in the inner left quadrant was excised. In 1881 the entire breast was removed. In 1888, 1889, and 1898 recurrences were excised. On the last occasion there was no evidence of enlargement of axillary glands, but the clavicle and coracoid process were removed. Much relief was given, and the wound healed well. In 1900 recurrence took place, and she died three years later at the age of 71. At the post-mortem examination secondary nodules were discovered down the vertebræ, and extension had occurred entirely by continuity. Mr. Greig had expected a diagnosis of sarcoma, but the pathological report was that the tumour was an alveolar carcinoma.

RECENT ADVANCES IN MEDICAL SCIENCE.

MEDICINE.

UNDER THE CHARGE OF

W. T. RITCHIE, M.D., EDWIN MATTHEW, M.D., AND JOHN D. COMRIE, M.D.

Clinical States Produced by Disorders of the Pituitary Body.

In his recently published monograph, *The Pituitary Body and its Disorders*, Professor Harvey Cushing, who has been one of the foremost investigators in this field of research, presents a most interesting account of the brilliant results that have accrued from an experimental study of the hypophysis and from clinical observations upon the morbid states resulting from disorders of this gland. He draws attention to the fact that its well-protected position, its presence in all vertebrates, its persistence throughout life, and its remarkably disposed and abundant blood supply would of themselves be enough to stamp the hypophysis as an organ of vital importance. It consists of two distinct portions, an anterior lobe or pars anterior and a posterior lobe. From the researches of Schäfer, Vincent, Herring, Borchardt, Pal, Ott, Mackenzie, and other investigators we know that the effects induced by injection of extracts of the posterior lobe bear a close resemblance to those obtained by using extracts of suprarenal medulla. They differ from the latter, however, in the primary depressor and longer pressor response of the general circulation, in the slowing of the pulse-rate even after atropin or section of the vagi, in the constriction of the coronary and dilatation of the renal vessels (adrenalin having an opposite effect), in the production of diuresis from a specific action on the renal epithelium, and in their direct action on the voluntary muscles rather than on the sympathetic nerve endings.

The constitutional disturbances observed by Cushing in animals that had recovered after partial hypophysectomies are of particular interest, for these findings gave the first experimental proof that certain hitherto recognised clinical syndromes are a consequence of lessened pituitary activity. The most striking changes observed in the experi-

mental dogs were widespread adiposity, dryness of the skin, falling out of the hair, subnormal temperature, lowering of the cardiac and respiratory rate, retardation of skeletal growth, dulling of the mental condition, and the onset of secondary changes in other ductless glands. Puppies remained sexually infantile. Moreover, experimental research has demonstrated that normal functional activity of the posterior lobe of the pituitary is essential for effective carbohydrate metabolism. An intravenous injection of posterior lobe extract produces glycosuria, and its continued administration in excessive amounts leads to emaciation. A diminution of posterior lobe secretion occurring in certain conditions of hypopituitarism leads to an acquired high tolerance for sugars, with a resultant accumulation of fat.

Clinical Manifestations.—In the case of the thyroid gland we are familiar with states of overactivity (hyperthyroidism, exophthalmic goitre), of underactivity (hypothyroidism, myxœdema), and transitional states (dysthyroidism). According to Cushing the clinical affections resulting from disorders of the pituitary are most appropriately regarded as manifestations of dyspituitarism, the symptoms of which are :—

I. *Neighbourhood Signs and Symptoms*—(1) *Subjective Phenomena.*—Headache is usually bitemporal and often severe and persistent. Photophobia may be associated with orbital discomfort and sensitiveness of the eyes to pressure. (2) *Deformation of the Sella Turcica.*—Since Oppenheim in 1899 drew attention to X-ray studies of the pituitary fossa these have proved most valuable in the investigation of pituitary disease. Stereoscopic plates are desirable in all cases and are essential in some instances, in order that the full depth of the sella turcica may be recognised. The enlargement of the sella may be accompanied by thickening of its walls, as in cases of acromegaly and gigantism ; or there may be marked thinning with perforation of the sellar floor and of the dorsum in consequence of pressure atrophy in cases of advanced hypopituitarism. In a third variety the sellar landmarks, with the exception of the anterior clinoid processes, are effaced, a result that may arise in cases of malignant growth of the hypophysis. (3) *Visual Disturbances.*—The optic nerves are apt to suffer, but the degree of implication of the optic chiasma, nerves, or tracts bears no direct relation to the size of the sella turcica. In most of Cushing's cases of acromegaly there was an enlarged sella without visual disturbance, whereas in many patients with primary hypopituitarism profound visual disturbances were noted. The resulting optic atrophy is a so-called primary one, and the disc presents no œdema except in the late stages when general pressure phenomena have arisen. Some distortion of the visual fields is usually detected in cases with pronounced neighbourhood symptoms, but typical bitemporal hemianopia with a vertical meridian bisecting the macula is comparatively rare. Homonymous

