CUSHING'S SYNDROME

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In 1932 Harvey Cushing described a number of patients presenting a similar clinical picture which he had collected from the literature, and he added two more from his own records. The presence of minute adenomata of basophil cells in the anterior lobe of the pituitary gland was demonstrated at autopsy on some of them and Cushing regarded these as the causative lesions and called the syndrome 'pituitary basophilism.' Since that time many additional case reports have been published in which a similar clinical picture has been associated with a variety of different pathological lesions in the endocrine system. Much new information has been collected about the disorder and it is recognized that Cushing's conception of the pathological basis is wrong, but the complete picture of disordered function has not yet been fully elucidated despite extensive research and prolonged controversy.

The clinical manifestations had been described earlier, particularly by Parkes Weber (1926) who considered that they were due to a primary adrenocortical disorder, and also by Leyton, Turnbull and Bratton (1931) who reported them in association with thymic carcinomata. But they are known by the term *Cushing's syndrome* because of the larger series of patients presenting similar symptoms which was collected and recorded by Cushing.

Pathology

The adrenal cortex may be the site of a primary benign or, more often, malignant neoplasm. The tumours are often large, irregular, soft and friable and contain numerous necrotic, haemorrhagic, liquefying areas. The cells in the viable parts have a similar general appearance to cells in the normal adrenal cortex, but often vary greatly in size and multinucleate forms are common. An interesting and remarkably constant finding is severe atrophy of the remaining cortical tissue which is not involved by the tumour. In other patients the adrenal cortex is the site of bilateral hyperplasia and the glands often weigh two or three times as much as normal. On histological examination it is found that the zona fascicularis is

most severely affected, although all zones are involved to some extent. Occasionally, however, no macroscopical or microscopical abnormalities are found in the adrenal glands from patients with active Cushing's syndrome.

The pituitary gland is the site of the only constant pathological change in this disease (Crooke, 1935). In the basophil cells of the anterior lobe the cytoplasmic granules are replaced by a dense homogeneous hyaline material which stains a uniform greyish-blue with Mallory's acid-fuchsin aniline-blue. This change appears first in the cytoplasm mid-way between the nucleus and the periphery of the cell and extends in all directions. Usually a group of normal basophil granules remains adjacent to the nucleus or in a rim against the periphery of the cell. In extreme cases the entire cytoplasm is filled with the material. The cells are often larger than normal, many of them measuring 40 μ in diameter, and much larger ones are occasionally found. The nuclei appear to be normal but cells with multiple nuclei are not uncommon and as many as five have been seen in a single cell.

The amount of hyaline change in the cells and the number of cells involved vary greatly from case to case. They tend to be greater when symptoms have progressed rapidly. Although no adequate series of differential cell counts have been reported the total number of basophil cells of all types also varies greatly from case to case, sometimes appearing to be present in greater number than normal and sometimes to be relatively scanty. Rarely these hyaline basophil cells have been observed in adenomata in the anterior lobe and in cells invading the posterior lobe.

Adenomata usually composed of basophil but sometimes of chromophobe cells are common in Cushing's syndrome, especially in patients with no adrenocortical tumours, but many cases have been reported in which no tumour could be found anywhere. The pituitary adenomata may be microscopic, but sometimes they are large enough to cause symptoms of the chiasmal syndrome and very rarely they have been malignant (Cohen and Dible, 1936; Forbes, 1947).

In a few instances Cushing's syndrome has been associated with carcinoma of the thymus (Leyton, Turnbull and Bratton, 1931; Hubble, 1949) and of the ovary (Kepler, Dockerty and Priestly, 1944), but even more remarkable is the association of Cushing's syndrome with carcinomata which apparently have not originated from endocrine tissue (Crooke, 1946; Del Castillo, Trucco and Manzuoli, 1950) and it has been suggested that there is a peculiar propensity for tumour formation in this disease.

