 147 mm³ greater than mean volume in males (range 320–718 mm³). This difference is significant at the 0·1 per cent level.

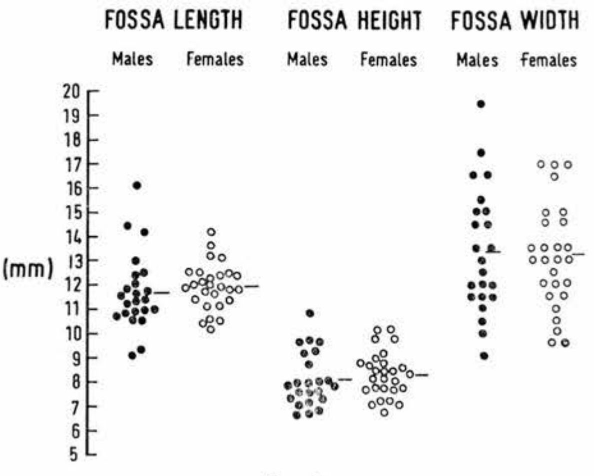


FIG. 6.

Linear fossa dimensions (mm), measured from radiographs, shown separately for males and females. There is no significant difference in the means. Note the relatively small variation in fossa height in the females compared with gland height shown in Fig. 5. The mean in each group is shown by the horizontal line.

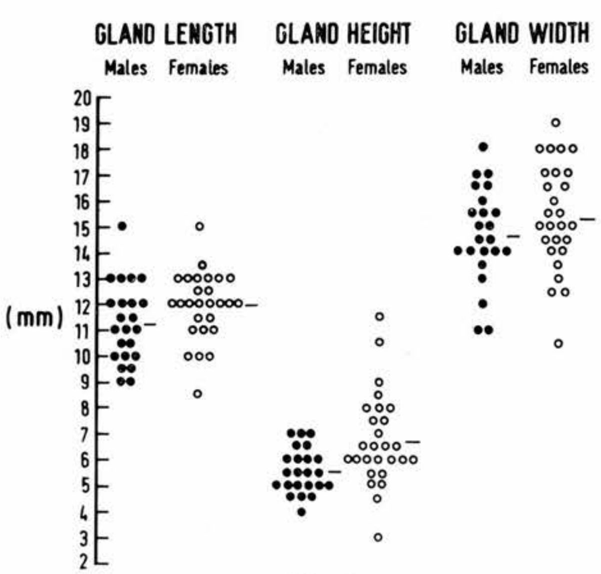


FIG. 5.

Linear gland dimensions (mm) plotted separately for males and females. Mean linear dimensions in the females are all slightly greater than in the males. Note the greater variation in gland height in the females than in the males. The mean in each group is shown by the horizontal line.

and width showed slightly higher mean values in the females, but this was not statistically significant ($0{\cdot}4 < p < 0{\cdot}5$).

Correlation of linear measurements of the gland with linear sellar measurements

1. *Length of gland: length of sella* (Fig. 7).

Males. Correlation between the length of the pituitary gland and the length of the sella is good ($r=0{\cdot}73$, $p<0{\cdot}001$). Average sellar length is 0·4 mm greater than average gland length.

Females. Again correlation is good ($r=0{\cdot}73$, $p<0{\cdot}001$). Sellar length equals gland length on average.

2. *Height of gland: height of sella* (Fig. 8)

Males. Correlation between the height of the gland and sellar height is poor ($r=0{\cdot}45$, $p<0{\cdot}05$). Average sellar height is 2·5 mm greater than average gland height.

Females. There is no significant correlation ($r=-0{\cdot}02$). Mean sellar height is 1·5 mm greater than mean gland height.

3. *Width of gland: width of sellar floor* (Fig. 9)

Males. Correlation between the width of the gland and sellar width as measured from its floor is moderately good ($r=0{\cdot}60$, $p<0{\cdot}01$). Average floor width is 1·2 mm *less* than average gland width.

Females. Correlation is again moderately good ($r=0{\cdot}53$, $p<0{\cdot}01$). Average floor width is 2·2 mm *less* than average gland width.

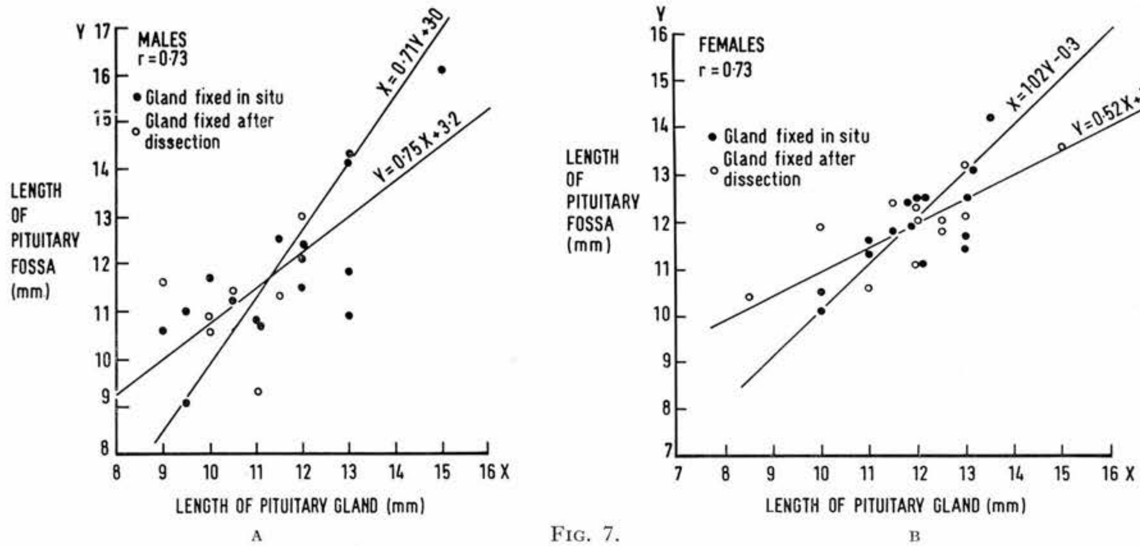


Fig. 7.

Correlation between gland length and fossa length for males (A) and females (B). This is good in both sexes (p < 0·001). No differences were apparent between the glands fixed *in situ* and those fixed after dissection (see also Figs. 8–10).

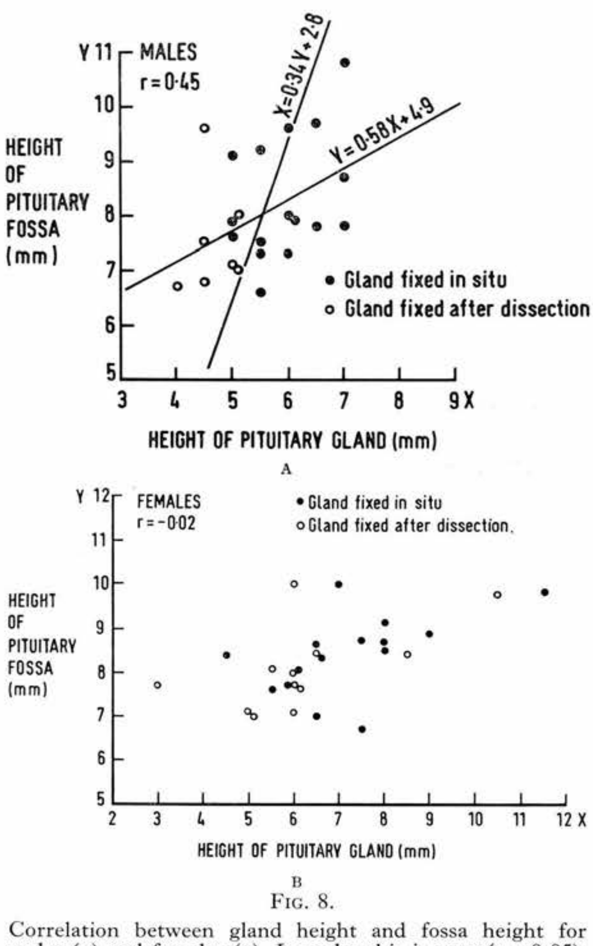


Fig. 8.

Correlation between gland height and fossa height for males (A) and females (B). In males this is poor ($p < 0{\cdot}05$). In females there is no correlation.

4. *Width of gland: width of dorsum* (Fig. 10)

Males. Gland width correlates less well with the width of the dorsum than with floor width, ($r = 0{\cdot}41$, $0{\cdot}05 < p < 0{\cdot}1$). Average width of the dorsum is 0·3 mm *greater* than average gland width.

Females. By contrast, correlation is good in the females, being better than correlation with floor width ($r = 0{\cdot}62$, $p < 0{\cdot}001$). Average width of the dorsum is 1·3 mm *less* than average gland width.

Correlation of three-dimensional sellar estimations with measured gland volume

1. *Comparison of length* (L) × *height* (H) × *sellar floor width* (W) *with gland volume* (Fig. 11)

Males. A good correlation exists ($r = 0{\cdot}68$, $p < 0{\cdot}001$). The best estimate of gland volume is obtained from the regression equation:

Volume of gland $= 0{\cdot}30\,(L \times H \times W) + 131$ mm^3.

Females. Correlation is less satisfactory ($r = 0{\cdot}49$, $p < 0{\cdot}01$). The best estimate of gland volume is obtained from:

Volume of gland $= 0{\cdot}24\,(L \times H \times W) + 333$ mm^3.

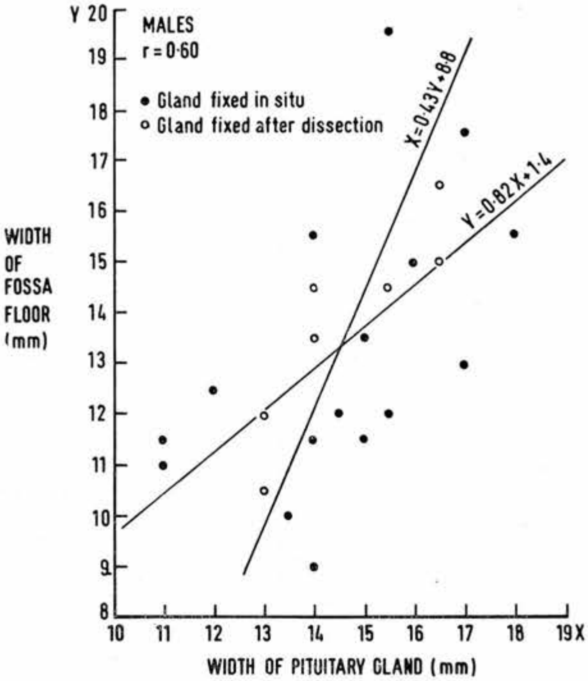
2. *Comparison of lateral sellar area* (A) × *sellar floor width* (W) *with gland volume* (Fig. 12)

Males. Correlation is not significantly better than that obtained by using the product $L \times H \times W$ ($r = 0{\cdot}69$, $p < 0{\cdot}001$). The best estimate of gland volume can be derived from the regression equation:

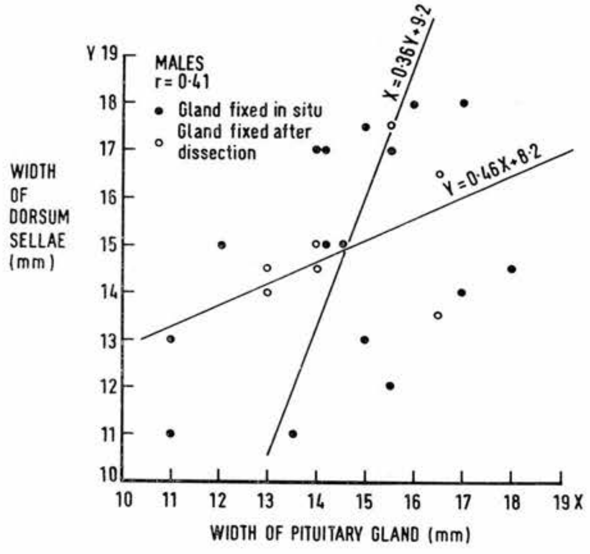
Volume of gland $= 0{\cdot}36\,(A \times W) + 121$ mm^3.

