can be no doubt that when insulin comes to be more available its exhibition along with intelligent control of diet will have the same beneficial results in all the serious forms of the disease. In cases of threatened coma its value is undoubted, and this is also the case when it is used as a precautionary measure against post-operative risk in surgical practice.

Until the clinical effects have been more thoroughly investigated it would be out of place here to discuss in further detail the therapeutic value of insulin.

Preparation on the Large Scale.

It remains to explain the steps that have been taken by the University of Toronto to safeguard the production, standardization and distribution of insulin. Realizing that the publication of the method of its preparation might be followed by an uncontrolled commercial exploitation of insulin, with the consequence of its improper use in general practice, the chief originators of the method generously offered to apply for patents covering its production, and to hand these over to the University provided this body would assume the function of licensing approved manufacturers to produce and sell it at a reasonable cost. Patents have therefore been applied for in Canada, the United States, Great Britain, and other countries, and the University has appointed a committee, composed partly of those who have participated in the investigations and partly of members of the Board of Governors, to advise it with regard to the conditions under which licences should be granted.

As a first step this committee recommended that licences should not be freely granted until every possible detail of the manufacture on a large scale of a preparation of known and constant potency had been thoroughly worked out. This step was taken because of the unexpected difficulties which were encountered when large scale production was attempted in the Connaught Antitoxin Laboratories of the University. It was found that whereas non-irritating preparations of insulin of constant potency could readily be obtained by Collip's procedure in the laboratory, the yields were for some time extremely unsatisfactory when a large scale production was attempted.

Protection from Commercial Exploitation.

After these difficulties had been overcome it was decided still further to expand the production by collaborating with some firm engaged in the manufacture of extracts from slaughterhouse materials. This was done under a special agreement by which the University undertook not to issue licences to other firms until the lapse of a period during which the large scale method could be carried out so as to yield the maximal output of preparation of standard and uniform potency both when assayed by the rabbit test and when tested therapeutically on diabetic patients. For the clinical assays this firm agreed to distribute a sufficient number of free samples of their preparation to various physicians specializing in the treatment of diabetes in properly controlled clinics. This collaboration between the committee of the University and a firm in the United States is proceeding at the present time, and the physicians receiving insulin are reporting their experiences as to its potency and value. Whenever it is certain that a thoroughly reliable large scale method for a product of constant potency has been worked out the special agreement between the University and the collaborating firm will terminate, and the University will issue licences to other approved firms.

Realizing that it could not exercise proper supervision over the production of insulin in more countries than Canada and the United States, the University has offered to the Medical Research Council the assignment of the patents applied for in Great Britain for the purpose of safeguarding the production and standardization of insulin in that country.

REFERENCES.

- ¹ Lépine: *Le diabète sucré*, Paris, 1903, p. 54. ² Von Mering and Minkowski: *Archiv. f. exp. Path. u. Pharm.*, 1889, xxxi, p. 371. ³ Knowlton and Starling: *Journ. Physiol.*, 1912, xiv, 146. ⁴ Murlin: *Journ. Biol. Chem.*, 1913, xv, 365. ⁵ Kleiner: *Ibid.*, 1919, xl, 153. ⁶ Scott, E. L.: *Amer. Journ. Physiol.*, 1912, xxix, 3. ⁷ Clarke: *Johns Hopkins Hosp. Reports*, xviii, 229. ⁸ Banting and Best: *Journ. Lab. and Clin. Med.*, 1922, vii, 251. ⁹ Banting and Best: *Ibid.*, 1922, vii, No. 8. ¹⁰ Banting, Best, and Macleod: *Proc. Amer. Physiol. Soc.*, December, 1921. ¹¹ Banting, Best, Collip, Macleod, and Noble: *Trans. Roy. Soc. Canada*, 1922, vol. xvi, Sec. V. ¹² Banting, Best, Collip, Macleod, and Noble: *Amer. Journ. Physiol.*, 1922, lxii, 162. ¹³ Banting, Best, Collip, Macleod, and Noble: *Ibid.*, 1922, lxiii, 14. ¹⁴ Hepburn and Litchford: *Ibid.*, 1922, lxii, 177. ¹⁵ Banting, Best, Collip, Campbell, and Fletcher: *Canadian Med. Assoc. Journ.*, March, 1922.

Remarks

ON THE

SURGERY OF THE PITUITARY GLAND.*

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[With Special Plate.]

EVEN in adult life the two portions of the pituitary gland remain distinct, and each appears to have a very different function. Their somewhat complicated development will therefore have to be briefly considered before discussing the manifestations of disease of the gland.

DEVELOPMENT.

In the adult the pituitary gland forms a small oval structure, which is somewhat flattened from above downwards, and fills the pituitary fossa of the sphenoid bone. Its longest diameter, which usually lies transversely, is about half an inch. On section it can be seen to be distinctly formed of two parts, an anterior and a posterior. The anterior portion, often described as the epithelial or glandular part, is in man considerably the larger, and forms about two-thirds of the total gland. It is immediately in front of, and in part envelops, the posterior lobe, which may be regarded as being embedded in its posterior surface. Blair Bell has shown that this position is largely dependent upon the shape of the fossa, for in animals with a deep fossa, such as the cat, the pars nervosa lies posteriorly; while in dogs, which have a shallow fossa, it is placed superior to the glandular part. The glandular portion is developed from the stomadeum at a very early age from a recess, known as Rathke's pouch, which grows upwards from the junction of the pharyngeal membrane with the roof of the primitive stomadeum, and which, according to Bell, may be visible even in a foetus of 2.5 mm. Such a method of development is remarkably constant within the vertebrate series, and may be found in some form even as far back as the Cyclostomata. The pouch so formed passes upwards in front of the notochord and between the trabeculae cranii to the base of the brain. The neck of the sac becomes constricted, but the upper portion dilates to form what is known as the pituitary sac. Later, as the sphenoid develops, the stalk becomes constricted and disappears, so that the pituitary sac is entirely shut off from the stomadeum. The position of this stalk is usually regarded as lying between the pre-sphenoid and post-sphenoid, but Cope has shown that it traverses the anterior part of the post-sphenoid. Although the stalk by these means is as a rule entirely destroyed, Duffy has shown that certain squamous-celled tumours which arise in or about the pituitary probably originate in the remnants of this stalk, which may persist in the post-sphenoid or beneath the capsule of the anterior lobe. Erdheim has reported a case of acromegaly in which a tumour formed of cells resembling those of the anterior lobe was imprisoned in the posterior part of the sphenoid. The pituitary sac thus cut off from the primitive pharynx undergoes very considerable proliferation. It becomes more or less triradiate in outline, and later gives off a large number of diverticula, so that it comes to have a glandular appearance.

