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THE DIFFERENTIAL DIAGNOSIS OF CUSHING'S SYNDROME (BASOPHILISM) OF PITUITARY OR ADRENAL ORIGIN

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The clinical syndrome described by Cushing in 1932, and which bears his name, was assigned by him to basophil adenomas of the pituitary body (basophilism). In the same year attention was drawn (Broster, Gardiner-Hill, and Greenfield, 1932) to a similar clinical condition in association with bilateral hyperplasia of the adrenal glands. Some three years ago my interest in the subject was further stimulated by a visit to the late Dr. Harvey Cushing at Yale University, where I had the privilege of discussing the subject and examining some of the original sections of these basophil adenomas. Cushing in his article had mentioned that the adrenal glands in his series of cases were either normal or hyperplastic.

Essentially the syndrome is characterized by two changes—disturbances in the sex mechanism and disturbances of metabolism. The typical picture is that of a young woman who acquires hirsuties of the male type, experiences irregularities or cessation of the menstrual function, and becomes abnormally and permanently fat. In the male there is a similar increase in weight, a diminution in the size of the external genitalia, and a loss of sex function. Accompanying these changes are more variable secondary symptoms, such as a low sugar tolerance with or without glycosuria, a raised blood pressure, erythrocythaemia, and cholesterolaemia, and the skin is coarse and marked by striae distensae, most commonly in the flanks. Broster, Gardiner-Hill, and Greenfield (1932) drew attention to a case:

"in which the adrenal lesion appears to be only one element in a pluriglandular syndrome. This patient presents the symptom complex described by Achard and Thiers (1921) as 'diabetes of a bearded woman,' a condition associated with adrenal hyperplasia and changes in other ductless glands—namely, ovarian sclerosis and atrophy, colloid hypersecretion of the thyroid, cirrhosis of the liver, and pericanalicular sclerosis of the pancreas with increase in the islands of Langerhans, the pituitary being normal. The chief symptoms were hypertrichosis of the face of the masculine type, without other signs of virilism, the breasts and external genitalia being normal, obesity, glycosuria with decreased carbohydrate tolerance, hypertension, and usually amenorrhoea or irregular menstruation. These authors were of the opinion that the adrenal glands played an important part in the aetiology of this condition, but were probably not primary. Our case appeared to be a typical example of this syndrome in a young girl."

The results of unilateral adrenalectomy in this patient proved disappointing, for I reported some years later that,

although there was some improvement in the hirsuties, the hypertension, menstruation, and carbohydrate tolerance remained much the same. Dr. Gardiner-Hill was of the opinion later that this case might well have been one of Cushing's syndrome. However, it was interesting that the adrenal factor was only proved subsequently when Vines had definitely established his ponceau-fuchsin stain in relation to adrenal virilism (Broster and Vines, 1933), for the specimen of the gland had been kept, and the adrenocortical cells gave a positive fuchsinophil reaction.

Comparison of Cushing's Syndrome with the Adreno-Genital Syndrome

In order to obtain some insight into the adreno-pituitary mechanism a comparison of Cushing's pituitary syndrome with the adreno-genital syndrome in its purest form (adrenal virilism) would not be out of place.

First there is a marked similarity in the mode of onset. In both there occurs in a young woman after puberty an irregular growth of hair of the male type and irregular menstruation. There seems to be no absolute rule in the sequences of these two main symptoms. The growth of hair may first appear or the change in the menstrual cycle, but sooner or later the two occur together during what seems to be a phase of definite endocrine instability, and then comes the parting of the ways. In Cushing's syndrome there develops a rapid and marked increase in adiposity, which becomes permanent and pathological, followed by the secondary symptoms already referred to. In adrenal virilism the weight usually remains stationary, but in some there is a definite increase, which is either transitory or not excessive. None of the secondary symptoms of Cushing's syndrome appear, and instead of fat the patient develops muscle and secondary male characters, which are the essential features of virilism.

However, between these two extremes there exists quite a large clinical group of hefty hairy women who cannot be labelled Cushing's syndrome on the one hand or virilism on the other.

Laboratory Investigations

Although clinical symptoms are valuable in suggesting new avenues for investigation, it is difficult to assess their relative significance, especially in a mixed syndrome, unless backed by special laboratory tests. Fortunately, in the pure adrenal syndrome recent advances have established standards of comparison by both histological and

biochemical means. The ponceau-fuchsin stain of Vines has been already referred to; not only does it confirm the diagnosis of virilism, but there is now evidence that the colour intensity whereby the cortical cells absorb the vivid red fuchsin dye bears some relation to the clinical degree of virilism (Broster, 1939). The biochemical experiments of Patterson and Greenwood (Broster *et al.*, 1938) have for some time shown an excess of an androgenic substance in the urine of these patients. These observations were originally established by the capon test, and later have been corroborated by the "colour test"—that is, the colorimetric determination of keto-steroids. Furthermore, reference might also be made to the substances found by Marrian and Butler (Broster *et al.*, 1938) in the urine of these patients with adrenal virilism, and not found in normal individuals—namely, pregnane-triol and, accompanying other keto-steroids, iso-androsterone. The amounts of keto-steroids, their androgenic moiety, and also pregnane-triol are all reduced in the urine after unilateral adrenalectomy. From this it will be seen that we now possess methods of determining adreno-cortical function, of which at least two are practicable in their application to clinical cases.