Females. Correlation is significantly better than that obtained using $L \times H \times W$ ($r = 0{\cdot}65$, $p < 0{\cdot}001$). The best estimate of gland volume is obtained from:

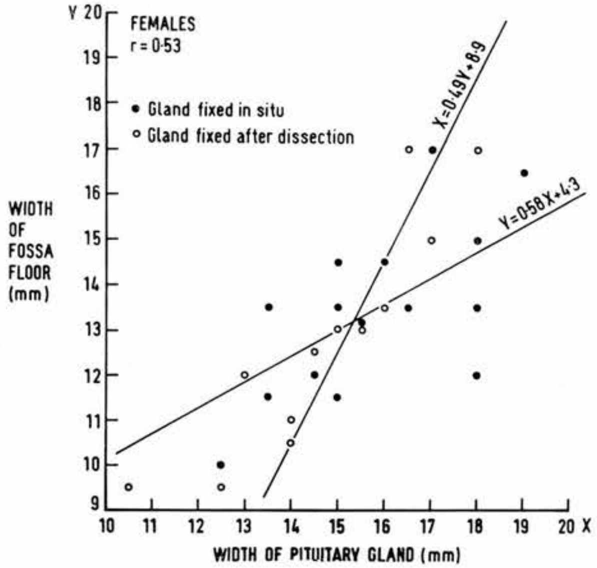
Volume of gland $= 0{\cdot}39\,(A \times W) + 226$ mm^3.



A



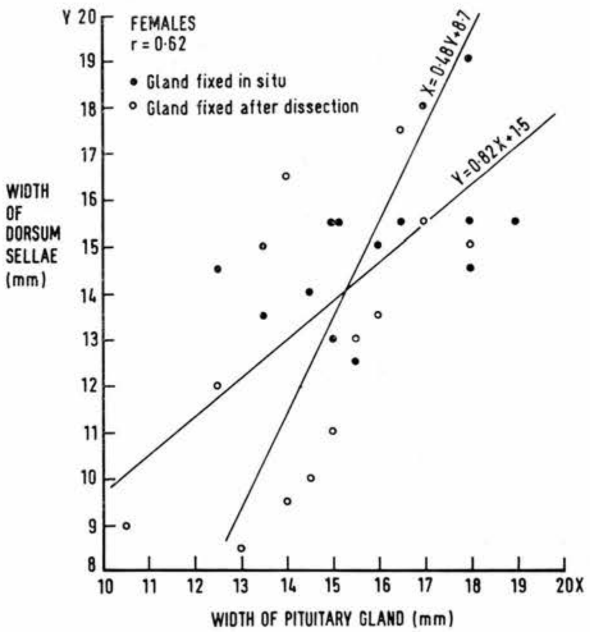
A



B

FIG. 9.

Correlation between gland width and sellar floor width for males (A) and females (B). This is moderately good in both sexes ($p < 0{\cdot}01$).



B

FIG. 10.

Correlation between gland width and dorsum width for males (A) and females (B). In males this is poorer than in Fig. 9A ($0{\cdot}05 < p < 0{\cdot}1$). In females, correlation is better than in Fig. 9B ($p < 0{\cdot}001$).

DISCUSSION

In a random post-mortem sample, the pituitary gland is larger in women than in men. This fact has been overlooked in the radiological literature. In our series, mean gland weight is 685 mg in females and 533 mg in males. Our results correspond to those of Rasmussen (1928; 1934) who, like us, removed as much as possible of the dural covering and cut off the stalk flush with the upper surface of the gland. He found a mean gland weight of 620 mg

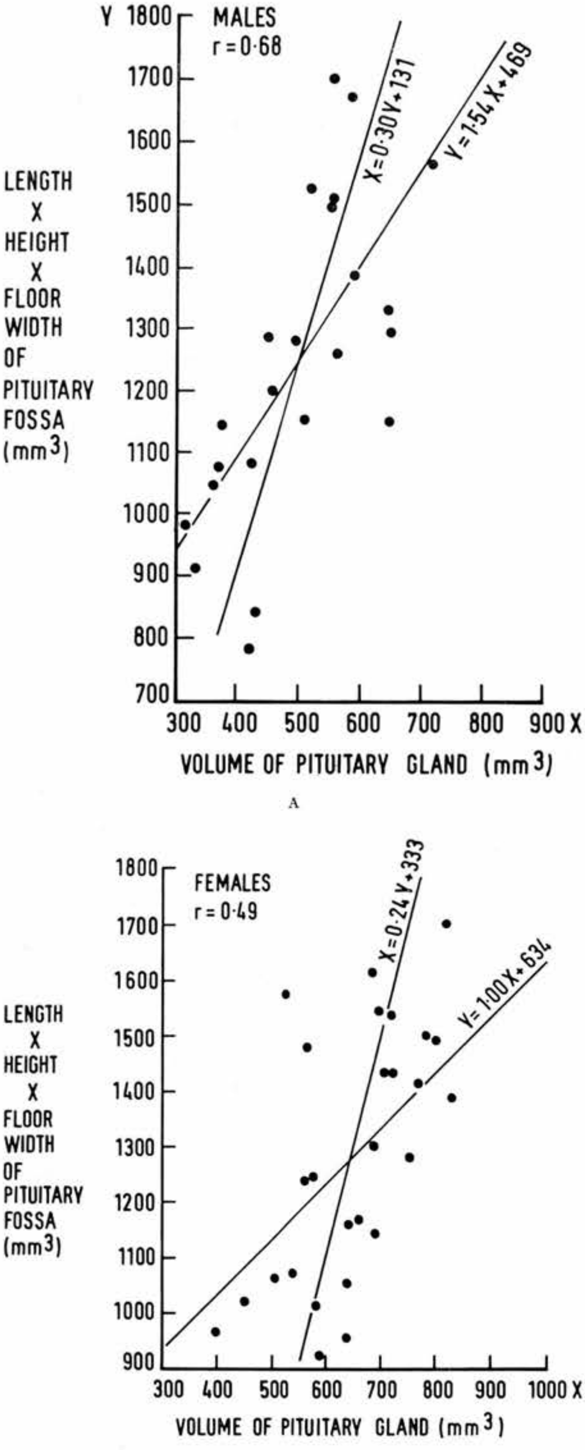


Fig. 11.

Gland volume plotted against L × H × W for males (A) and females (B). Correlation is good in males ($p < 0{\cdot}001$) and moderately good in females ($p < 0{\cdot}01$).

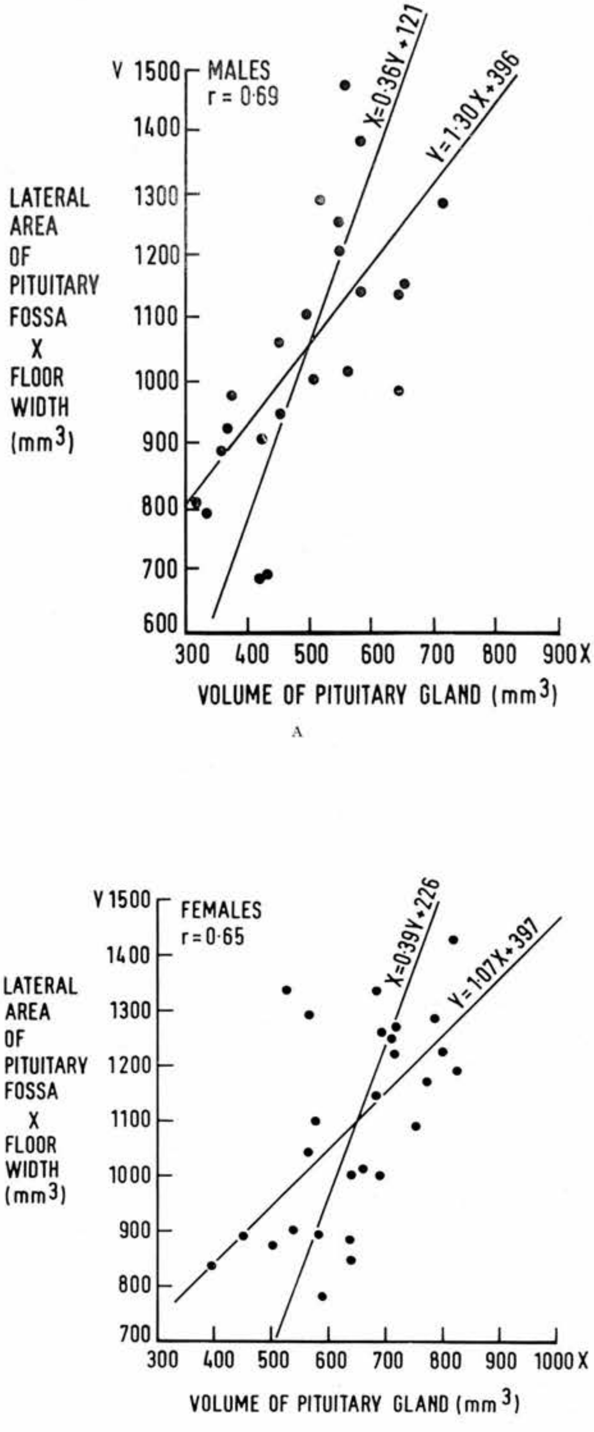


Fig. 12.

Gland volume plotted against $A \times W$ for males (A) and females (B). Correlation is good in both sexes ($p < 0{\cdot}001$). Note that in females this is significantly better than in Fig. 11B.

in 33 women and 499 mg in 47 men aged over 50. The figures of Erdheim and Stumme (1909), obtained from routine necropsy studies, suggest that increased gland size in females is mainly due to past pregnancies. They quote a mean gland weight of 669 mg in 14 nullipara aged 20–49, and 629 mg in 59 males of the same age ($0{\cdot}2 < p < 0{\cdot}3$). Their post-mortem measurements show that the female pituitary gland enlarges throughout pregnancy, reaching a maximum at 40 weeks and within one week post-partum. In 22 multipara dying at term or within one week of delivery, mean gland weight was 1,070 mg. Thereafter the gland diminishes in weight. In 13 multipara dying one to seven weeks post-partum, mean gland weight was 788 mg. In ten multipara dying three and a half months to 18 years after pregnancy, mean gland weight was 735 mg. These figures suggest that reduction in gland weight after pregnancy is rapid but incomplete. In our series, the female population is a mixture of multipara and nullipara. Our numbers are insufficient for separate analysis of the effects of parity on gland size.

Although the pituitary gland is larger in females, we have confirmed other work (Mahmoud, 1958; Joplin, 1965) that there is no sex difference in radiographic sellar dimensions. Haas (1954) found an insignificant sex difference in lateral sellar area. In our series, the sex difference in lateral sellar area was also insignificant ($0{\cdot}3 < p < 0{\cdot}4$). Derivation of pituitary gland dimensions from fossa dimensions should be separate for males and females. To be rigorous, separate analyses should be done for parous and nulliparous women.

We made no attempt to measure actual sellar volume in our specimens. Removal of the intact gland by fracturing the dorsum precluded this. Mahmoud (1958) claimed that "the pituitary gland fills most of the sella turcica". Di Chiro and Nelson (1962) measured the volume of the sella after removal of its contents. They found that on average, the gland occupied 79 per cent of measured sellar volume, but quote a range from the German literature of 50 to 85 per cent. Volume measurement of a space bounded superiorly and laterally by soft-tissue structures is obviously open to considerable error. Moreover, the pituitary gland can clearly enlarge by displacement of soft-tissue structures without altering the bony contours of the sella.