The fully developed anterior lobe comes therefore to be composed of well-defined epithelial cells supported by a framework of fine connective tissue and showing large blood vessels and sinuses. Not uncommonly the cells are arranged in the form of small vesicles containing a granular-like material somewhat resembling colloid. The work of Bell and Cushing, among others, shows that there is a very great variation in the appearance of this portion of the gland in different physiological and pathological states. It can always be determined, however, that there are two main types of cells: one of these stains well and is spoken of as the chromophil cell, which may be either basophil or acidophil; the other stains poorly, and is spoken of as the neutrophil or chromophobe cell.

The anterior lobe appears to become larger and more active in certain conditions—such as during pregnancy, after

* An abstract of this paper was presented to the Section of Surgery at the Annual Meeting of the British Medical Association at Glasgow.

thyroidectomy, and after castration. It is also always larger in adult parous females than in men or nulliparae.

The posterior part, or *pars nervosa*, has an entirely different origin. Shortly after the appearance of Rathke's pouch a depression is seen in the floor of the forebrain. As development proceeds this pouch dilates while its stalk becomes constricted. The dilated portion comes into close relationship with the posterior surface of the anterior lobe and is in part enveloped by it. As it grows its wall becomes thickened, and as a rule the cavity entirely disappears, but occasionally a small part may remain as a minute vesicle which is still lined by ciliated columnar epithelium. The stalk, unlike that of the anterior lobe, does not disappear but persists as the infundibulum or stalk of the pituitary gland. This is attached above to the anterior part of the tuber cinereum, which is a thin layer of grey matter alone separating the pituitary fossa from the cavity of the third ventricle. Indeed, a small pouch of the third ventricle is continued downwards into the upper part of the infundibulum. In adult life this portion of the gland is seen to consist of cells and fibres which are apparently neuroglial in character. Occasionally large cells, apparently from the *pars intermedia*, may be seen in the substance of the *pars nervosa*, and generally there can be distinguished a peculiar brown pigment.

It has been shown that as the anterior lobe develops the original pituitary sac throws out buds which by irregular growth form the glandular-like anterior lobe of the pituitary. The posterior wall of the sac remains, however, simple and comes to lie in close relationship with the infundibulum of the posterior lobe, while the pituitary sac itself persists as a narrow cleft which appears to separate the anterior from the posterior lobe. This thin posterior wall of the sac remains epithelial in character and is usually spoken of as *juxtaneural epithelium*. This portion forms in the adult the *pars intermedia*. It is developmentally a portion of the anterior lobe, and it and the anterior lobe are generally spoken of together as the *hypophysis*. Like the rest of the gland, it varies very considerably in its size and extent in different animals. In man the epithelium is very scanty, and only forms a thin layer over the *pars nervosa*, where it adjoins the narrow cleft. The cells are faintly granular and either neutrophil or slightly basophil. A colloid-like secretion is sometimes found in this part and also in the cleft. Whereas the anterior lobe has a very fair blood supply from the internal carotid arteries, the *pars intermedia* appears to contain no blood vessels or lymphatics.

ANATOMY.

The anatomical relations of the gland are of extreme importance surgically, and it is owing to the inaccessibility of the fossa and to the importance of the surrounding structures that surgical measures have been so limited in the past.

The gland itself lies in a deep hollowed-out fossa in the sphenoid bone, and therefore lies in the centre of the base of the cranium and almost equidistant from the root of the nose and the posterior margin of the foramen magnum. The shape of the fossa varies considerably. Cope has shown that the antero-posterior measurement is from 7 to 14 mm., the transverse from 9 to 15 mm., and the depth from 3 to 10 mm. Immediately beneath it the basisphenoid is hollowed out by the presence of the sphenoidal sinus, but both the size of the pituitary fossa and the size of the sphenoidal sinus are subject to very considerable variation. Gibson, who took careful tracings of 107 skulls, found that the sphenoidal sinus was completely absent in 3 per cent., very small in 9 per cent., and was separated from the sella turcica by a thick anterior wall in 9 per cent. What is perhaps of more importance surgically is that he was able to show that the sinus did not project below the sella turcica in 22 per cent. of the cases. The sphenoidal sinus not infrequently shows an inter-sphenoidal septum which is variable in its position, and may be so much to one side that if taken for a guide in an intranasal operation it may lead to one of the cavernous sinuses being opened in mistake for the pituitary fossa. The floor of the sphenoidal sinus is formed laterally by the cornua sphenoidalia and medially by the ethmoidal spine, to which is attached the vomer bone. It will thus be seen that any approach to the pituitary fossa by the intranasal route, which is the operation of choice, is not only associated with considerable difficulties owing to the variations in the anatomical conditions, but, the opening being small, it is impossible to remove completely any of the larger tumours in this region.

The bony floor of the fossa is slightly concave and is limited laterally by a slight ridge of bone which separates it from the carotid groove. Posteriorly the cavity is overhung by the *dorsum sellae*, which separates it from the pons Varolii and the basilar artery. The upper portion of this ridge projects on either side and overhangs the pituitary fossa to form the two posterior clinoid processes. Anteriorly the fossa is limited by a transverse ridge of bone, the olivary eminence or *tuberculum sellae*, which is often continued outwards laterally into two small spurs of bone—the middle clinoid processes. These middle clinoid processes limit posteriorly the groove for the carotid artery where it turns upwards from the cavernous sinus. Sometimes the middle clinoid processes may be sufficiently long to join with the anterior clinoid process and thus convert the carotid groove into a canal. In front of the olivary eminence is the optic groove, which terminates on either side in the optic chiasma. The pituitary fossa thus formed is lined by a layer of dura mater and is covered in above by a fold of the same structure, which is the *diaphragma sellae*. This is complete except for a small opening in the centre through which passes the infundibulum.

The pituitary, therefore, lies in a closed box, which anteriorly, posteriorly, and inferiorly is formed of bone, and above and on both sides is formed of dura mater. Each lateral wall is separated to enclose the cavernous sinus containing the carotid artery, the third, fourth, sixth, and branches of the fifth nerves. Just external to the third division of the fifth nerve is the middle meningeal artery. These lateral relationships of the pituitary are of considerable importance and make an approach to the gland by the temporal route a difficult and dangerous procedure. To obtain adequate access by this route it would be necessary to lift up the temporal lobe and with it the optic tract, and to open the *diaphragma sellae* above and internal to the cavernous sinus. Separating the structures of the interpeduncular space from the base of the skull and the pituitary fossa is a large subarachnoid space, the *cisterna basalis*, through which passes the infundibulum. Anteriorly the fossa is in part shut in by the anterior clinoid processes and the olivary eminence, and it is said that sometimes they may project so far over the pituitary fossa as to make approach by the anterior or frontal route difficult. In practice, however, this is found not to be the case, for by lifting up the frontal lobe it is always possible to reach to the bottom of the pituitary fossa.