• Certain changes are commonly found in other organs. The heart is usually hypertrophied, sometimes greatly so, the left ventricle in particular being involved. Arteriosclerosis may be severe and the kidneys in particular may be affected. The characteristic changes of malignant hypertension have been found in a few cases. Osteoporosis is common but variable in amount. Although the whole skeleton may be severely affected it is usually most marked in the spine where it causes kyphosis, and next in the ribs where pathological fractures may occur. Fractures heal with the formation of apparently healthy callus. The histological appearance of the bones is little altered and there is no increase in the number of osteoclasts, but the amount of calcium salts in the bones is deficient. The bone marrow does not appear to be altered in amount or in histological appearance.

Pathogenesis

Almost all of the symptoms and signs of Cushing's syndrome have been reproduced in man by treatment with large doses of adrenotrophic hormone (ACTH) or of cortisone (Sprague, Power, Mason, Albert, Mathieson, Hench, Kendall, Slocumb and Polley, 1950), and there is no question that the disease is due to an excessive formation of glucocorticoids by the adrenal cortex or by a cortical tumour. The part played by the pituitary gland in the syndrome is still unknown and it will remain so until more reliable methods are available for the assay of adrenotrophic hormone in the blood and urine of man. Most authorities hold that the pituitary gland plays no important part in the disease. They say that the hyaline change in the basophil cells of the anterior lobe are degenerate despite the healthy appearance of their nuclei, or that they are regressive and represent storage of secretion since it has been claimed that they can be produced by treatment with ACTH or cortisone (Golden, Bondy, Sheldon and Beeson, 1950; Laqueur, 1951), but this needs fuller investigation.

As further evidence for this hypothesis it is said that the remarkable atrophy of adrenocortical tissue which is not involved by a secreting cortical tumour is the result of suppression of the forma-

tion of adrenotrophic hormone by the high level of circulating glucocorticoids produced by the tumour. It is also suggested that in cortical hyperplasia a similar mechanism must cause the suppression of adrenotrophic hormone formation but no attempt is made to explain how hyperplasia of the cortex can be correlated with relative pituitary insufficiency. Actually, the opposite is true since dramatic cures have followed subtotal destruction of the pituitary gland by insertion of radon seeds into the sella turcica (Crooke, 1944). This proves that the disease cannot progress without adequate assistance from the pituitary gland.

It is more likely that the essential disorder of function is a failure of the normal process in which a rise in the level of circulating glucocorticoids inhibits the formation of adrenotrophic hormone. In the case of cortical hyperplasia it is probable that the pituitary gland can produce enough adrenotrophic hormone to catalyze the formation of glucocorticoids from both adrenal cortices. The hyperplasia is therefore bilateral. In the case of a rapidly growing glucocorticoid-secreting tumour, however, the demand for adrenotrophic hormone by the tumour cells may exceed the maximum available supply and the remaining adrenal tissue is starved of this hormone by the tumour and atrophies.

The pattern of hormonal excretion may also be explained by this hypothesis. In Cushing's syndrome with bilateral cortical hyperplasia mainly glucocorticoids are excreted in excess and the output of androgens is little increased. This is because sufficient adrenotrophic hormone is available to catalyze glucocorticoids completely. In Cushing's syndrome with a cortical tumour the excretion of both glucocorticoids and androgens is greatly increased. This is because the supply of adrenotrophic hormone is inadequate to catalyze glucocorticoids completely in the rapidly growing tumour cells and more androgens are produced instead. It seems certain that an increased supply of adrenotrophic hormone is not required for the production of abnormally large amounts of androgens because the pituitary gland is histologically normal in the adrenogenital syndrome. This is characterized by greatly increased excretion of androgens and a normal output of glucocorticoids.