The discrepancy between the radiological estimates of sellar volume of Di Chiro and Nelson (1962) and Oon (1963) arises from different assumptions about the shape of the sella. Di Chiro and Nelson (1962) considered that this could be regarded as an ellipsoid. Oon assumed that the volume of the sella could be derived by multiplying its lateral area by the floor width. The only estimates of fossa dimensions that can be made from radiographs are the length (L), height (H) and area (A) from lateral films and the floor width (W) or width of dorsum from antero-posterior or postero-anterior films. We have shown that, except for height, there is a reasonable correlation between the linear dimensions of gland and fossa. We have related the product of three linear sellar dimensions ($L \times H \times W$) and the product of ($A \times W$) to gland volume, using regression analysis and making no assumptions about sellar shape. We have shown a good linear correlation between gland volume and the products ($L \times H \times W$) and ($A \times W$). In women, though not in men, the product ($A \times W$) correlates slightly better with gland volume than the product ($L \times H \times W$). From the regression equations a "best estimate" of gland volume can be made from fossa measurements of length, height and floor width, or of lateral area and floor width.

The end-points used in our sellar measurements in general follow the recommendations of Di Chiro and Nelson (1962). We have chosen a slightly different posterior limit of the diaphragma, namely the most anterior part of the convexity of the tip of the dorsum rather than the highest point. This is a compromise reached after consideration of other published views (Silverman, 1957; Mahmoud, 1958; Joplin and Fraser, 1960; Di Chiro, 1960). It is supported by our own unpublished observations.

The closest correlation in linear measurements is that between gland and sellar length ($r = 0{\cdot}73$ in men and women). Sellar length is easier to estimate than width and height. Width is measured from bony landmarks which do not themselves define the lateral limits of the sella. Nevertheless, gland and floor width correlate reasonably well. In this respect we are in agreement with Di Chiro and Nelson (1962) and with Oon, Lavender and Joplin (1962). In our series, the width of the dorsum provides a better estimate of gland width than floor width in women but not in men (Fig. 10). Gland and sellar height correlate poorly in men and not at all in women. Since we measured gland height from the centre of the concavity on the upper surface of the gland (Fig. 2), it is reasonable that, on average, sellar height should exceed gland height. To measure sellar height, we have assumed a constant position of the diaphragma. This takes no account of a diaphragma pushed upwards by a bulky gland, or of a gland whose upper surface lies some distance below the line of the diaphragma as defined by us. The lack of correlation between gland and fossa height in females may be related to the fact that we did not separate the data of parous and nulliparous women.

The "best estimate" of pituitary gland volume from pituitary fossa measurements requires the use of regression analysis. A simpler though less precise estimate of gland volume can be made by assuming that the relationships between gland volume and the products $(L \times H \times W)$ and $(A \times W)$ are linear and start from the mathematical origin. These approximate formulae in men are:

$$V = 0{\cdot}40\ (L \times H \times W);\ V = 0{\cdot}48\ (A \times W).$$

In women they are:

$$V = 0{\cdot}50\ (L \times H \times W);\ V = 0{\cdot}59\ (A \times W)$$

These formulae were derived ignoring the 3 per cent gland shrinkage produced by formol-fixation. If used in life, correction factors for radiographic magnification would have to be applied. The formula quoted by Di Chiro and Nelson (1962), $V = 0{\cdot}50\ (L \times H \times W)$, already incorporates a correction for geometrical magnification and does not discriminate between males and females.

Our concern in this study has been to estimate dimensions of normal pituitary glands from radiographs of the sella turcica. Techniques of pituitary ablation other than surgical excision require an accurate knowledge of the relationships between gland and fossa dimensions. We agree with du Boulay and El Gammal (1966) that sellar dimensions provide an insensitive indicator of pathological enlargement of the pituitary gland. In clinical practice, alterations in sellar contour and localised resorption or thinning of bone are better guides to the presence of an intra-sellar tumour.

Abstract

Measurements of length, height, width and volume of the pituitary gland have been correlated with radiological measurements of corresponding dimensions of the sella turcica in 23 male and 27 female necropsies. The pituitary gland is significantly larger in women than in men. The pituitary fossa is not significantly different in size in men and women. Gland and fossa dimensions were correlated separately for each sex. Sellar length and floor width correlate well with gland length and width. Sellar height correlates poorly with gland height, especially in women. Sellar volume, derived from the product of length, height and floor width or from the product of lateral area and floor width, correlates well with gland volume.

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Applied anatomy of the pituitary gland and fossa

A radiological and histopathological study based on 50 necropsies

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Variations in the anatomy and relations of the pituitary gland have become of practical as well as academic interest since the introduction of pituitary ablation by implantation of radioactive seeds, heavy particle therapy, cryotherapy and transethmoidal hypophysectomy. In a previous publication (McLachlan, Williams, Fortt and Doyle, 1967), the relationship between the dimensions of the pituitary gland and radiological estimations of fossa size was considered. In the present work we have studied the variations in the soft tissue boundaries of the pituitary fossa. These are of importance in planning dosimetry and operative procedures and may explain some failures of ablation and some complications.

Material and Methods

The material consisted of the 50 post-mortem preparations from 27 adult women and 23 adult men (average age 59 years) referred to in a previous publication (McLachlan *et al.*, 1967). A block was cut from the sphenoid to include the pituitary fossa with the carotid siphons, the diaphragma being intact. The block was radiographed in antero-posterior, lateral and supero-inferior projections. Powdered bismuth was sprayed on the diaphragma and antero-posterior and lateral radiographs repeated. The carotid siphons were then insufflated with bismuth powder and further antero-posterior, lateral and supero-inferior radiographs were taken. Measurements were made from the films without correction for magnification (linear magnification $=2$ per cent).

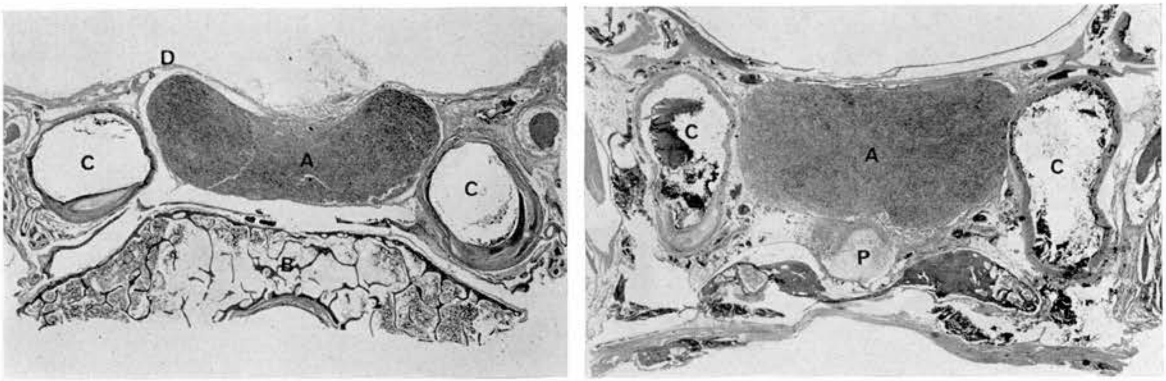
The gland was then removed intact from the sella and its coverings dissected off. It was then radiographed in antero-posterior, lateral and supero-inferior projections to provide a permanent record of gland shape.

Measurements and Results

1. *Lateral wall of fossa*

The anatomy is illustrated in Fig. 1. The carotid siphons lie nearest to one another posteriorly and here may be separated from the gland only by the medial wall of the cavernous sinus. We found many examples of impressions on the lateral aspects of the gland by tortuous carotid arteries and a few examples of narrowing of the gland related to marked carotid impressions (Fig. 2). This narrowing is obviously most likely to occur posteriorly, and the gland can follow carotid configuration to a remarkable degree (Fig. 3). In an attempt to quantify this, we have related measurements of maximum gland width to minimum intercarotid distance (Fig. 4). Minimum intercarotid distance is defined as the distance between the medial aspects of the carotid siphons at the point of maximum convergence. This measurement was made on supero-inferior and antero-posterior radiographs in which the carotid siphons had been opacified. In the very few specimens where the point of maximum convergence was posterior to the fossa, the distance was measured immediately anterior to the dorsum. In two preparations carotid filling was too poor to allow measurement. Intercarotid distance varied from 8·5 to 22 mm with no significant sex difference. There was a significant correlation with gland width ($p<0.001$ in females and <0.01 in males). In 13 out of 25 females, but only in three out of 23 males, maximum gland width exceeded minimum intercarotid distance.

Tortuous carotid arteries may not only compress the pituitary gland; they may erode the dorsum sellae. In 38 out of 48 cases the arteries were so tortuous that they came into contact with the upper half of the dorsum. In the more extreme cases the posterior clinoids were undercut, with erosion of the lateral margins of the dorsum (Figs. 5 and 6). The apparent thickness of the dorsum sellae in lateral radiographs is due in part to the curving forward of its lateral margins (Fig. 7). This thickness is diminished by erosion of the curved lateral margins. Increased carotid tortuosity in old age may therefore account for senile "thinning" of the dorsum. The curve of the dorsum is also responsible for the multiple "contours" of the dorsum commonly seen



A Fig. 1. B

(A) Coronal section through intact fossa from a male of 44. (H & E × 4·5.)

(B) Horizontal section through intact fossa from a male of 63. (H & E × 4·5.)

A = anterior lobe; P = posterior lobe; D = diaphragma; C = internal carotid arteries; B = bone (sphenoid).

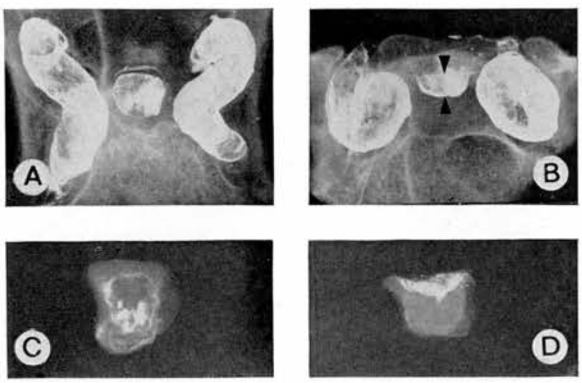
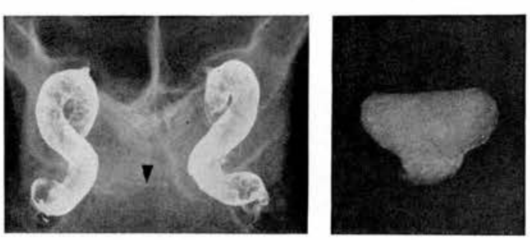


Fig. 2.

Gland compression by tortuous carotid arteries. (A) and (C) are supero-inferior radiographs of fossa and gland. (B) and (D) are antero-posterior projections. The gland has been compressed laterally by the tortuous, dilated arteries. Note also the large infundibular foramen in the diaphragma in (A) and (B). In (B) the upper arrow points to the diaphragma, the lower arrow to the upper surface of the gland.



A Fig. 3. B

Supero-inferior radiographs of pituitary fossa (A) and gland (B). The configuration of the carotid arteries parallels the lateral contours of the gland. Maximum gland width exceeds minimum intercarotid distance by 6·5 mm in this instance. The dorsum sellae is arrowed in (A).

on lateral radiographs. A further variant of the "contour lines" of the dorsum is shown in Fig. 8, in which an example of a "fossula hypophyseos" (Karlas, 1948) is illustrated.

2. *Roof of fossa*

(a) *Attachments of diaphragma.* Lateral radiographs of all specimens demonstrated that the diaphragma was attached anteriorly to the tuberculum and postero-laterally to the most anterior point of the posterior clinoids. This confirms the findings of Bloch and Joplin (1959). We have also considered the mid-line attachment to the dorsum. In 45 of the present series the diaphragma was attached to the most anterior point of the convexity of the tip of the dorsum. In the others, it was attached to the most superior point.