Running transversely across the front of the gland in the optic chiasma and at a somewhat higher level is the anterior communicating artery. Antero-laterally are the carotid arteries turning forwards and the optic tracts. Although the optic chiasma lies close to the bone it will nearly always be found that a tumour of the pituitary elevates the chiasma from the bone, and presents in the triangular space between the two optic nerves. Thus it often happens that at operation, although a tumour the size of a walnut is readily removed and the floor of the pituitary fossa freely exposed, yet the optic chiasma has been pushed so far upwards and backwards that it is not seen in the operating field.

The arterial relationships to the gland are of considerable importance. Posterior to the *dorsum sellae* runs the basilar artery, which divides superiorly to form the two posterior cerebral arteries. Running forwards from these arteries close to their origin and encircling the infundibulum are the two posterior communicating arteries, which join the internal carotid arteries almost immediately after they have appeared above the middle clinoid process. They thus lie upon the *diaphragma sellae* and the superior surface of the pituitary gland. The two internal carotids pass upwards and give off the anterior cerebral arteries, which are united by the anterior communicating artery. It will thus be seen that the posterior communicating arteries run beneath the optic tracts, whereas the internal carotid and the anterior cerebral arteries run external and superior to the optic nerves. Hence a pituitary tumour, pushing upwards the optic chiasma, will compress the optic nerves between itself and the anterior ring formed by the circle of Willis. We therefore have an explanation as to why it is that sometimes a pituitary tumour will give only a bitemporal hemianopsia and sometimes will lead to complete optic atrophy and blindness.

FUNCTIONS.

That the internal secretions of the pituitary gland have a very important bearing upon the general metabolism has been known for a considerable period, but accurate knowledge has

been almost wholly developed since Marie's observations in 1888 upon the changes in the gland that were found associated with acromegaly. This knowledge is in part based upon observations of the effects of administered extracts of pituitary, partly upon experimental operations upon animals, and partly upon observations of the changes found in certain physiological and pathological states. At one time it appeared as though the whole of the patient's appearance and character might depend upon slight changes in this small gland. More recent work makes it evident, however, that there is a very real interrelationship between this and other glands in the body, for under certain circumstances the whole of the gland may be removed and only beneficial effects will result.

A study of the internal secretion of this gland is associated with peculiar difficulties, for not only do the anterior and posterior parts appear to have entirely different functions, but the effects will differ according to whether the changes occurred before or after puberty. There is still, therefore, some uncertainty as to what are the parts played by the individual portions of the gland, for both experimentally and clinically it is difficult to obtain a lesion which is limited to one or other lobe. There even seems to be a certain amount of doubt as to what is the effect of complete extirpation of the gland. The evidence produced by Cushing would seem to show that complete destruction of the gland is incompatible with life, but Sir Victor Horsley brought forward a considerable amount of evidence to show that an animal could survive this operation. My own experience is very definite. I have two cases in which the gland has been completely extirpated; the pituitary fossa at operation was left absolutely bare and lined with smooth dura. Both these cases have survived and have made very good progress. It would appear, therefore, quite certain that the function of the gland can be almost wholly undertaken by other glands in the body.

The Anterior Lobe.

Since Pierre Marie first pointed out that cases of acromegaly were always associated with changes in the pituitary gland a large amount of evidence has accumulated to make it perfectly definite that this portion controls the metabolism and growth of the skeleton, including the bones, cartilage, and connective tissues. If there is an increase in the internal secretion before growth is completed the patient will develop into a giant. There will be a very great overgrowth of the bony skeleton, which, however, is rarely if ever symmetrical, and the patients will generally show not only structural weakness but many of the irregular outgrowths which are found in all cases of acromegaly. Should the oversecretion be delayed until adult life then there will be an irregular overgrowth of the bony and connective tissue, giving rise to that curious syndrome known as acromegaly. In addition to these clearly defined effects upon the skeletal tissues it is probable that an overgrowth of the gland is associated with changes in the sexual glands, for most cases of acromegaly are clearly asexual. It is possible also that the anterior lobe may to a certain extent control the deposit of fat.

Pars Intermedia.

It is very difficult, if not impossible, to distinguish the functions of this portion from those of the posterior lobe, but Evans holds the view that the pars intermedia produces a colloid-like material which affects the blood pressure and the urinary secretion. It may lower or raise the blood pressure and may increase or decrease the secretion of urine. It is held by many observers that all the effects which are described as due to changes in the posterior lobe are really due to changes in the pars intermedia, for it is difficult to see what secretion, if any, could be formed from the posterior lobe, which is apparently made up of neuroglia alone.

The Posterior Lobe.

It is a curious fact that whereas the functions of the anterior lobe are shown clinically to be so distinct, those of the posterior lobe are less well defined, yet extracts are much more easily prepared from the posterior, probably with the pars intermedia, and have a very definite effect. So far no demonstrable changes have been seen to follow the administration of extracts of the anterior lobe, although Goetsch has claimed that the administration of such extracts leads in young animals to an increase in the rate

of growth and early sexual development. The effects of extracts of the posterior lobe are many, and may be grouped as follows:

1. *A Pressor Effect.*—Howell in 1898 first showed clearly that it was the posterior lobe extracts alone which gave pressor effects. This has since been confirmed by many observers, who show that this pressor effect is due to a slowing and increase in force of the heart's action. Second and subsequent injections given soon after the first have little or no effect until the first has all been destroyed or excreted by the organism. The effect is maintained for a much longer period than that obtained by suprarenal extract.

2. *A Depressor Effect.*—It has been noted by many observers that an injection of this portion of the gland may lead not to a rise but to a fall in the blood pressure. Schafer and Vincent noticed that this fall followed second and subsequent doses if they were given soon after the first. Others have noticed that such a depressor effect followed shortly after the pressor effect had died away. Blair Bell, on the other hand, has shown that there is a preliminary fall before the blood pressure rises. It is this uncertainty as to the relationships between the pressor and depressor effects that has made the use of this drug in the treatment of surgical shock not entirely free from danger.

3. *A Diuretic Effect.*—Magnus and Schafer first showed that injections of posterior lobe extract had a diuretic effect. With this they observed that the arteries of the kidney were dilated, whereas the arteries of the rest of the body were constricted. The diuretic effect was not, however, simply a vascular phenomenon, for later Schafer and Herring showed that it was present even when general vaso-constriction was absent. Herring also showed that this effect was produced entirely by the pars nervosa and not by the whole posterior lobe. It is not, therefore, as has sometimes been thought, due to pressure upon the fourth ventricle.

4. *A Galactagogue Effect.*—The use of extract of the posterior lobe has come into considerable favour for its value in increasing the flow of milk in lactating women. Blair Bell points out that the effect is so rapid that it would seem improbable that it is due to the active principle being excreted by the gland and so stimulating the cells. It is an interesting point, however, that the increased flow is only of short duration and that the daily flow does not seem to be increased in amount. The increased flow shows a slight increase in the amount of fat, but is otherwise normal. The later excretion, however, shows a slight diminution in the amount of fat, so that the total excretion, like the total quantity, is not increased. Blair Bell holds the view that the increase in the rate of expulsion is simply due to the effect upon the muscle fibres, so that there is in reality an increased excretion rather than an increased flow.