defects are at least half as frequent as bitemporal ones. In all cases the colour fields are involved first, the form fields later. (4) Nystagmus, anosmia, trigeminal neuralgia, epileptiform seizures with a gustatory or olfactory aura, and evidences of involvement of the frontal lobes may be observed in some instances. Among naso-pharyngeal signs mention may be made of epistaxis, mucous discharge from the sphenoidal cells, which is common, and genuine cerebro-spinal rhinorrhœa, which is rare.

II. *General Pressure Symptoms* may result from intra-cranial extension of a pituitary tumour or of a coincident growth elsewhere. Headache and choked disc are not infrequent, vomiting is exceptional. Among other signs there may be fulness and tortuosity of the palpebral venules and of the larger veins of the scalp.

III. *Glandular Manifestations*—(1) *Modifications of Skeletal Development:* (a) *Overgrowth.*—The theory attributing the skeletal changes in acromegaly and gigantism to a functional hyperplasia of the pars anterior of the pituitary with production of an excessive or perverted secretion, although not universally accepted, affords the most acceptable working hypothesis. There can be little doubt, however, that in the greater number of cases of acromegaly glandular insufficiency supervenes as the malady progresses. Cushing's studies on carbohydrate tolerance show that in acromegaly the individual's capacity to assimilate sugars progresses from a state in which carbohydrates are metabolised rapidly to one in which they are merely stored; in other words, from a state in which there is either a low assimilation limit or an actual hyperglycæmia with glycosuria to one in which alimentary glycosuria is difficult or impossible to elicit. Cushing advances this fact as the strongest argument in favour of the transitional character of acromegaly from hyper- to hypo-pituitarism and on this character he lays particular emphasis. The skeletal changes in gigantism and acromegaly result from the same morbid influence. If all giants are not acromegalics they are destined to acquire acromegalic attributes with advancing years, provided epiphyseal ossification occurs before the pituitary overactivity subsides. Cushing sums up the evidence in stating that acromegaly is the expression of a functional instability of the pars anterior occasioned by some underlying biochemical disturbance which leads to the elaboration of a perverted or exaggerated secretion containing a hormone that accelerates skeletal growth—growth of the long bones if epiphyseal union is incomplete, of the acral parts if epiphyseal ossification has taken place. Since the functional disturbance is probably a fluctuating one, with periods of increase and remission, epiphyseal ossification may occur during a period of quiescence. A subsequent resumption of the perverted functional activity will then serve to superimpose acromegalic manifestations on primary gigantism. Thus acromegaly cannot precede gigantism, but always occurs as

gigantism that has become acromegalised. (b) *Skeletal Undergrowth.*—The most marked cases are those in whom the pituitary insufficiency occurs before adolescence. Many cases of skeletal undergrowth associated with genital dystrophy have been recorded, but not all forms of infantilism are necessarily due to hypopituitarism (Herter, Peretz). When hypopituitarism dates from the period of adolescence the arrested development of the long bones may be accompanied by pronounced adiposity, and in males by a feminine type of skeleton with broad pelvis and genu valgum. The smallness and delicacy of the extremities, the tapering type of hand, and the persistence of epiphyseal lines are notable. In some instances a maxillary prognathism is observed in contradistinction to the mandibular prognathism of acromegaly.