The tuberculum may be difficult to define. It usually lies 5–8 mm behind the limbus sphenoidale (Joplin, 1965), which is normally quite easily identified but may be absent. The sulcus chiasmaticus may lie horizontally or at various degrees of angulation and may be almost vertical (Fig. 9A). According to Schaeffer (1924) this latter configuration is unusual and is due to failure of development of the post-sphenoid. In this situation the tuberculum may not be obvious, and there is a danger that on radiographs a point on the limbus sphenoidale may be taken for the tuberculum. Sometimes a gently curving sulcus is present and the tuberculum may be no more than an insignificant projection (Fig. 9B). Radiological interpretation may be further confused by the presence of middle clinoid processes (Figs. 9C, 9D and 10). We have found 14 examples in the present series, their position on lateral radiographs being 3–4 mm below the tuberculum. Occasionally

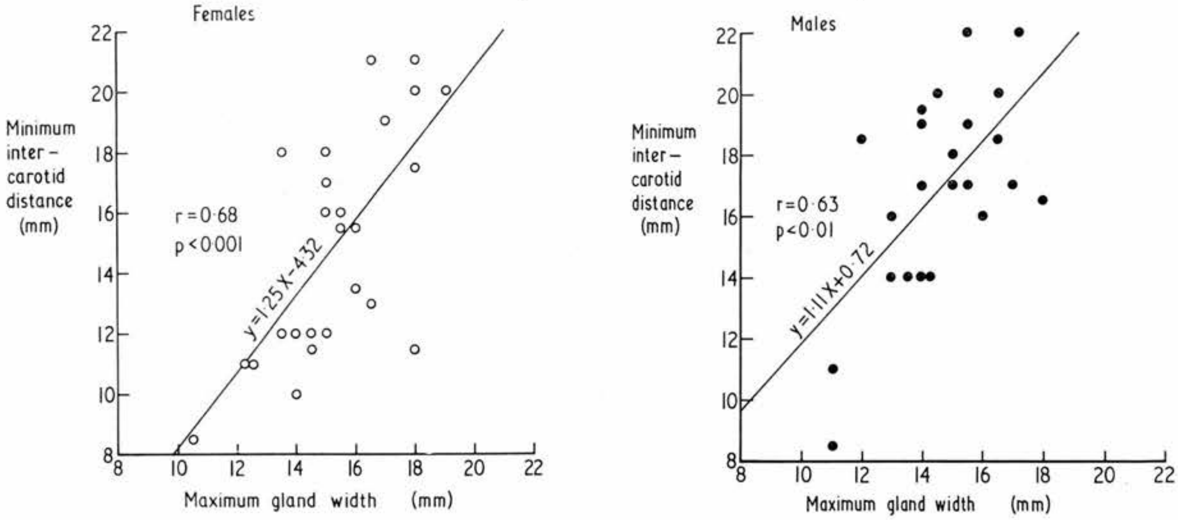
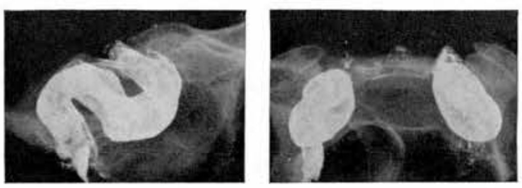
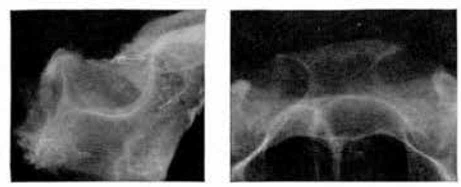


FIG. 4.

Correlation of maximum gland width and minimum intercarotid distance (defined in the text). Minimum intercarotid distance varied from 8·5 to 22 mm with a mean of 14·9 mm for females and 17·0 mm for males. In 13 out of 25 females, but in only three out of 23 males, maximum gland width exceeded minimum intercarotid distance.



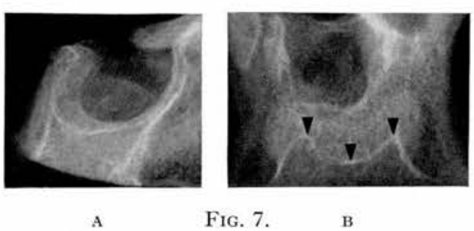
A FIG. 5. B



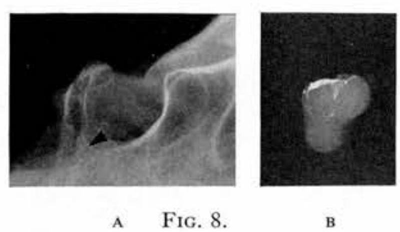
A FIG. 6. B

FIG. 5. Lateral (A) and antero-posterior radiograph (B) of a sella in which the carotid siphons are outlined by bismuth powder. Tortuous carotid siphons may reach the upper half of the dorsum and undercut the posterior clinoids.

FIG. 6. Lateral radiograph (A) of a fossa showing "thinning" of the dorsum, and antero-posterior radiograph (B) showing undercutting of the posterior clinoids. Petro-clinoid calcification is present. The diaphragma is outlined by bismuth in (A).



A FIG. 7. B



A FIG. 8. B

FIG. 7. Configuration of a normal dorsum sellae. Lateral (A) and supero-inferior (B) radiographs showing how the apparent thickness of the dorsum in a lateral radiograph is due in part to the curve of the dorsum (arrowed in B). Anterior aspect is uppermost.

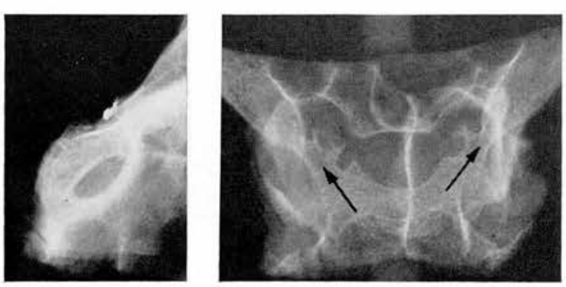
FIG. 8. Lateral radiographs of the fossa (A) and gland (B). The recess in the lower part of the dorsum (arrowed in A) was occupied by a long postero-inferior projection of the pituitary gland. This recess has been called the "fossula hypophyseos". Bismuth powder is shown on the upper surface of the gland in (B).

A B Fig. 9. C D

The tuberculum sellae may be difficult to define. (A) and (B) are examples of markedly different anterior configurations. The tuberculum sellae is arrowed in each case. In (A) the chiasmatic sulcus is the vertical step immediately above the tuberculum. In (B) the chiasmatic sulcus curves gently and the tuberculum is merely a tiny projection on this curve. (C) and (D) are lateral radiographs of a fossa before and after outlining of the diaphragma with bismuth. A middle clinoid process is arrowed in (C). In (D) the diaphragma, which is slightly sunken in its central part, is shown attached to the tuberculum. This configuration could be confused with the one shown in (A).

Fig. 10.

Photograph of superior aspect of a fossa (anterior aspect uppermost) showing a middle clinoid process on the left (arrowed). The anterior and posterior clinoids are bridged and on the right, the middle clinoid is joined to this bridge to form the carotico-clinoid foramen, the centre of which is marked "O".



A Fig. 11. B

"Bridged" fossa. Lateral (A) and supero-inferior (B) radiographs. In (A) the diaphragma has been outlined and is normal in position. In (B) arrows lie along the bony bridges between anterior and posterior clinoids and point to the anterior clinoids.

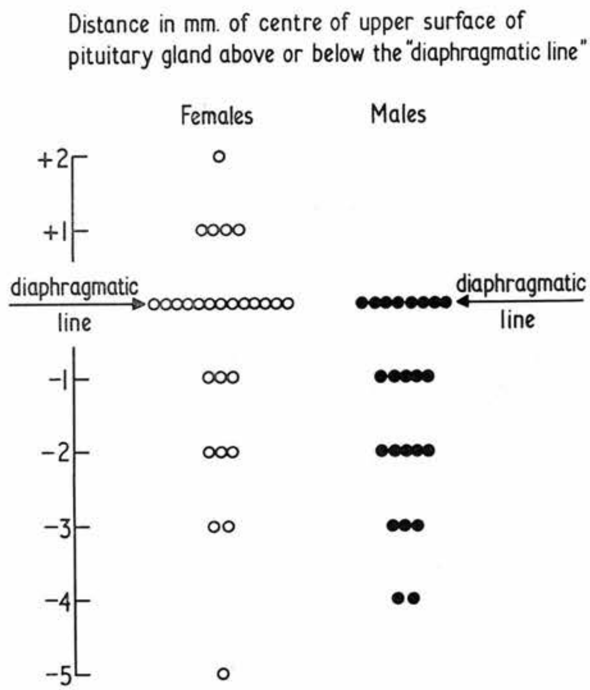


Fig. 12.

Variation in position of the centre of the upper surface of the gland above or below the "diaphragmatic line". The variation is greater in women. In five women the centre of the upper surface of the gland was above the "diaphragmatic line". The most markedly "sunken" gland was also found in a woman, illustrated in Fig. 13.

these form prominent projections on the lateral part of the anterior wall and may fuse with the anterior clinoids to form the carotico-clinoid foramina through which pass the carotid arteries (Fig. 10).

This latter situation is most likely to occur in the "bridged fossa" where anterior and posterior clinoids are also joined. It should be remembered that these bridges do not form a roof for the fossa but are placed more laterally. Diaphragmatic position on lateral radiographs can be assessed, as in more normal sellar configurations, by defining the tuberculum and the most anterior point of the convexity of the tip of the dorsum (Fig. 11).

(b) *Diaphragmatic contour.* Since the diaphragma is generally envisaged on lateral radiographs as a straight line, the frequency with which actual diaphragma position varied from this was checked. The lateral film in which the diaphragma had been outlined by bismuth was chosen. A straight line was drawn on the film from the tuberculum to the most anterior point on the convexity of the tip of the dorsum, this over-simplified representation of diaphragma position ("the diaphragmatic line") being a compromise of other published views (Silverman, 1957; Mahmoud, 1958; Joplin and Fraser, 1960; Di Chiro, 1960). The distance of the central part of the actual diaphragma above or below this line was measured, and a considerable variation found (Fig. 12). In 14 of the 27 women the centre of the diaphragma deviated from its predicted position by 1 mm or more (either above or below the "diaphragmatic line") and in seven of these the deviation was 2 mm or more. The extremes of variations are illustrated (Fig. 13), and a further example (not in the consecutive series) is shown in Fig. 14. In 15 of the 23 males the central part of the diaphragma was 1 mm or more below the predicted position. None was above. In ten males the deviation was 2 mm or more. In a total of eight cases from both sexes the central part of the diaphragma lay 3 mm or more below its predicted position.

The diameter of the infundibular foramen, through which the stalk passes, is known to vary considerably (Sunderland, 1945; Mahmoud, 1958). While we did not measure this variation, one unusually large infundibular foramen was noted (Fig. 1) and a fenestrated diaphragma, another recognised variant, is also illustrated (Fig. 14). Subarachnoid extensions into the sella are known to occur (*e.g.*

A B C D

Fig. 13.

Variations in contour of diaphragma.

(A) and (B) are lateral radiographs of the fossa and gland of a 79-year-old woman. The diaphragma (outlined with bismuth), is markedly sunken, as is the upper surface of the gland, the centre of which lies 5 mm below the "diaphragmatic line".

(C) and (D) are lateral radiographs of the fossa and gland of a 22-year-old female. The diaphragma is pushed upwards by a bulky gland which was otherwise normal. The centre of the diaphragma lies 2 mm above the "diaphragmatic line".

A

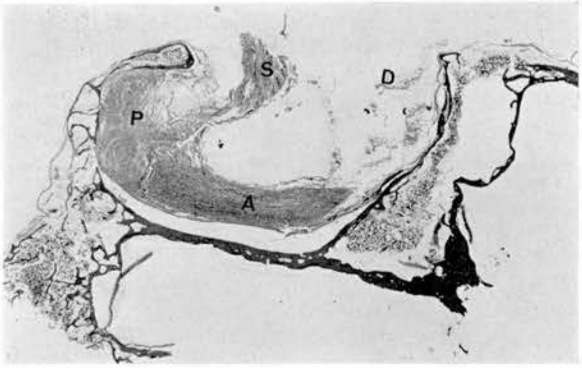
Fig. 14.