5. *A Stimulative Effect upon Unstriated Muscle.*—One of the most valuable effects of pituitary extract is its power of causing rapid and powerful contraction of unstriated muscle. Bell has shown clearly that although the extract has no effect upon the resting uterine muscle it causes powerful contraction of the uterus in menstruating and pregnant animals. It has thus been largely used in gynaecological work. Similar powerful effects have been found in the case of the intestinal muscles, and the drug is now very largely used in many forms of ileus. A similar effect is seen upon the muscular wall of the bladder.

6. *Effects upon Carbohydrate Tolerance.*—Many diseases of the pituitary gland are associated with a very distinct and definite change in the patient's tolerance to carbohydrate, so that not infrequently there has been noticed the presence of glycosuria. There is some doubt as to which portion of the gland is responsible for this effect. It may be said to have been definitely established that with lesions such as acromegaly there is a diminution in the tolerance to carbohydrates. One of my own patients, who was a clear case of this disease, had a marked glycosuria. Lesions of the posterior lobe, on the other hand, show as a rule an increased tolerance, but it is not possible to say definitely whether the effect is due to over- or under-secretion. It might be possible that in acromegaly the glycosuria is due to overaction of the anterior lobe or due to underaction of the posterior lobe owing to the pressure of the enlarged anterior part.

PATHOLOGY.

In some of the cases in which the clinical symptoms clearly indicate that there is a diminution in the secretion of

the pituitary a skiagram may show that this fossa is smaller than normal. Few, if any, of these cases have had the pituitary examined, but the smallness of the fossa and the absence of local pressure symptoms would indicate that the symptoms are due to a simple atrophy of the gland. In the majority, however, the pituitary fossa is much enlarged, and this is true whether the symptoms are those of increase or decrease. If the symptoms are those of increased secretion there is an overgrowth of the pituitary gland which has a positive function, but where the symptoms point to a diminution of the secretion there may be a tumour such as a fibroma or sarcoma of the pituitary itself, or a neoplasm of the surrounding tissue which has caused local pressure symptoms and widening of the pituitary fossa, but having no internal secretion leads to a destruction of the pituitary with a diminution of its secretion. A similar condition may be found with cysts, and in my own experience the majority of the cases of hypopituitarism are found associated with a cystic change.

Much attention has been given to the nature of the pathological lesions found with an increased secretion. Cope has analysed 64 cases which were published by Cushing, Hirsch, and von Eiselsberg. Of these 64, 45 were adenomata and 7 were cysts. Others have been certified as endotheliomas, mixed tumours, epithelial cancer, sarcomas, etc. It is probable, however, that the majority of these latter were really adenomata. Such tumours are very richly cellular and give a microscopic appearance which is very suggestive of a carcinomatous change. They are, however, quite localized, are not associated with secondaries, and would seem not to recur after complete removal. Frazier has also laid stress upon the great variation in the published reports of the pathology, and in many which are reported as malignant there has been no evidence of recurrence or of secondary deposits after a number of years. Sekiguchi has carried out an interesting investigation in cases that had died of mammary cancer. In two such cases he found that there were secondary deposits in the posterior lobe, and in both cases the patient had polyuria, which he regards as being due to compression of the pars intermedia by pressure of the secondary deposits in the pars posterior. It may be said, then, that the majority of cases that show an increased secretion are due to the presence of functioning adenomata. When there is clinical evidence of a diminished secretion the lesion is most commonly a cyst or a parapituitary tumour, but may occasionally be due to a simple atrophy. The diagnosis of the latter type is simple, for there will be no local pressure symptoms and a skiagram will show a diminution rather than an increase in size of the pituitary fossa.

CLINICAL MANIFESTATIONS.

There are certain diseases in which it is well established that there is a lesion of the pituitary gland, but there are others in which the evidence is much less certain. Cope, for instance, has shown that there is a close relationship between the pituitary and the thyroid, and that a diminution in the thyroid gland may be associated with an overgrowth in the pituitary. He has found that the fossa may be enlarged in cases of cretinism and is often considerably enlarged with achondroplasia. In the well-established cases the pituitary lesion will give rise to symptoms which may be placed in three groups. There are, first, those which are dependent upon some alteration in the secretion, which is either diminished or increased, and according to whether this variation in the secretion occurs in early or adult life so will different symptoms arise. Secondly, there are symptoms due to local pressure of the enlarged pituitary on the surrounding tissue. Lastly, there are a group of symptoms which are due to a general increase of the intracranial pressure.

Disturbances of Internal Secretion.

There are still many points of doubt as to which portion of the gland is actually at fault with individual disease, and not uncommonly curious combinations of symptoms may be found. It is possible, for instance, that an adenoma of the anterior lobe will give rise to an increased secretion in this portion, but at the same time the tumour might cause a pressure atrophy of the posterior lobe and so give rise to symptoms of hypopituitarism. Such a combination of Fröhlich's disease and acromegaly has been reported by Frazier and another by von Eiselsberg. It is therefore not yet possible to say with certainty what symptoms correspond

with different lesions of the gland, but it is probable that the following classification is a correct one:

Classification of Symptoms.

Anterior Lobe:—

- (a) Increase of function: (1) In young patients = gigantism. (2) In adults = acromegaly.
- (b) Decrease of function: (1) In young = ateliosis (Lorain's disease), possibly achondroplasia. (2) In adults doubtful; possibly fragilitas ossium.

Posterior Lobe:—

- (a) Increase of function: Doubtful; possibly some forms of precocious development and some cases of congenitally high blood pressure.
- (b) Decrease of function: (1) In young = dystrophia adiposogenitalis (Fröhlich's disease). (2) In adults = adipositas dolorosa.

Gigantism.

The relationships of gigantism to lesions of the pituitary gland have been well appreciated since Sternberg showed that 20 per cent. of acromegals were giants and 40 per cent. of giants developed acromegaly. Cushing has reported several cases of giants with lesions of the pituitary gland, and it has been realized that a similar change existed in many of the well-known giants. It is also interesting to note that very few of these so-called giants are normally developed. Most of them show an unusual size of the hands and feet, and many of them, although so big, show many of the irregular changes in growth which are associated with acromegaly. For instance, they often have very long arms and legs, irregular overgrowth of the facial bones, and marked kyphosis. Brissaud was the first to point out that acromegaly was probably gigantism of adult life, or that gigantism could be regarded as acromegaly occurring during the period of growth. He also showed that examples of acromegaly and gigantism might be found in the same family.

Acromegaly.

This condition has been so frequently described, and so many cases have been reported since Pierre Marie's first complete description in 1886, that it will suffice to give a very brief account of the clinical condition.