(2) *Cutaneous and Subcutaneous Changes.*—In hyperpituitarism it is usual to find hypertrophy of the epidermis, the hair follicles, the papillæ and secretory glands of the skin, and an increase of the subcutaneous tissues. In primary hypopituitarism, on the other hand, the skin is often remarkably smooth, transparent, and free from moisture. The nails are usually small, and do not show crescents at their base. Although the hair of the scalp may be abundant the axillary and pubic hair may be almost entirely absent, or in males the latter may assume the feminine type of distribution. Pigmentation, with asthenia and low blood-pressure, due to suprarenal inadequacy, may be observed.

Adiposity is often a striking feature. The particular symptom-complex of adiposity—high sugar tolerance, subnormal temperature, slow pulse, asthenia and drowsiness—is attributed by Cushing to secretory deficiency of the posterior lobe. The reverse condition—emaciation, glycosuria, and elevated temperature—follows administration of posterior lobe extract. Various types of adiposity have been described (Frohlich's, Marburg's, etc.). Insufficiency of the posterior lobe may be associated with either stimulation or inhibition of anterior lobe activity. Consequently, in childhood, obesity may be associated with (1) overgrowth and either sexual precocity or genital hypoplasia, or with (2) undergrowth and sexual precocity or the reverse. In adults the fat may tend to occur in lipomatous masses, and in some of Cushing's cases the four cardinal signs of adiposis dolorosa (Dercum's disease), namely adiposity, tenderness and pains, asthenia, and psychoses, were noted.

(3) *Carbohydrate Tolerance.*—Borchardt found that intravenous injection of posterior lobe extracts produced glycosuria, and that after removal of the posterior lobe the assimilation limit for carbohydrates was raised. Patients with obvious manifestations of hypopituitarism usually present a high tolerance for sugars, and Cushing regards the sugar tolerance of these individuals as a measure of the activity of the posterior lobe. Polyuria and glycosuria may be the main clinical manifestations of acute hyperplasia of the pituitary, and moreover

the glycosurias of pregnancy and of adolescence may possibly be due to functional hypophyseal hyperplasia.

(4) *Temperature.*—In experimental pituitary insufficiency the temperature is subnormal, and the same holds good for clinical cases of hypopituitarism. A transient rise of temperature may follow an injection of pars anterior extract.

In hypopituitarism the arterial blood-pressure is low, the pulse-rate is infrequent, and drowsiness and torpidity may be observed. The resemblance between the state of extreme hypopituitarism and that of hibernation is highly suggestive.

(5) *Psychical Disturbances* have been noted in many cases of pituitary disease. Irritability, insomnia, low intellectuality and impairment of memory may be observed. Epileptic seizures are not uncommon. In many cases there are further symptoms referable to disorders of other glands—ovary, testis, thyroid, thymus, pancreas, etc.

Treatment.—In each case, according to Cushing, it is necessary to determine the local conditions and, as far as possible, the state of hypophyseal activity. One patient may need sellar decompression, another may require partial extirpation of the diseased gland, and yet another may require glandular feeding; or combinations of these measures may be necessary. Surgical intervention may be indicated to relieve general pressure disturbances or to combat functional hyperplasia, but more especially to relieve neighbourhood symptoms. In many instances the symptoms of hypopituitarism can be ameliorated by administration of pituitary gland. Dry powdered extracts of the whole gland should be given. Cushing uses the sugar tolerance of the patient as an effective measure of the organo-therapeutic dosage. Thus, while the pituitary extract is being given by the mouth, the patient is given daily an amount of glucose (or lævulose) that would suffice to set up temporary glycosuria in a normal individual of equal body weight. Meanwhile an increasing amount of the glandular extract is administered daily until a trace of sugar appears in the patient's urine. Some patients, however, are intolerant of the sugar tests, and others, even although taking massive doses of pituitary extract, fail to develop glycosuria, and yet nevertheless their general condition improves.

W. T. R.

SURGERY.

UNDER THE CHARGE OF

J. W. STRUTHERS, F.R.C.S., AND D. P. D. WILKIE, F.R.C.S.

The Surgery of Nerves.

The researches of Stoffel (*Münch. med. Woch.*, 1911, No. 47) on the minute anatomy of the larger nerves, and the disposition in them of the bundles of nerve fibres supplying different groups of muscles, have