Fenestrated diaphragma (not from consecutive series).

(A) is a photograph of the diaphragma from above. The anterior arrows lie on the optic nerves, the posterior arrow on the pituitary stalk. The web-like diaphragma is clearly shown.

B

(B) is a lateral radiograph of the same case. The diaphragma and part of the upper surface of the gland are outlined with bismuth. The upper surface of the gland is well below the diaphragma.



C

(C) is a decalcified sagittal section of the fossa and gland. Despite the extreme central depression of the gland, it was histologically normal, and it formed a layer spread over the floor and lateral walls of a large fossa. (H & E × 4·5.) A = anterior lobe; P = posterior lobe; S = stalk; D = diaphragma.

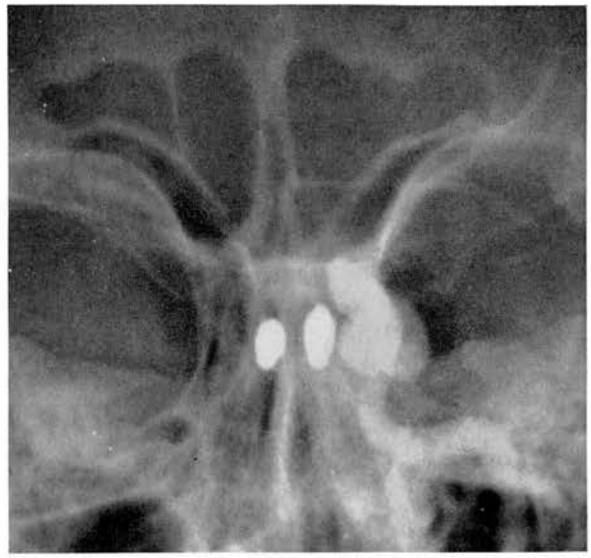


FIG. 16.

Left carotid arteriogram a few days after a technically satisfactory pituitary implant in which modified Forrest screws were used. The patient, suffering from metastatic breast cancer, subsequently died from a subarachnoid haemorrhage. The left screw is within 1 mm of a previously undeclared aneurysm of the carotid siphon.

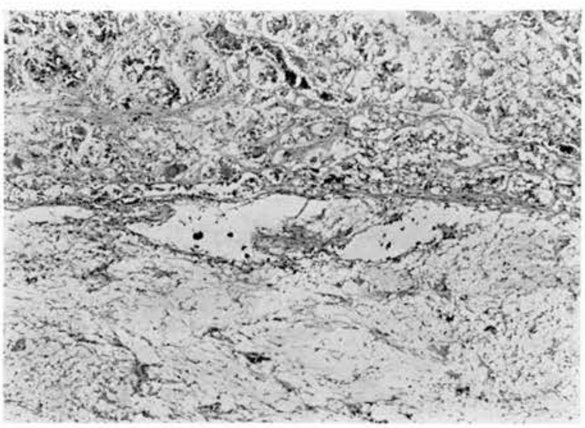


FIG. 15.

Horizontal section through a pituitary from a male of 68. Note the central cavity containing black bismuth particles which lies between the anterior lobe (above) and the posterior lobe (below). This cavity was shown on serial section to be a tubular structure in communication with the subarachnoid space. (H & E × 70.)

Sunderland, 1945). All glands were examined microscopically in horizontal section and small collections of bismuth in minute spaces lying between the anterior and posterior pituitary lobes were found in eight instances (Fig. 15). Serial sections demonstrated that these spaces were of subarachnoid origin, and in one instance the tubular subarachnoid extension was followed for nearly 1 mm before it merged with the gland surface.

DISCUSSION

Compression of the lateral surfaces of the pituitary gland by carotid arteries has been described by previous writers. Simmonds (1914) comments on this, and Kraus (1926) illustrates a good example of pituitary compression by "sclerotic" carotid arteries. Bull and Schunk (1962) measured the distance between the carotid siphon and the mid-line in a series of control patients and patients with pituitary and other intracranial tumours. In the patients without tumours this distance (approximately half the distance measured by us) varied from 5 to 11 mm, a range which is in good agreement with our own studies. Our measurements of intercarotid distance (range 8·5 to 22 mm) show how closely the carotid siphons can approach each other. The pituitary gland is often much narrower posteriorly than anteriorly. In pituitary implantation, posteriorly placed seeds are more likely to lie near the carotid siphons. The potential danger is underlined by the death of a patient from a subarachnoid haemorrahge a few days after pituitary implantation for metastic breast cancer. The haemorrhage occurred from an aneurysm of the left carotid siphon unrecognised before implant (Fig. 16). This complication is rare but the danger is obviously greater in older patients who are likely to have tortuous carotid arteries.

In our series, the carotid siphons came into contact with the upper half of the dorsum in 38 out of 48 cases. This figure probably reflects the high average age of our subjects since both Mahmoud (1958) and Joplin (1965) found that the carotid arteries in their series were related to the lower half of the dorsum. Undercutting of the posterior clinoids should be looked for, particularly in elderly patients; if present, pre-implantation carotid angiography should be considered.

A seed giving uniform radiation throughout its length should not be placed too far posteriorly in these patients. Since 13 out of 25 females had a minimum intercarotid distance which was less than maximum gland width, this consideration may be more important in women.

The variation that we have found between the actual position of the diaphragma and the position deduced from the bony landmarks is also considerable in terms of the size of the gland. This has not been measured in any large series of glands and it is obviously very difficult in any routine way to identify actual diaphragma position. Our measurements show that the mean actual diaphragmatic position in women does not differ significantly from the predicted position. In men, however, the mean actual position is 1·5 mm below the diaphragmatic line. This difference is measured at the centre of the upper surface of the gland; it is probable that the mean difference over the whole upper surface of the gland is about half this. Allowance for this should be made in calculating gland height from radiographs.

A serious complication of pituitary implantation is the development of cerebrospinal fluid leakage. This complication may be manifest shortly after implant or it may occur many days or even weeks later. An accepted explanation of this occurrence is excessive radiation damage to the diaphragma sellae. In eight out of 50 necropsies the central part of the diaphragma has been shown to be 3 mm or more below the "diaphragmatic line". We have previously found mean fossa height estimated from radiographs to be 8 mm (McLachlan *et al.*, 1967). The anatomical variations that we have documented here are likely to contribute significantly to the incidence of CSF leaks. A radioactive rod placed centrally in the fossa as judged radiologically would have been within 1 mm of the true position of the diaphragma in eight out of our 50 cases. A minor variation in the position of the rod could obviously lead to an immediate drip. The risk of a delayed drip from radiation effects would in any event be high with a β-emitting rod only 1 mm from the diaphragma. A prolongation of subarachnoid space between the anterior and posterior lobes, found in eight of our 50 necropsies, is a further possible cause of leakage of CSF immediately after implantation. We would suggest that anatomical variations in the diaphragma and subarachnoid space account for the majority of cases of CSF drip after pituitary implantation. In a gland showing the extreme variation from normal illustrated in Fig. 14 it would obviously be impossible to produce satisfactory pituitary ablation by present implantation techniques without placing a seed virtually in contact with the subarachnoid space.

Abstract

The radiological anatomy of 50 pituitary glands and fossae has been studied in detail. Particular attention was paid to variations in the position of the diaphragma sellae relative to bony landmarks of the sella and to the relationship of the carotid siphons to the gland. Marked variations in the shape of the gland and in the level of the centre of the diaphragma sellae were observed. The carotid arteries have a more intimate relationship with the gland than standard anatomical texts imply, and in several of the specimens studied, appeared to compress the gland and to undercut the posterior clinoids. Erosion of the curved lateral margins of the dorsum sellae by tortuous internal carotid arteries may explain senile "thinning" of the dorsum. All glands were studied microscopically, and in eight out of the 50, a sub-diaphragmatic extension of the subarachnoid space was observed. Other anomalies of the diaphragma and variations in the bony contour of the fossa are commented upon and illustrated. Attention is drawn to the implications of these observations for operative procedures on the pituitary gland.

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Plain film and tomographic assessment of the pituitary fossa in 140 acromegalic patients

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Introduction

The pituitary fossa is said to be abnormal in about 90 per cent of acromegalic patients (Steinbach, Feldman and Goldberg, 1959; Lang and Bessler, 1961; Cecchini, 1968). In the light of these claims we have assessed the frequency and extent of sellar abnormality in our own series of 140 acromegalic patients. We were particularly concerned to evaluate criteria of abnormality when changes in sellar configuration were sufficiently subtle to cause difficulty in diagnosis and to assess the value of tomography.

Material and Methods

One hundred and forty patients aged 22 to 74 years (mean 50 years) were studied. All had obvious clinical features of acromegaly. Seventy-one were female, 69 male. One hundred and nineteen patients had no previous local treatment to the pituitary gland. Twenty-one patients had radiotherapy to the pituitary four months to 28 years before (mean 6·5 years). Postero-anterior and lateral films of the skull were available in all, and coned films of the sella in most patients. In a preliminary study patients were classified into three groups: A, B and C. In *Group A* (77 patients; 55 per cent) the sella was grossly abnormal (Fig. 1). In *Group B* (38 patients; 27 per cent) sellar abnormality was shown on lateral films by a double contour. However, the area bounded by the inner contour was normal or only slightly enlarged (Fig. 2). Abnormality was confirmed by central or lateral depression of the sellar floor where this was visible on the postero-anterior films. It was considered that an observer with experience of pituitary tumours would have little difficulty in recognising this type of sellar abnormality. In *Group C* (25 patients; 18 per cent) plain film abnormality was minimal or indefinite or was detectable only after the most careful analysis.

Group C was thought to provide particular diagnostic difficulty and was therefore subjected to detailed study as follows:

(1) Lateral plain films were analysed and compared with those from control patients according to five commonly accepted criteria.

(2) Lateral tomograms were analysed to assess their value *vis-à-vis* plain films.

(3) Sellar measurements from frontal and lateral plain films were compared with those from post-mortem specimens known to be free from pituitary disease.

The preliminary classification was made by two radiologists with considerable experience in the assessment of pituitary fossae. Their assumptions were tested by presenting randomly mixed examples of plain films from Groups A, B and C and controls to two observers from whom clinical details were withheld.

1. *Lateral plain films*

The lateral plain films from all patients in Group C were carefully analysed by the two radiological authors and compared with lateral skull films of 24 patients without clinical evidence of pituitary disease. Twelve were diabetic and 12 had been referred for skull examination because of minor head injury (Table I). Five criteria of abnormality, *viz.*: sellar enlargement (assessed subjectively), abnormality of sellar shape, pathological double contour, reduction in thickness of the cortical bone forming the sellar outline (the "lamina dura") and erosion of this cortical bone were separately analysed and scored as follows. For each criterion, a score of 2 was given if the fossa was abnormal, a score of 1 if the abnormality was indefinite, and a score of 0 if the fossa showed no abnormality. The scores for each fossa were then summated and the control group compared with Group C.

2. *Lateral tomography*

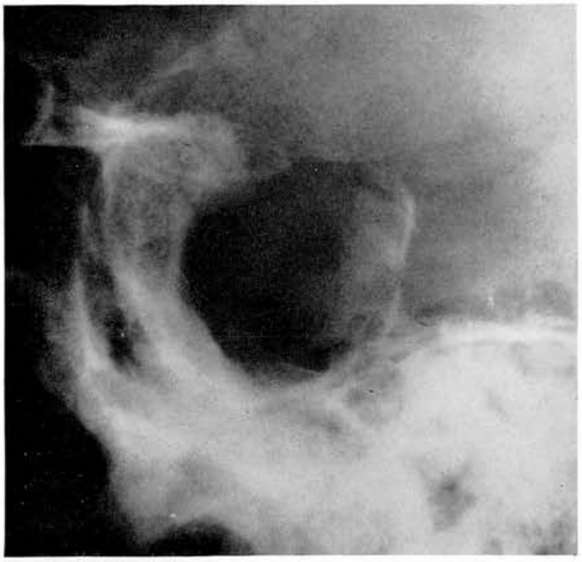
Lateral tomography of the sella was available in 24 patients from Group C. This was linear in four and hypocycloidal in 20. The same five features were scored. The tomographic equivalent of double contour was an excessive change in fossa size or contour on adjacent tomographic cuts. Major tumour

TABLE I

Group C patients and controls

	No. of patients	Age range (years)	Mean age (years)	Males	Females
Group C	25	29–69	52	9	16
Controls	24	19–59	42	19	5

Fig. 1.