In nearly all cases there is a definite change in the pituitary gland which takes the part of an adenomatous overgrowth. Even in the few cases that have been reported where acromegaly has occurred without any visible change in the gland, it is probable that a microscopic examination would show a definite overgrowth, as in cases reported by von Eiselsberg. As a general rule the disease commences after the age of 30, and males and females appear to be almost equally affected. There is a remarkable similarity in the appearance of all such patients. The face as a whole shows general hypertrophy, especially in the vertical direction. The forehead appears low and narrow, the orbital margins are much enlarged and thickened, and a skiagram will show an increase in size of the frontal sinuses. The temporal areas appear to be depressed. The nose is widened and enlarged, the upper jaw shows slight overgrowth, and there is marked hypertrophy of the lower jaw. With this enlargement of the inferior maxillary there is a separation of the teeth, so that in time they come to form an arch greater than that of the upper teeth. The jaw itself projects and is enlarged from above downwards. The tongue is hypertrophied and the ears are somewhat thickened and enlarged. The lips are thickened and often appear to be negroid in type. A skiagram will reveal some thickening of the tables of the skull and considerable overgrowth of the orbital margins and jaws. The pituitary fossa is enlarged and the clinoid processes may be eroded. The spine shows a definite kyphosis and some of the patients may have a distinct increase in height. In three of my patients, although adults, the height had increased from one to three inches since the onset of the disease. The thorax is enlarged, widened, and deepened. There is a wide subcostal angle. The pelvis is enlarged in all directions and the bones are generally thickened. Perhaps the most characteristic change is that in the hands and feet. They are generally increased in size, especially in the lateral direction. The patients will often have noticed that since the onset of the disease they have had to take much larger boots and gloves. The thickening consists of all the tissues. At first the soft tissues are enlarged so that the fingers are more or less cylindrical, the hands wider, and the heels thicker. The toes, like the fingers, are cylindrical, and the foot is much wider at the base of the toes. At this stage a skiagram will show no

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FIG. 1.—The inferior relationships of the pituitary fossa. A, Sphenoidal sinus. B, Pituitary gland.

FIG. 3.—The superior and lateral relationships of the pituitary gland. A, Optic nerve. B, Anterior cerebral artery. C, Anterior communicating artery. D, Pituitary gland. E, Third nerve. F, Posterior cerebral artery.

FIG. 2.—The lateral relationships of the pituitary gland. A, Fifth nerve and Gasserian ganglion. B, Sixth nerve. C, Third nerve. D, Fourth nerve. E, Optic nerve. F, Middle cerebral artery.

FIG. 4.—Relationships of the circle of Willis to a pituitary tumour. A, Middle cerebral artery. B, Anterior cerebral artery. C, Anterior communicating artery. D, Posterior communicating artery. E, Posterior cerebral artery. F, Basilar artery.

FIG. 5.—Case v. Acromegaly before operation.

FIG. 6.—Case v. Acromegaly five months after operation.

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FIG. 7.—Case VI. Acquired Lorain, aged 19. Before onset of symptoms.

FIG. 8.—Case VI. Acquired Lorain, aged 23. Day before operation.

FIG. 9.—Case VI. Acquired Lorain. Three months after operation.

FIG. 10.—Case VI. Acquired Lorain. Pituitary tumour removed by frontal route.

FIG. 11.—Fröhlich's disease.

FIG. 12.—Exposure of pituitary tumour by frontal route. A, Tumour of pituitary gland. B, Optic chiasma. C, Middle cerebral artery. D, Frontal lobe of cerebrum.

evidence of any bony change, but later there is a subperiosteal overgrowth, especially of the proximal phalanges. In advanced cases there may be a hypertrophy of the muscles of the arms and legs, which later is repaced by an atrophy, and the *x* rays will show a deposit of new bone beneath the periosteum of the long bones. Sexual changes are definite. In women the breasts atrophy and amenorrhoea is an early symptom. The external genitalia are hypertrophied and there is a decrease in sexual desire. The heart is often hypertrophied. The thyroid may be small and the larynx hypertrophied, so that in women the voice becomes deeper and stronger and resembles that of a man. The skin may show profuse sweating and pigmentation, and the hair becomes coarse and wiry. The intelligence is as a rule good, but later, when there is evidence of general pressure, the mental functions may be impaired. The patients will often complain of severe, but ill-defined, pain in the limbs, back, and joints. Local or general pressure symptoms may be present in addition, and it is not uncommon, as in one of my cases, for glycosuria to be present and to require treatment before an operation is undertaken.

Ateliosis, or Lorain's Disease.

This condition may be regarded as the exact reverse of gigantism. The condition generally occurs quite early in life, and thus the patient remains small and stunted, and never arrives at full development. In some interesting cases the condition starts late in life, and then, as in one of my cases, the patient may become smaller and of poorer physique after he has developed along normal lines. This lack of growth is even, so that the proportions of the different parts of the skeleton remain more or less normal, and hence the condition is easily distinguishable from achondroplasia. Several observers, however, have noticed changes in the pituitary in association with achondroplasia. With the lack of growth there is a failure to develop the secondary sexual characteristics, so that the patients appear to be younger than they really are, and at the age of 35 or 40 may seem to be only 14 years of age. The bones are small and relatively fragile, and the muscular attachments are poorly developed. The junction at the epiphysis is greatly delayed, but the formation of the bones is regular, and there is no enlargement of the epiphyseal ends, as may be seen with achondroplasia. The skull is small with thin bones, and a skiagram may show very definite changes in the pituitary fossa, which varies with the nature of the lesion. If, as is not uncommon, there is a simple cyst, the fossa may be much dilated and the clinoid processes may be absorbed. The lower jaw is badly developed and there is a poor eruption of the teeth. The muscles are ill developed and are feminine in character. The skin is also soft, delicate, and white. The body and face remain hairless, and the voice is thin, high, and piping, so that the patient, if a male, retains many of the female characteristics. The intelligence is generally below normal. The appetite is poor, and there may be alterations in the secretion of urine, there being generally polyuria. Glycosuria is not present and as a rule the sugar tolerance seems to be increased. Later, local pressure symptoms, and especially those upon the optic chiasma and nerves, will become evident. Headache and other signs of general pressure will appear as late manifestations.

If the symptoms appear soon after puberty, as in the sixth case of my series, these changes of general atrophy will appear after the patient has reached a normal height, and after operation they will gradually disappear. This progress throws a certain amount of doubt upon the belief that the symptoms are due to a simple hyposecretion of the anterior lobe, for in my own case there was an enormous improvement after the whole of the pituitary had been removed, and the patient is now rapidly passing again into a normal condition, and this in spite of the fact that he has taken no pituitary extract by mouth. Cases of atrophy occurring in late adult life have not been recorded, but the changes that are found in cases of fragilitas ossium would suggest that they might be due to a hyposecretion of the posterior lobe, and it will be of interest to note in the future whether such changes are recorded.

Posterior Lobe Increase.