The part played by the hyaline basophil cells in the syndrome is obscure, but the original claim that they represent an alteration of fundamental significance still seems likely. They bear a similarity to the 'castration cells' in the pituitary glands of rats after gonadectomy, a condition which is known to be associated with an increased production of gonadotrophic hormone. They are also like the 'thyroidectomy cells' in the pituitary glands of the thyroidectomized rats which have

been shown to be associated with an increased amount of thyrotrophic hormone (Zeckwer, Davison, Keller and Livingood, 1935), and they are very like the cells which occur in pituitary remnants after incomplete hypophysectomy in rats (Crooke, 1938). These remnants have also been shown to be actively functioning. It may be, therefore, that hyaline basophil cells represent some stage in the production of adrenotrophic hormone.

Clinical Features

Cushing's syndrome is a rare disease. It occurs twice as often in females as in males and in the majority of cases it begins in the third or fourth decades, but it has been reported at all ages. The disease is not familial and there is no known predisposing cause although in a number of instances symptoms have begun during pregnancy.

The onset is insidious. Generally an increase of weight is the first symptom to attract attention although it frequently causes no concern until broad purple striae begin to appear on the abdomen. Sometimes the swollen dusky appearance of the face, associated in the female with the growth of facial hair, is the first feature to be noticed, and sometimes a disturbance of menstruation occurs first.

In the fully developed syndrome psychological disorders are sufficiently common to be regarded as a significant part of the clinical picture. Some disturbance occurs in about half of the patients, but there is no consistency in the character of the psychosis (Spillane, 1951; Starr, 1952). It may be a reaction to the grotesque appearance or, directly, to the excess of glucocorticoid or adrenotrophic hormones but the usual reaction produced by treatment with an excess of these hormones is euphoria, which is rare in Cushing's syndrome.

The obesity is very characteristic. When the onset is acute it may progress rapidly and a gain of 30 to 40 lb. in weight may occur in the first six months, sometimes causing the skin to become so tense that it is painful. When chronic, the weight increases much less rapidly, a similar increment being spread over one to three years. Fat is laid down very characteristically on the face, neck and trunk, and pads of fat form in the supraclavicular regions and over the lower cervical vertebrae. The limbs tend to remain unaffected or to increase only slightly in girth in their proximal segments. Occasionally the obesity is generalized. Loss of strength and muscular wasting are very characteristic, but general wasting often occurs in the later stages of the disease, especially when it is associated with a malignant tumour. In rare instances it may occur earlier from inanition associated with psychological disorders. Usually the contour of

the face remains rounded as if fat is lost from this site last and sometimes the face appears to grow fat at the same time that wasting occurs everywhere else.

The abnormal appearance of the skin is one of the most important and constant features of the disease. The skin, particularly of the face, is a dusky plum colour caused by a cyanosed flush associated with an increase of diffuse brown pigmentation. It is tense, warm and greasy, and often covered with acne vulgaris which spreads on to the chest and back. Striae atrophicae appear in situations where the rapid increase of fat causes undue stretching of the skin. They are commonest on the lower abdominal wall, the flanks and the groins, running downwards onto the upper parts of the thighs and they frequently run transversely on the inner sides of the thighs. Sometimes they are found on the anterior and, to a less extent, the posterior axillary folds, running downwards onto the arms. Occasionally small striae are found on the sides of the knees. The striae are characteristically cyanosed, the colour varying from pale lilac to deep purple. In patients who are recovering they become pink and finally white, and the colour may be taken as a rough guide to the activity of the disease.

Alteration in the character and distribution of the hair is much less constant. In both sexes the scalp hair tends to become thin and to fall out. In women a more or less pronounced moustache and beard may appear and hair increases in the axillary and pubic regions but recedes on the temples. Menstruation is also affected early in nearly all cases. Usually amenorrhoea follows a period of infrequent and scanty flow, but very rarely menstruation continues normally until late in the disease. The clitoris is occasionally enlarged and the uterus may be reduced in size. Impotence is common in the male. In rare cases feminization occurs. Men lose their facial hair, the pubic hair acquires a feminine distribution and the breasts enlarge and have occasionally been reported to secrete milk.