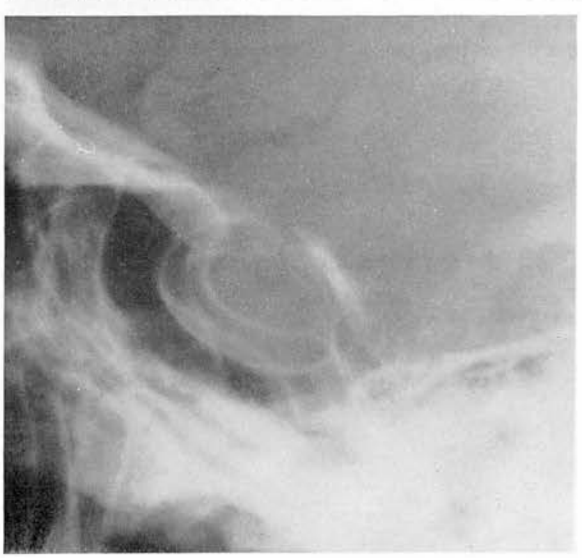


Fig. 2.

Fig. 1. Example of Group A fossa. Marked sellar enlargement. (In this and all subsequent lateral films of the fossa, anterior aspect lies to the left.)

Fig. 2. Example of Group B fossa. Well-marked double contour, the inner one being intact. Petro-clinoid calcification.

extensions, unsuspected on the plain films, were sometimes revealed by tomography. An additional score of 2 was then given. Plain film and tomographic scores were compared.

3. *Sellar measurements*

From lateral plain films of patients in Group C, sellar height, length and lateral area were measured. When the floor could be identified on posterio-anterior films, its width was measured. Central or lateral depression of the floor was quantified by measuring on postero-anterior films the vertical distance between its highest and lowest points. Measurements were corrected for magnification and compared with similar measurements from 50 post-mortem specimens in which the pituitary gland was macroscopically and histologically normal (McLachlan, Williams, Fortt and Doyle, 1968).

Blind assessment

Postero-anterior and lateral plain films of the control group were mixed with eight examples from Group A, five from Group B and 23 from Group C. Clinical details and tomograms were withheld and films were masked to an area 6 cm in diameter, so that only the sella was visible. They were viewed by an endocrinologist (A.D.W.) and by a third radiologist without special experience of the radiology of the sella. These observers were asked to categorise sellar appearances as abnormal, normal or doubtful.

Results

Seventy-seven patients (55 per cent were allocated to Group A, 38 (27 per cent) to Group B and 25 (18 per cent) to Group C (Fig. 3). Analysis of patients in Group C is now considered in greater detail.

Plain film scores in controls and patients in Group C

These are summarised in Fig. 4. There is a considerable overlap between the two groups. In our judgment, the two control fossae with scores of 5 are unequivocally abnormal (see discussion). If the normal range is represented by scores of 0 to 3, then only 11 of the 25 fossae can be regarded as abnormal

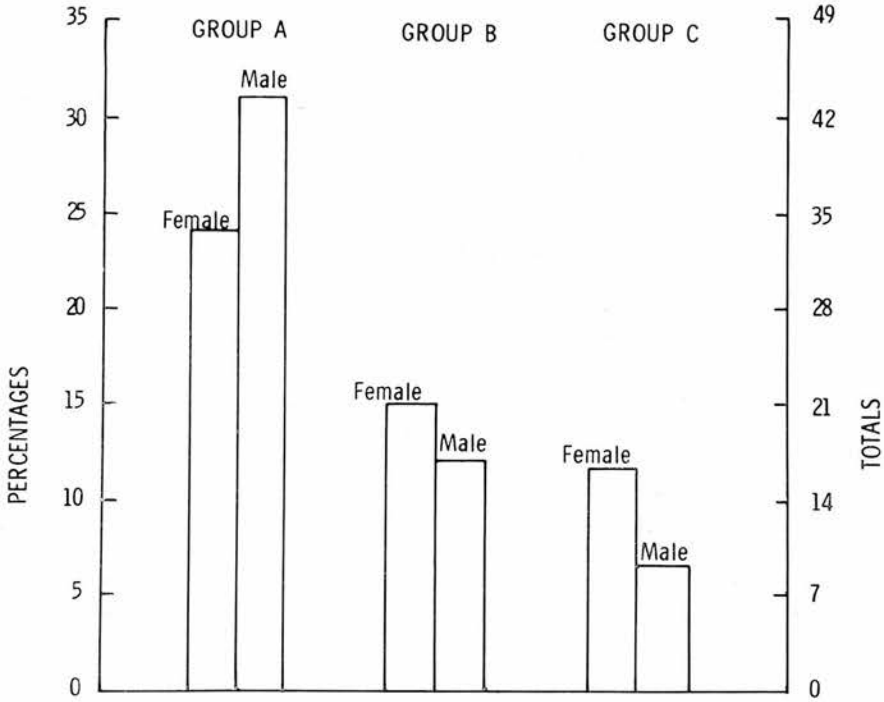
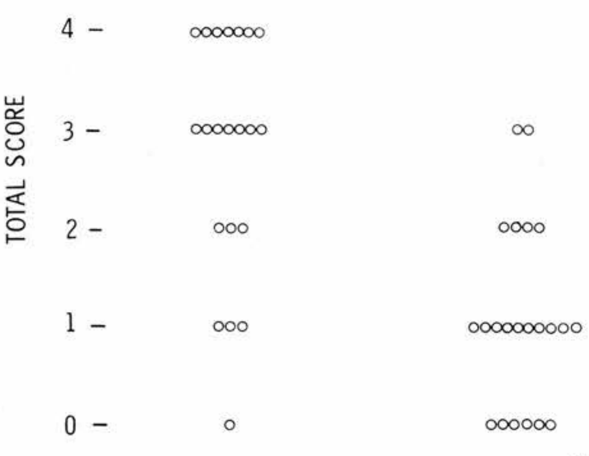


Fig. 3.

Numbers and percentages of acromegalic patients in Groups A, B and C, sexes shown separately.



on critical assessment of plain films. The scores for each of the five features separately assessed are shown in Fig. 5. Fossa shape and reduction of cortical thickness (thinning of the "lamina dura") discriminate poorly between control fossae and fossae in Group C. Subjective assessment of sellar enlargement, the presence of an abnormal double contour and bone erosion discriminate only slightly better.

Comparison of plain film and tomogram scores in Group C

Results are summarised in Fig. 6. In nine of the 24 patients an unexpected major extension of the pituitary tumour into the sphenoid was revealed by

Fig. 4.

Total scores for plain film analysis in Group C acromegalic fossae and controls. Each circle represents one patient. If the two control fossae with a score of 5 are considered to be abnormal (see text), the normal range is represented by scores of 0 to 3.

Plain film and tomographic assessment of the pituitary fossa in 140 acromegalic patients

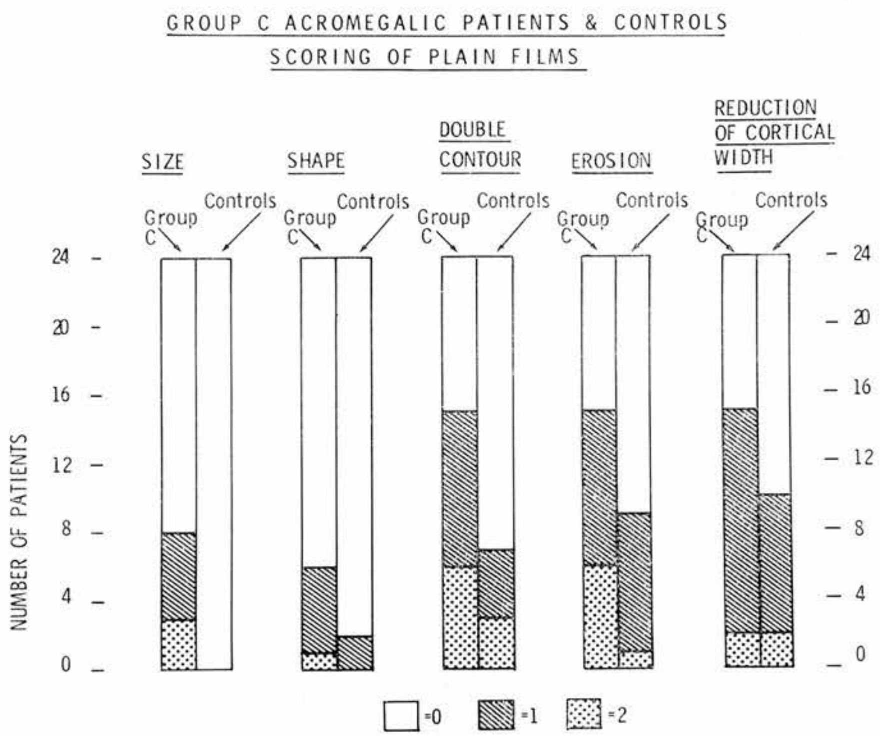


FIG. 5.

Plain film scores in Group C fossae and controls. Each of the five features compared. For each feature, a score of 0, 1 or 2 indicates that it was judged to be within normal limits, doubtful or abnormal respectively.

tomography. Tomogram scores exceeded plain film scores in 23 of the 24 patients in whom tomography was carried out. Mean increase, including scores for downward extensions, was four points (range 0 to 7). In one patient plain film and tomogram scores were identical. Tomogram score was never less than plain film score. If the normal range for tomogram scores is taken as 0 to 3 points, then all but one of the 24 patients in Group C, in whom tomography was available, would be classified as having an abnormal fossa. (One patient in Group C did not have tomography; his plain film score was 3). Scores for each feature separately assessed are shown in Fig. 7. Abnormalities, except for abnormality of shape, were twice as frequent in the tomograms as in the plain films. Bone erosion, thinning of cortex or a pathological double contour were each evident in at least two-thirds of the tomographed sellae.

Sellar measurements

Measurements of length, height, width and lateral area are summarised in Fig. 8. Length and floor width are of no value in distinguishing between the fossae in the necropsy series and in Group C patients. Fossa height is a slightly better discriminant. In five Group C patients, fossa height exceeded 10·8 mm. Lateral area in four Group C patients exceeded 128 sq.mm. The figures quoted refer to the upper limits established in the necropsy series. Two fossae showing excess height had a normal lateral area.

Figure 9 summarises measurement of central or lateral depression of the fossa floor. Central depression of up to 2 mm was observed in the necropsy specimens. In two Group C patients this was exceeded by 0·5 mm. Maximum lateral depression in the necropsy series was 1 mm. This was exceeded in four Group C patients. In two of these abnormality of the floor was not apparent on lateral radiographs.

Blind assessment (Table II)

Group A. All eight fossae shown to both observers were called abnormal.

Group B. Of the five fossae assessed blind in this group, one was classified as normal and only one as abnormal by both observers.

Group C. Only two of 23 fossae were classified as abnormal and four as normal by both observers.

TABLE II

Blind assessment by two observers

	Total	N/N	N/D	N/A	D/D	D/A	A/A
Group A	8	0	0	0	0	0	8
Group B	5	1	1	0	0	2	1
Group C	23	4	7	1	3	6	2
Controls	24	17	4	1	0	2	0

N/N: both observers called the fossa normal.
N/D: one normal, one doubtful.
N/A: one normal, one abnormal; and so on.