There is some doubt as to the actual changes which occur with an increase of function of the posterior lobe. One would imagine that this would give rise to a greatly increased blood pressure, polyuria, and a generally active metabolism. Thus theoretically it would seem possible that some of the cases of chronic nephritis in early life would be due to such changes.

On the other hand, certain cases have been reported of children who have rapidly developed, and at the age of 8 or 9 have shown an abnormal development both physically and sexually. Poynton reports a case, for instance, of a boy aged 8 who had a well-marked moustache, beard, and whiskers. He regarded the case as being due to a pituitary lesion and not to a suprarenal growth. Similar cases of precocious development, both psychically and physically, have been reported in association with pineal tumours. Such cases have been reported by Howell, Ogle, Frankl-Hochwart, Heubner, Gutzeit, Marburg, Oestreich and Slawyk. Marburg believes, however, that in the case of a pineal tumour they are due to hyposecretion, while with a lesion of the pituitary there is a hypersecretion of the posterior lobe.

Dystrophia Adiposo Genitalis (Fröhlich's Disease).

It is of interest to note that many of the cases of this condition have shown the presence of a cyst in the pituitary gland. My own cases are of special interest from this point of view, for the patient who showed Lorain's disease had a large semi-calcareous cyst, which in the *x*-ray photograph was well forward and showed destruction of the anterior clinoid processes; whereas the girl who had typical Fröhlich's symptoms had also a calcareous tumour, which was shown by the skiagram to be far back and had led to a destruction of the posterior clinoid processes. The changes in the body are remarkably characteristic. There is an enormous overgrowth of the subcutaneous fat, the deposit of which is more or less general, but has a tendency to be placed so as to exaggerate the female outline of figure. Thus, in a male, there is a relatively greater thickening of the buttocks and thighs and a subcutaneous deposit in the breasts. With this increase of fat there is a low blood pressure and a good or increased tolerance to carbohydrates. Sometimes there are other changes, which are possibly due to an associated diminution of the anterior lobe secretion, so that they may be small in size with late union of the epiphyses, softness of the skin, and no growth of hair. There is always a diminution in the sexual development. The genitalia remain small and the voice is high-pitched and squeaky and the thyroid small. It is probable that what Earnside has described as the "pudding-face type" is a mild degree of the same disease. There may be a slight general increase in the subcutaneous fat—the face is fat and rounded with red prominent cheeks, and the voice is high and piping. The thyroid is small and amenorrhoea is generally present. As in the Fröhlich's type there are frequently alterations in the visual fields which may, if left, progress to complete blindness.

Adiposis Dolorosa.

There is an increasing amount of evidence that a large number of the cases which have been described as adiposis dolorosa are in reality examples of hypopituitarism which have developed after adult life; they therefore bear the same relationship to Fröhlich's disease as acromegaly does to gigantism. Cushing quotes several cases in which lesions of the pituitary have been found under such circumstances, and Dercum himself has included certain mental changes as one of his four cardinal symptoms of the disease.

The disease is generally seen after middle age, and is more common in women. It is characterized by a rapid increase in weight, which is due to large irregular and frequently painful deposits of fat. The deposits may be diffuse in outline or may be more or less localized, so that they form large irregular lipomata. The deposition of the fat is very characteristic. It is almost wholly localized to the trunk and pelvis, while the face, neck, and extremities are as a rule free. The hands are not enlarged and the fingers are usually tapering. Sometimes the portions of the body above the waist will remain entirely free while the buttocks and thighs are enormously enlarged. In other cases there is also a big deposit in the back and shoulders, and sometimes even in the posterior aspects of the arms. There is frequently with this an increase in the sugar tolerance, and not uncommonly some local evidence of pressure, as shown by changes in vision. Occasionally there are well-marked evidences of general pressure, as shown by headache and drowsiness, and very frequently there is amenorrhoea.

Local Pressure Symptoms.

The most frequent change which occurs with the local pressure of the growth is an affection of vision. The pituitary gland, with so close a relationship to the optic tracts, chiasma, and nerves, is liable as it enlarges to press upon these

structures and give rise to changes in vision. Little will be said about these changes, as they will be described in detail by other contributors. It is sufficient to say that the most characteristic change is due to pressure upon the inner part of the optic tracts and the inner part of the chiasma, so that the fibres passing in the two nasal fields of the retina are those which are chiefly affected. In these circumstances patients will develop a bitemporal hemianopsia, and it will often be noted that they complain that they are unable to see objects on one side of them, and that they appear to be looking through opera glasses or through tubes. It must be remembered, however, that with some of the larger tumours of the gland the whole chiasma is pushed upwards and backwards. In these circumstances the pressure is more even, and the fibres running to the nasal fields will not be so much affected. As, however, the chiasma is drawn upwards the tumour will compress the two optic nerves in that portion of the circle of Willis which is formed by the two anterior cerebral and the anterior communicating arteries. There will thus be a constriction of both optic nerves, which explains why in some cases the patient will develop a complete optic neuritis or atrophy giving a general impairment or even complete loss of vision.

Much less frequently there is evidence of interference with the changes of the fifth nerve; the patient may then suffer from severe attacks of neuralgic pain on one or other side of the face, and there may be an area of hyperaesthesia limited to one or all of the divisions of the fifth nerve. In my own experience there has only been one case of diplopia and no example of any interference with the first, fourth, or sixth nerve. Cushing, however, states that in several of his cases there have been periods of double vision suggesting oculomotor implication, and in advanced cases an anosmia may be complete. These local pressure symptoms may or may not be associated with changes in the general metabolism.

General Pressure Symptoms.

The pituitary tumour, like all other intracranial tumours, will sooner or later give rise to evidences of a generally increased pressure, but it must be remembered that headache alone is not of necessity such an evidence. Severe local headache may be found quite apart from other signs of pressure, and may be due to pressure upon or erosion of the basisphenoid. On the other hand, tumours which are not entirely pituitary in origin may arise in the base of the brain and by pressure upon the pituitary may interfere with the functions of this gland and so give rise to changes in the metabolism. If the case be left for any length of time, evidences of general pressure, such as increased headache, mental dullness passing on to drowsiness, optic neuritis, and perhaps even slowing of the pulse, will be certain to appear. It must be remembered here also that although one of the strongest cases of evidence of a pituitary lesion is that presented by the *x*-ray appearances, a general intracranial pressure from some remote cause, or even a hydrocephalus, may give rise to a considerable enlargement of the pituitary fossa, and hence the condition may be mistaken for a primary tumour of the gland.

INDICATIONS FOR OPERATIVE TREATMENT.