Abnormal bruising is a common symptom in severely ill patients. Trivial injuries sometimes cause large extravasation of blood into the tissues, and slight pressure such as that which is caused by the wearing of a wrist watch may result in bruising. Often there is no gross abnormality in the blood. Although Cushing described erythrocytosis as one of the signs in his original description of the disease it does not occur in more than a third of the patients. Later a microcytic anaemia is common, especially with malignant tumours. Leucocytosis sometimes occurs, especially in the presence of infection, and the relative number of eosinophil cells is reduced. Very

ill patients have a poor resistance to infection which may develop easily at the site of venepuncture or in the urinary tract after catheterization.

Osteoporosis may be discovered on radiological examination. It occurs chiefly in the spine and ribs, but rarely the whole skeleton is severely affected. It may cause cervico-dorsal kyphosis or pathological fractures of the ribs. Old fractures are often found accidentally on radiological examination or at autopsy, but they apparently heal quite readily.

The heart is generally affected early, and often severely. The left ventricle is generally enlarged and the blood pressure raised, but they may be normal, especially in younger patients with an acute onset of symptoms. In the later stages congestive heart failure is common. Albuminuria and impaired renal efficiency may occur and are sometimes associated with malignant hypertension. Nephrolithiasis is found sometimes. Glycosuria and hyperglycaemia or a decreased sugar tolerance occur in about half of the patients. Usually when frank diabetes mellitus is present it runs a fairly benign course but sometimes it is severe and it may be difficult to control with insulin. In rare instances diabetes insipidus has been reported. The thyroid gland is occasionally enlarged but the basal metabolic rate is generally within the normal range. Exophthalmos is sometimes present, but it does not appear to bear any relationship either to the goitre or to the basal metabolic rate.

Extensive metabolic studies have been carried out and the most characteristic feature of Cushing's syndrome is the severe loss of intracellular potassium and protein at the same time that fat is stored in the body. The protein loss is responsible for the muscular wasting and weakness. Typically there is an alkalosis with low serum levels of potassium and chloride ions. When the intake of potassium is increased to high levels potassium, chloride and nitrogen are retained and sodium is lost from the body. A similar change can be effected by treatment with testosterone. The balance of calcium and phosphorus generally runs parallel with those of potassium and nitrogen (Kepler, Sprague, Clagett, Power, Mason and Rogers, 1948; Teabeaut, Engle and Taylor, 1950).

The assay of certain steroids show that characteristic changes may occur in Cushing's syndrome. The excretion of corticoids in urine measured as formaldehydogenic steroids is increased in all forms of the disease but the changes cannot be used to distinguish the neoplastic group from the rest (Talbot, Wood, Worcester, Christo, Campbell and Zygmuntowicz, 1951; Forbes, Griswold and Albright, 1950). The principal corticoid is probably Kendall's Compound F, or 17-hydroxy-

corticosterone, and large amounts have been isolated from urine (Sprague, Hayles, Power, Mason and Bennett, 1950). The more specific assays of 17-hydroxy steroids (Nelson, Samuels, Willardson and Tyler, 1951) and also of 3-ketosteroids (Butt and Crooke, 1952) in plasma show that the circulating levels of these substances are significantly raised. The urinary level of 17-ketosteroids is much more variable. In Cushing's syndrome associated with adrenocortical hyperplasia or a benign tumour it is generally within, or only slightly above, the normal range, but with a malignant tumour it is generally very high (Forbes and Albright, 1951) and the β 17-ketosteroid fraction constitutes up to 50 per cent. of the total instead of 10 to 15 per cent. as in the normal. This is due to the high level of excretion of dehydroisoandrosterone. An elaborate method which has been evolved for the assay of circulating adrenotrophic hormone suggests that the level of this substance is raised (Bornstein and Trehwella, 1950), but this needs confirmation.