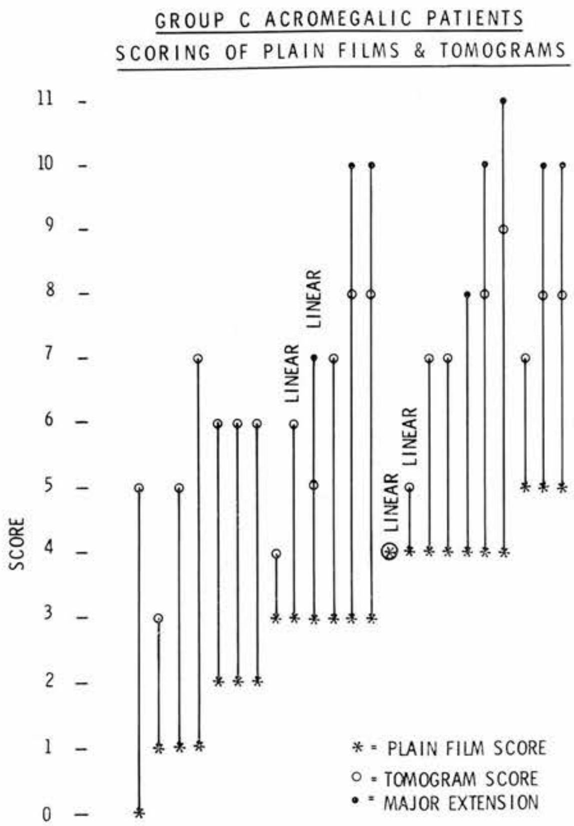


Fig. 6.

Comparison of total scores for plain films and tomography in Group C. A major downward extension of tumour (for which 2 points were added to the tomogram score) was shown in nine patients. Tomography was hypocycloidal in all except four (labelled).

Controls. Only 17 of the 24 fossae were classified as normal and none as abnormal by both observers.

Blind assessment and plain film scores are compared in Fig. 10.

Discussion

Previously published series suggest that the pituitary fossa is abnormal in about 90 per cent of patients with acromegaly; 89 per cent of 27 patients (Steinbach *et al.*, 1959), 93·5 per cent of 31 patients (Lang and Bessler, 1961) and 87 per cent of 35 patients (Cecchini, 1968). Of these authors only Cecchini refers to the use of tomography. Our own figures suggest that 55 per cent of pituitary fossae in acromegaly will show gross abnormality obvious on lateral radiographs. In a further 27 per cent abnormality will be apparent on lateral radiographs as a double sellar contour, the inner one being of normal or near-normal dimensions and frequently intact. Postero-anterior radiographs will confirm abnormality in many. However, we underestimated the difficulty that may be encountered in this group, and only one of the five fossae from Group B presented blind to two observers was consistently called abnormal. One was called normal by both observers (Fig. 11). Since this type of abnormality occurred in over a quarter of our patients the importance of recognising this radiological presentation is obvious.

We encountered particular difficulty in 25 patients (18 per cent). Only two fossae in this group were called abnormal by both blind observers. Even our system of itemised analysis and scoring failed to distinguish 14 Group C patients from controls, *i.e.*, 10 per cent of the whole series of 140. Thus it appears that even the most rigorous plain film assessment will reveal pathology in only 90 per cent of acromegalic fossae.

Minimal sellar abnormality is difficult to detect. Individually, the five criteria of abnormality we chose are only moderately helpful in plain film analysis. Sellar shape is a poor discriminant. Normal variations (*e.g.* Mahmoud, 1958) make assessment of generalised contour abnormality difficult. Local variations like the fossula hypophyseos (Karlas, 1948) compound the problem. Reduction of cortical thickness also discriminates poorly and bony erosion is only slightly better. However, we have not used the very meticulous radiographic

Plain film and tomographic assessment of the pituitary fossa in 140 acromegalic patients

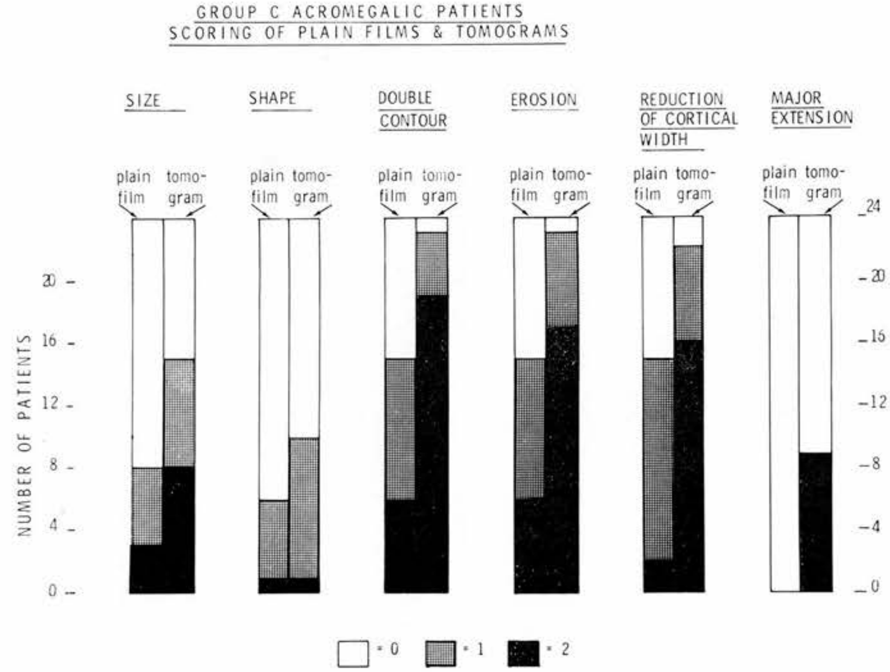


FIG. 7.

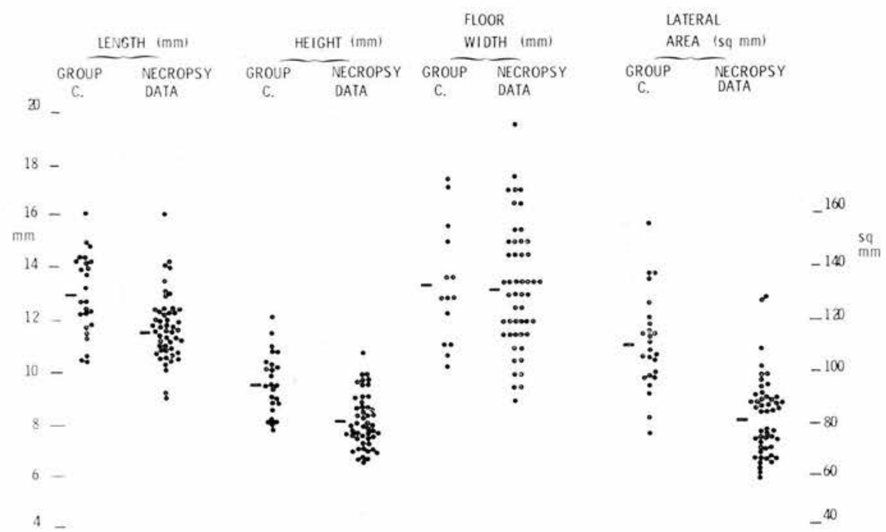


FIG. 8.

FIG. 7. Comparison of plain film and tomogram scores in Group C. For each feature, separately assessed, a score of 0, 1 or 2 means within normal limits, doubtful or abnormal respectively.

FIG. 8. Sellar measurements in Group C and necropsy fossae. No Group C fossa showed increased length or width. Lateral area was increased in four, height in five. The floor was visible on postero-anterior films in only 14 fossae in Group C. The horizontal lines denote the means in each group.

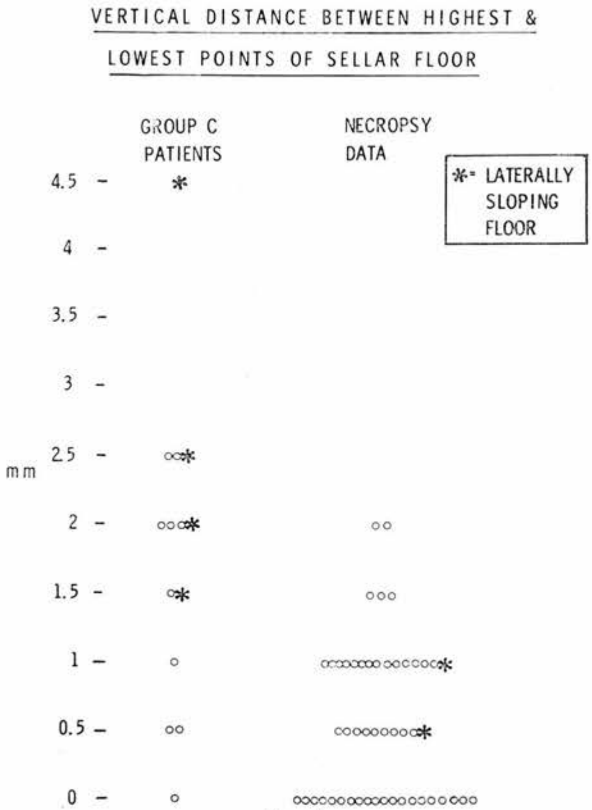


Fig. 9.

Central and lateral depression of the sellar floor measured on frontal films. Comparison with necropsy data. Central depression exceeded the normal range in only two Group C fossae. Lateral depression occurred less commonly in both groups but was greater in Group C than in necropsy fossae.

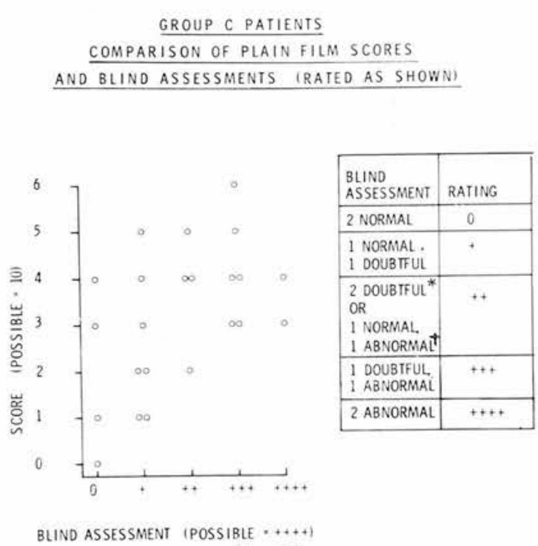


Fig. 10.

Twelve Group C fossae were called normal by at least one observer. *three patients; †one patient.