It has been pointed out that cases both of hypersecretion and hyposecretion are generally due to a tumour or cyst, and thus both would seem amenable to surgical treatment. The first essential is therefore to exclude the possibility of a case of hypopituitarism being due to a primary atrophy of the gland. In such a case there would, of course, be no evidence of local pressure and an *x*-ray photograph would show a small fossa. These cases are not operated upon, for in the light of our present knowledge it would seem that removal of the gland would only increase the hypopituitarism. This opinion may later have to be altered, for it is interesting to note that two of my cases, one of which was an acromegaly, had the gland completely removed, and have not developed hypopituitarism; whereas another, who had Lorain's disease and also had the tumour and pituitary gland completely removed, has lost his symptoms of hypopituitarism although no gland extract has been administered. There is, however, another question which has to be considered, and that is a comparison of the dangers of operative treatment as compared with the danger of the disease. Some forms of acromegaly are very slowly progressive and may, in fact, after a certain period of time become stationary, so that the patient may live in comfort for many years. On the other hand, the operation must always be considered as a

serious one and at present has a relatively high mortality. For this reason the majority of physicians and surgeons would not advocate operative interference for simple hypo- or hyper-pituitarism. When future experience has reduced the mortality of surgical treatment it will probably be applied more frequently in this type of case. At present the indications for operation are:

1. The presence of some enlargement of the gland either from a tumour or cyst.
2. A rapid increase in the symptoms.
3. The presence of local pressure symptoms, especially diminution in the field of vision.
4. The presence of general pressure symptoms, such as headache, vomiting, or early optic neuritis.
5. The presence of glycosuria.

In regard to the presence of glycosuria it must be remembered that this is directly due to the lesion of the pituitary, and that very frequently by careful medical treatment and diet it may be eliminated, and if the operation be then performed it will not return, although medical treatment is not continued.

CHOICE OF OPERATION.

I do not propose to consider in detail the different methods of operative technique, for in my own experience one path of approach is so greatly superior to all others that it alone need be considered. At the present time the operation which is most frequently performed is the intranasal method of trans-sphenoidal approach, but to my mind any form of approach through the sphenoid bone is incomplete and unsatisfactory. The opening is bound to be small and may give no idea of the size or position of the tumour. If there be a cyst it may be drained, but there is no evidence that it will not refill. A solid tumour can at best be scraped out piecemeal and therefore may recur. This method of approach must also, even if carefully performed by the submucous route, be associated with a certain danger of sepsis. All these objections are absent when performing the operation by the trans-frontal route. A perfect view may be obtained of the pituitary gland and its surrounding structures, the whole tumour can be carefully dissected free under direct vision, and a mass as large as or larger than a walnut can be taken away as a whole. Two objections are made to this route. The first is that it carries with it too high a primary mortality. In the past this has been so, but it is very largely due to the fact that operation has been delayed until the patient has developed increased intracranial pressure. In such circumstances any cranial operation is bound to carry with it a high mortality. If the operation is carried out before the onset of this complication there is no reason why there should be any mortality at all. Of my six cases where this operation has been performed two died as an immediate result, and both of these at the time had an increased intracranial pressure. Even with this intracranial pressure the transfrontal route shows a mortality no greater than that by the extracranial route, for Frazier has collected sixty-four tumours operated upon by the extracranial method with twenty-four deaths.

The other objection which has been raised to this method is that good access cannot be obtained to the floor of the pituitary fossa, and it is therefore usually stated that if the *x* rays reveal a deep erosion of the fossa the transsphenoidal route should be applied; whereas, if the *x* rays indicate an upward growth, the intracranial route is the one of choice. I believe that this suggestion is quite erroneous. In every case where I have operated by the transfrontal route I have been able to obtain access to the floor of the fossa, and by elevating the brain a good view of the dural floor has been obtained. The method which I advocate is a modification of the operation published by Frazier, which itself was a modification of the technique of the methods used by Krause and McArthur. The actual steps are as follows:

The approach is always carried out on the side of which the vision is most affected, for it may happen that the operative steps may cause a certain amount of trauma of the optic nerve, and if the eye is already blind on this side no harm will be caused.

A rectangular incision is made. It commences in the temporal region just above the zygoma and passes along the line of the eyebrow to the middle of the forehead. From here a second limb passes vertically upwards for a distance of about four inches, and from this upper extremity a third incision is made parallel to and of the same length as the first. The soft tissues are then elevated from the four corners of the flap marked out, and openings are made with

a trephine at these corners. The discs of bone so removed are placed under the portions of the scalp around the flap and so kept until the termination of the operation. The four trephine openings are now united with a Gigli's saw, the cuts being made obliquely upwards and outwards so that the bony flap is larger externally than internally. The whole flap is now elevated and turned outwards. The dura is gently raised from the roof of the orbit until the posterior edge of the lesser wing of the sphenoid is exposed. By this means the greater part of the retraction of the brain is performed with the dura still intact and is thus preserved from harm. When the lesser wing is exposed the dura is opened and very little further retraction will expose the olfactory tract, the optic nerve, chiasma, and the pituitary tumour. Gentle dissection with a Watson Cheyne dissector will usually determine the size and motility of the tumour, and as a general rule this can be elevated from the pituitary fossa and entirely freed and removed. Haemorrhage is not excessive and in no case have I found it necessary to ligature any vessels. If a cyst be present it may be necessary to aspirate it before dissecting out the cyst wall. The tumour having been removed the brain and dura are allowed to drop back into place, the dura is sutured, the bone flap replaced, the four trephine circles are removed from beneath the scalp and put back into place, and the soft tissues are sutured. The operation differs from that of Frazier in that the supra-orbital ridge is untouched, and it is found that by elevating the dura sufficient retraction is obtained to give a perfect view of the pituitary fossa. The trephine circles of bone are replaced at the end of the operation, for if this is not carried out an unsightly depression may persist in the forehead immediately above the root of the nose.

RESULTS OF OPERATION.

My experience includes the following cases:

CASE I.

I. J., female, aged 14, was brought to me on June 14th, 1915, with a history of having had headache for two years, fits for eighteen months, and blindness for seven weeks. She was extremely fat; there were no secondary sexual characteristics.

Operation.—Right frontal approach; orbital ridge divided; cyst with cholesterolin fluid drained.

Result.—Little improvement only. The fits returned, and she died in ten months.

CASE II.

S. B., female, aged 55; seen on October 23rd, 1915. She suffered from severe headache, had bitemporal hemianopsia, occasional diplopia, and later left blindness.

Operation.—Frontal flap; left optic nerve divided; tumour and pituitary removed entirely. The pathologist's report stated the tumour to be a solid acinous carcinoma of the pituitary.

Result.—Six years later the patient was doing well. She regards herself as a marvellous recovery, and is able to do all her work. Vision in right eye good.

CASE III.

M. S., female, aged 50; first seen July 17th, 1916. Symptoms: Headache, vomiting, vertigo, drowsiness, increase of fat; she had bitemporal hemianopsia.

Operation.—Left frontal flap; pituitary and tumour easily removed. Pathologist's report: Excess of acinous tissue containing secretion; probable adenoma.

Result.—Collapse followed the operation, and the patient died the next day.

CASE IV.