Variants of the Syndrome

It is exceptional for all the classical features of Cushing's syndrome to be present in one patient, and every gradation is seen between this and the adrenogenital syndrome. In children this leads to interesting differences in skeletal development. The excessive glucocorticoid secretion of Cushing's syndrome causes growth to be slow and if the course of the disease is prolonged the skeleton is stunted (Harrison and Abelson, 1952). In the great majority of affected children, however, the disease is complicated by some features of the adrenogenital syndrome caused by an increased secretion of androgens. The growth of bone is stimulated and children grow abnormally fast. It also hastens bony development and the epiphyses fuse with the diaphyses prematurely and cause growth to become arrested earlier than in the normal. The ultimate stature, therefore, depends upon the ratio of these substances to one another as well as to the age of onset and the duration of the disease. The androgen element also leads to the development of precocious puberty which is isosexual in boys and heterosexual in girls.

Diagnosis

It is not uncommon for obese women at the menopause to have moderate hirsuties, hypertension and sometimes mild diabetes mellitus, and a diagnosis of Cushing's syndrome is often made erroneously. It is only justified if the symptoms are rapidly progressive, the face has the typical dusky florid appearance and purple striae atrophicae appear on the abdomen. The recent methods of

determining the level of plasma corticoids is of great assistance in the diagnosis of these patients.

Treatment

Patients with adrenocortical, thymic or ovarian tumours require early surgical treatment. All operations should be conducted under a penicillin umbrella because of the poor resistance to infection which is characteristic of this disease. The removal of an adrenocortical tumour is followed by symptoms of severe post-operative collapse which requires treatment with cortisone until the opposite atrophied adrenal gland has had time to recover. It is very rare for tumours of the pituitary gland to be large enough to require surgery and there is no indication for operative interference except for local symptoms caused by pressure of a pituitary adenoma.

Radiotherapy of the pituitary gland has been used extensively for patients without abdominal or thoracic tumours, but the results are disappointing. It seems to have little effect when the disease is progressing rapidly and natural remissions are common. It is difficult, therefore, to assess the effect of irradiation because it seems to produce no histological changes in the pituitary gland and most patients relapse later. Extensive destruction of the pituitary gland by insertion of radon seeds has produced some dramatic cures, but the treatment is hazardous (Crooke, 1944). The treatment of choice is subtotal adrenalectomy (Priestly, Sprague, Walters and Salassa, 1951) which has been rendered practicable by the use of cortisone. The Mayo group recommend the intramuscular injection of 200 mg. of cortisone to be given 48 and 24 hours before, and on the morning before operation. They continue treatment at this dose level for a few days after operation and then gradually reduce it. The operation is carried out in two stages with an interval of about two weeks between them. At the first operation both adrenal glands are explored from the back. If no tumour is found in the first it is left intact and the wound closed. The second gland is then operated upon and nine-tenths of it removed. At the second operation the first gland to be explored is removed completely. The immediate post-operative collapse is avoided by treatment with cortisone but a delayed reaction follows removal of the second gland when the cortisone treatment is stopped. Anorexia, nausea and vomiting, weakness, fever and tachycardia may be severe but the blood pressure usually does not fall to the levels seen in Addison's disease. Symptoms of fibrositis and arthritis sometimes occur and may be severe. A bran-like scale may appear on the skin which peels in a few days and pigmentation, indistinguishable from that seen

in Addison's disease, may increase alarmingly for weeks despite the steady recovery to normal physical strength and well being.

Prognosis

Cushing's syndrome is generally fatal in from two to five years if untreated. Most of the abdominal tumours associated with the disease are malignant and recurrence is common. Successful removal of adrenocortical tumours, however, leads to a dramatic recovery. The operative mortality after subtotal adrenalectomy is high but the group of workers at the Mayo Clinic have reduced it to about 10 per cent. A recurrence of symptoms of Cushing's syndrome is rare but may require a further operation; persistent symptoms of chronic adrenal insufficiency are also rare but may necessitate continuous treatment for Addison's disease.

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