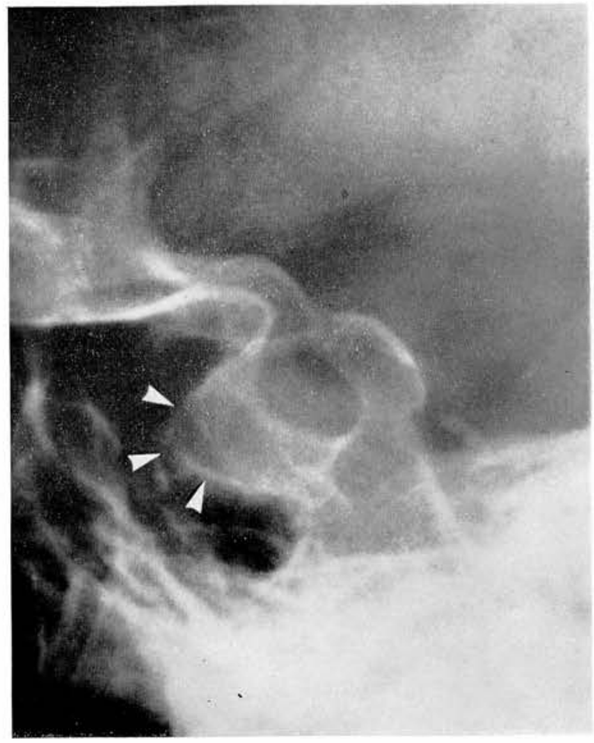
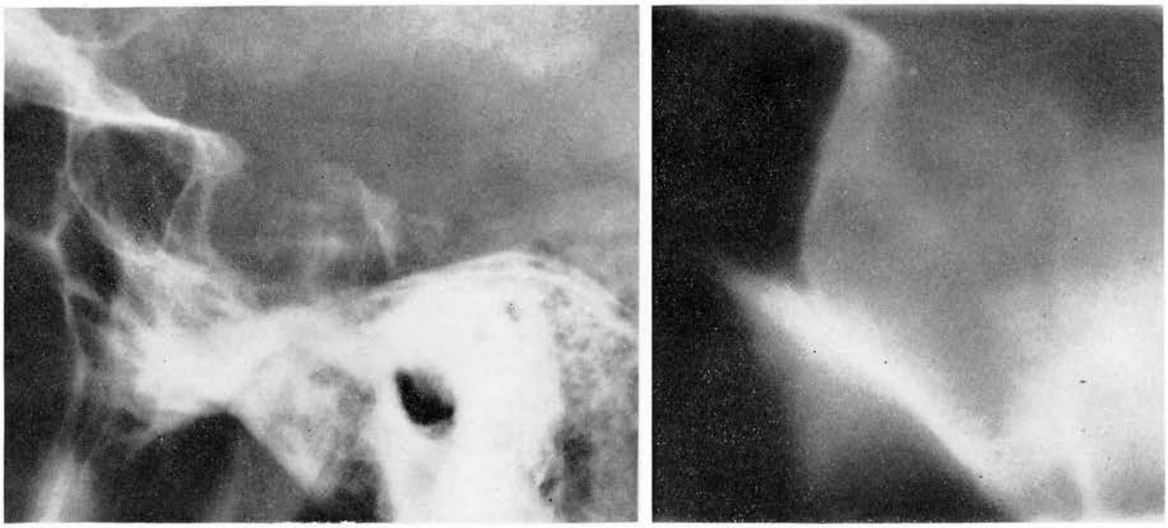


Fig. 11.

Example from Group B called normal by both blind observers. The intact inner contour distracts attention from the second outline (arrowed).

Fig. 12.

"Control" fossa. Fifty-year-old male diabetic. Plain film score of 5. Double contour which we judge to be pathological. Carotid siphon calcification partially obscures detail and appearances were originally called normal on routine reporting.



A FIG. 13. B

(A) Group A fossa showing enlargement and bone destruction. Petro-clinoid calcification.
(B) Lateral tomography reveals the extent of downward extension concealed on plain films by overlying temporal bone.

methods of Fry and du Boulay (1965) who emphasised the importance of erosion as a diagnostic feature. Subjective assessment of fossa size in the doubtful fossa is of little value and the presence of a double contour discriminates no better. (We distinguish between the obvious double contour of Group B fossae and the lesser degrees found in Group C and controls). The outline of the normal fossa is frequently double or even treble (Di Chiro and Nelson, 1962; Radberg, 1963). In addition, imperfect radiographic positioning may lead to a false impression of abnormality. Though no one feature discriminates well, itemised analysis compels attention to detail and allows better discrimination when all criteria are considered together. None the less, 14 of the 25 Group C fossae (56 per cent) were in our normal range. This number would have been greater if we had not judged the fossae of two diabetic patients to be abnormal. Both were originally passed as normal on routine reporting, partly, we feel, because carotid calcification obscured detail (Fig. 12).

We agree with du Boulay and El Gammal (1966) on the limited usefulness of sellar measurement in the diagnosis of pituitary tumours. Lateral sellar area exceeded the upper limit of our normal range (128 sq.mm) in only four of the 25 patients in Group C. Sellar height was increased in five patients, sellar length in none. Di Chiro (1960) claimed that increased width may be a valuable sign of a pituitary tumour. Measurements of sellar width in Group C patients were all within the wide normal range established in necropsy data (McLachlan *et al.*, 1968).

The value of postero-anterior films in the assessment of diagnostically difficult fossae is limited on two further counts. First, the floor may not be visible because of bone thinning and erosion, large nasal turbinates, poorly pneumatised sphenoid sinuses and perhaps inappropriate tube angulation (Radberg, 1963). In 11 of the 25 Group C patients (44 per cent), postero-anterior films did not demonstrate the floor. Secondly, central or lateral depression of the sellar floor occurs in the normal. Postero-anterior films showed abnormal depression of the floor in six Group C patients but in only two was this abnormality not evident on lateral radiographs. Thus in only two of the 25 patients did postero-anterior films make a positive contribution to the diagnosis of sellar abnormality.

Tomograms provide a much more detailed and accurate assessment of the morphology of the sella in all circumstances. Even in Group A patients in whom the sella is grossly abnormal on plain films (Fig. 13) tomography provides a much better estimate of tumour size and extension (Wright, McLachlan, Doyle and Fraser, 1969). The fossae in Group B caused our blind observers great difficulty in diagnosis. In this group, tomography will demonstrate dramatically the abnormality of the sella

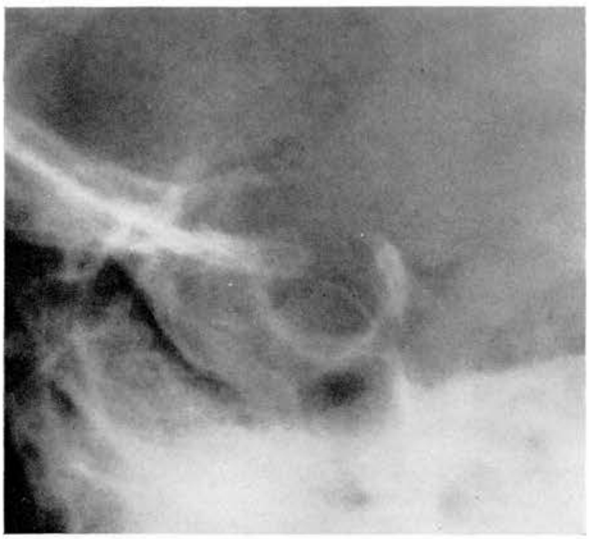
(Fig. 14). In Group C fossae in which no abnormality may be demonstrable on plain films, major downward extension may be shown on tomography. Such an extension was shown in over one-third of our Group C patients (Fig. 15). In addition, other abnormalities were found over twice as frequently on tomograms as on plain films. A pathological double contour, bony erosion or reduction in cortical thickness were revealed in at least two-thirds of these fossae. Even if major downward extensions were ignored, total tomographic scores were abnormal in 23 patients, more than double the number with abnormal plain film scores. Including scores for these extensions, mean increase in score on tomography was four points. Plain film and tomogram scores averaged 3 and 7 respectively. The increase in score was less on linear tomography than on hypocycloidal tomography. However, since linear cuts were made 5 mm apart and hypocycloidal cuts 3 mm apart, the difference may be partly due to the smaller number of films available for assessment on linear tomography. Only one patient had a tomographic score within our normal range. When we add to this the one patient in whom tomography was not performed 138 of our 140 fossae were abnormal on a combination of plain film and tomographic asessment.

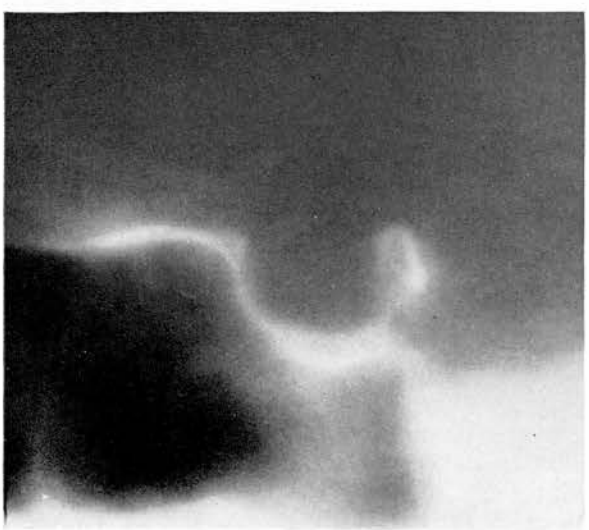
Thus, 90 per cent of acromegalic fossae are abnormal on critical analysis of plain films; 98·6 per cent are abnormal when tomographic assessment is included. Patients with clinical or biochemical evidence of abnormality of pituitary function should be investigated by tomography of the sella, even when plain films are within normal limits.

Acknowledgments

The majority of patients were under the care of Professor Russell Fraser to whom we are grateful. We thank Dr. B. E. Nathan who acted as one of our blind observers and Miss Susan Russell for her help.

A



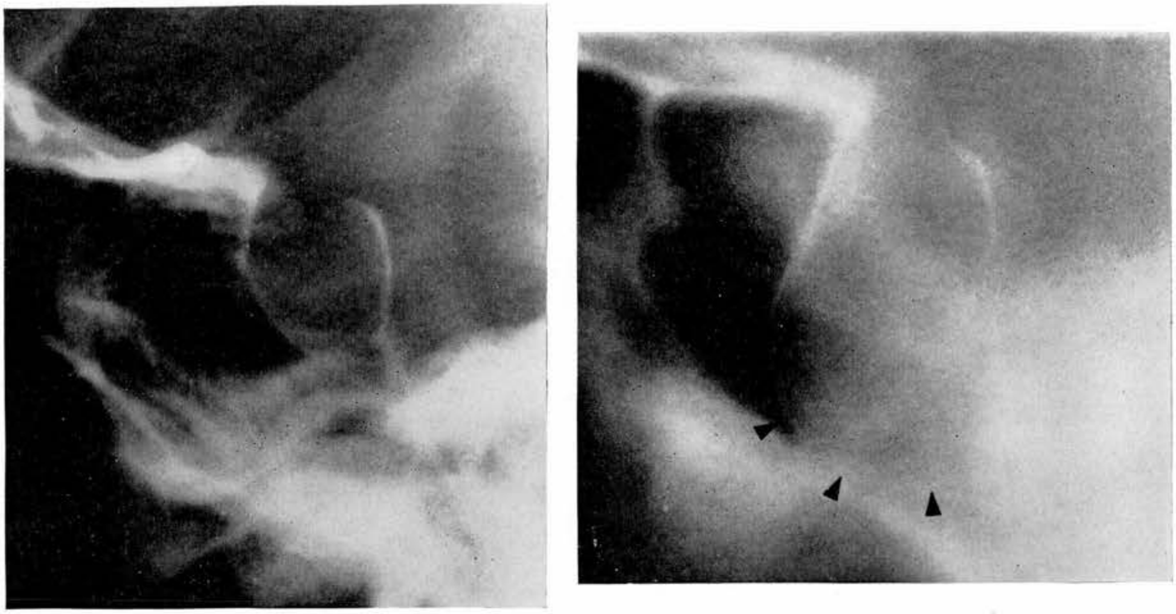


B

C

Fig. 14.

(A) Group B fossa. A second contour is seen anteriorly. (B) and (C) Lateral tomography shows the marked eccentricity of sellar enlargment. Tomography in a coronal plane is equally valuable in this situation.



A Fig. 15. B

(A) Group C fossa. Apparently normal sellar dimensions. Plain-film score of five.
(B) Lateral tomography shows a large extension into the sphenoid sinus, totally unexpected from the plain films. Tomogram score of 10.

Abstract

Radiographs of the pituitary fossae of 140 acromegalic patients have been studied. Patients were divided into three groups on the basis of plain film appearances. Group A (55 per cent) showed gross abnormality. In Group B (27 per cent) a double contour was present, the dimensions of the inner contour being normal or only slightly enlarged. Our findings suggest that abnormality is easily missed in this group. Group C (18 per cent) provided particular diagnostic difficulty and was studied in greater detail Commonly accepted criteria of abnormality on plain films and measurement of fossa dimensions discriminated poorly between control and Group C fossae. Tomography showed significant abnormalities in the majority of Group C fossae, and major downward extensions unsuspected on plain films in more than a third. Combined assessment by plain film and tomography showed abnormalities in 138 of the 140 patients. Tomography of the sella is indicated in patients with clinical or biochemical evidence of abnormality of pituitary function even when plain films appear normal.

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