S. S., female, aged 42, came to me on January 12th, 1918, with a history of having had changes of vision for seven years; she had bitemporal hemianopsia passing on to blindness, and suffered from vomiting and headache.

Operation.—Right frontal flap; tumour removed, apparently completely. The pathologist's report stated that the tumour was a cuboidal-celled carcinoma.

Results.—The patient collapsed the same evening and died. The post-mortem examination revealed the fact that removal of the tumour was incomplete.

CASE V.

J. S., female, aged 42; seen February 12th, 1921. History of typical acromegaly for seven years, bitemporal hemianopsia, and glycosuria (relieved by medical treatment).

Operation.—Left frontal flap; tumour (a small sphenoidal-celled carcinoma) removed entirely from under chiasma.

Result.—April 28th, 1922: Complete cure; vision nearly perfect; symptoms of acromegaly diminished; no glycosuria; still slight headache.

CASE VI.—Acquired Lorain.

E. P., male, aged 23; first seen October 28th, 1921. Symptoms: Headache, vomiting, loss of appetite, weakness, muscular atrophy; loss of secondary sexual characteristics; bitemporal hemianopsia.

Operation.—Right frontal flap; calcareous tumour (adenoma) removed from beneath chiasma.

Result.—June 5th, 1922: Complete cure. The patient has gained 3 st., and is regaining secondary sexual characteristics. Vision greatly improved; still has temporal hemianopsia.

BIBLIOGRAPHY.

- Bell, W. Blair: *The Pituitary*, London, 1919.
Cope, v. Zachary: The Pituitary Fossa and the Methods of Surgical Approach Thereto, *Brit. Journ. of Surg.*, vol. iv, 1916-17, p. 107.
Cushing, Harvey: *The Pituitary Body and its Disorders*, 1912.
Duffy, W. C.: Hypophyseal Duct Tumours, *Annals of Surg.*, November and December, 1920, pp. 537 and 725.
Erdheim: *Beitr. z. Path. Anat. u. z. allg. Path.*, 1909, 233.
Fearnside, E. G.: Diseases of the Pituitary Gland and their Effect on the Shape of the Sella Turcica, *Lancet*, July 4th, 1914.
Frazier, C. H.: An Approach to the Hypophysis through the Anterior Cranial Fossa, *Annals of Surg.*, vol. lvii, February, 1913, p. 145.
Frazier, C. H.: Lesions of the Hypophysis from the Viewpoint of the Surgeon, *Surg., Gyn., and Obstet.*, December, 1913, p. 724.
Gibson, W. S.: The Topography of the Hypophysis Cerebri, *Surg., Gyn., and Obstet.*, August, 1912, p. 199.
Goetsch, E.: *Bull. Johns Hopkins Hosp.*, 1916, xxvii, p. 129.
Gutzeit: Inaugural Dissertation, Königsberg, 1896.
Handelsmann, Dr., and Horsley, Sir V.: Preliminary Note on Experimental Investigations on the Pituitary Body, *BRITISH MEDICAL JOURNAL*, November 4th, 1911, p. 1159.
Heubner, O.: *Verhandl. d. Gesellsch. deut. Natur. f. u. Aerzte* (1898), Leipzig, 1899, lxx, part 2, 2 Hefte, p. 220.
Hirsch: *Berl. klin. Woch.*, 1911, li, p. 1933; *Arch. f. Laryn. u. Rhinol.*, 1912, xxxvi, p. 529.
Howell, W. H.: *Journ. Exper. Med.*, 1898, lli, 245.
Howell, C. M. Hinds: Tumours of the Pineal Body, *Proc. Roy. Soc. Med., Neurological Section*, March, 1910.
Magnus, R., and Schafer, E. A.: *Journ. Physiol.*, 1901-2, xxvii, p. 9.
Marburg, O.: *Deut. Zeit. f. Nervenheilk.*, 1908, xxxvi, p. 114; *Wien. med. Woch.*, 1907, lvii, p. 2512.
Ogle, C.: *Trans. Path. Soc. London*, 1839, l, p. 4.
Oestreich and Slawyk: *Virchow's Archiv f. Path. Anat.*, clvii, p. 475.
Poynton, F. J.: Demonstration of Cases of the Pituitary Body, *Proc. Roy. Soc. Med., Section of Neurology and Ophthalm.*, May, 1913, p. 18.
Schafer, E. A., and Vincent, S.: *Journ. Physiol.*, 1899, xxv, p. 87.
Schafer, E. A., and Herring, F. T.: *Proc. Roy. Soc. Biol.*, 1916, lxxvii, Ser. B, 571.
Sekiguchi, S.: Hypophysial Disorder in Mammary Cancer and its Relation to Diabetes Insipidus, *Annals of Surg.*, March, 1916, p. 297.
Von Küsselsberg: *Trans. Amer. Surg. Assoc.*, 1910; *Arch. f. klin. Chir.*, c, 8, et seq.
Von Frankl-Hochwart, L.: *Deut. Zeit. f. Nervenheilk.*, Leipzig, 1903, xxxvii, p. 455.

MENTAL SYMPTOMS IN PHYSICAL DISEASE.

BEING AN ABRIDGEMENT OF THE BRADSHAW LECTURE
DELIVERED BEFORE THE ROYAL COLLEGE
OF PHYSICIANS OF LONDON,

BY

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THE close relationship of mind and body has long been recognized, but in practice has been largely lost sight of, and the tendency has been to investigate them apart, to the detriment of our knowledge of each. It shows how dominated we are by tradition when we realize that it is customary for a student to pass through his medical instruction in the wards of a hospital with little or no thought given to the mental aspect of the patients he has been observing. It is true that he will hear something of hysterical manifestations, but this narrowed view is misleading, for it is apt to convey to the student that hysteria is the beginning and end of functional nerve disturbance. It is encouraging to learn that the term "mental" is now being generally used when reference is made to normal mind. This has a dual value: it brings the study of normal and abnormal mental states into closer relation, and it emphasizes the fact that both the healthy and the ill man have a mental outlook which should be investigated.

It must be conceded that all physical disease must have a concomitant mental change, just as all mind disorder is associated with variations in the bodily functions. The close interrelation of all the various systems of the body is increasingly emphasized by physiologists, pathologists, and clinicians, and the work done during recent years upon the vegetative nervous system calls for further careful investigation. There is always the danger that the pure clinician will seize upon an explanation which seems to fit in with any syndrome of symptoms with which he is confronted, and the physiologist working in his laboratory is apt to overlook a clinical picture which he never has the opportunity of seeing. Fortunately this is all changing, and in the future we shall see clinical physicians and pure scientists working in much closer relationship.

It is important to try to discover some fundamental principles as to how and why mental symptoms develop in association with physical disease. Since sensation is the most elementary of all conscious processes, and since it is largely upon sensation that we form a knowledge of self, alteration in sensation from whatever cause must give rise to mental symptoms. Sudden and extensive variation in sensation