Basophilism of the Adrenal Type

Recently there have been recorded several cases clinically indistinguishable from Cushing's syndrome, due to adrenal cortical carcinoma, notably by Kepler, Walters, and Piper (1938) in America, and in this country by Hare, Ross, and Crooke (1935) and by Lescher and Robb-Smith (1935). In both the latter cases no pituitary adenoma was present, but the adrenal tumour cells gave the positive fuchsin staining reaction. In the case presented by Hare, Ross, and Crooke the basophil cells of the pituitary were within normal limits, but the urine contained a marked excess of androgens. Crooke and Callow (1939) published a series of four cases of Cushing's syndrome, two due to basophil adenoma of the pituitary and two due to adrenal cortical carcinoma. The latter gave high values in the amount of urinary androgens both by the capon and colour tests, whereas the former gave low values. Those authors suggest that the determination of androgens in the urine gives valuable assistance in diagnosing the presence of cortical tumours in cases of basophilism. However, they do not state in all their cases whether the adrenal glands give a positive fuchsin reaction or not. This is an important point to decide, and Vines (Broster *et al.*, 1938) in a small series of nine cases of proven basophil adenoma at Charing Cross Hospital found that in three males it was negative and that of six females it was positive in four and negative in two. Crooke in 1936 made the important observation that in cases of basophilism, whether of adrenal origin or not, hyaline change in the basophil cells of the pituitary is always found. It therefore appears that in basophilism this hyaline change is a *sine qua non*, whereas the fuchsin stain in the adreno-cortical cells may or may not be present. The two cases recorded here confirm the work of Crooke and Callow, and the role of the adrenal in basophilism has been advanced a stage further—from malignant tumour to simple hyperplasia.

Case I

Basophilism due to Adenoma of the Pituitary by Exclusion, with Low Urinary Androgen

A man aged 21 complained on August 30, 1939, of a rapid increase of weight, sex changes, and increasing lassitude and weakness. He is the middle son of a family of three boys, and is a milkman by trade. His previous history is normal,

except that he was a premature child (one month) and was delivered by forceps owing to ante-partum haemorrhage. His grandfather was a stout man and his mother was stout until the age of 18.

He was perfectly well until fifteen months previously, when his attention was drawn to the fact that his face and neck were increasing in size and that he was putting on weight generally. Recently he has complained of headache across his brow and later of pain in the small of the back. His voice cracked normally after puberty. During the last year the hair on his head began to fall out excessively; and within the last six months he noticed a diminution in the size of his

FIG. 1.—Patient at age of 17.

FIG. 2.—At age of 19.

FIG. 3.—At age of 21.

genitalia, with a loss of erectile power. His genitalia are now about half their normal size, and he is acutely sensitive of his condition. Three months ago his legs began to swell, and he noticed that although his fluid intake was normal the output was greater, especially at night. His adiposity continues to increase, chiefly on the abdomen, face, neck, and trunk. He was forced to discontinue pushing his hand-cart, owing to weakness of his legs, and he now finds difficulty in climbing stairs.

The patient has a gross obesity of the buffalo type, confined to the face, neck, abdomen, and breasts. The limbs are relatively thin except for the oedema of his legs. Comparative photographs (Figs. 1, 2, 3) show that an increase in weight started at the age of 17, but it was not until the age of 20 that it suddenly became more marked. He weighs 13 st. 10 lb., and put on 3½ inches round the chest in three months. His face is moon-shaped and full, with the ruddy glow of a setting sun. This coloration is reflected in enormously enlarged vividly red striae atrophicae which cover his flanks, axillae, and thighs, and suggests that this condition is not due to a mere stretching of the skin. His general appearance is one of sluggish lethargy.

INVESTIGATIONS

The blood pressure was raised, and varied between 155/105 and 180/120 mm. Hg. The blood urea was 29 mg. per 100 c.cm. The urine showed a faint trace of albumin and reducing substance. In the blood count there were 4,620,000 red cells per c.mm., with 88 per cent. haemoglobin and a colour index of 0.95. A radiograph of the skull showed a small pituitary fossa and doubtful erosion of the posterior clinoids. Sugar tolerance was low (see Graph). The clinical diagnosis rested between a basophil adenoma of the pituitary and an adreno-cortical carcinoma.

Owing to the suspension in the work of the Wakefield Trust at Charing Cross Hospital due to the war, facilities for performing the male hormone test were not available when the patient was admitted to hospital on October 15. The pain in the back had increased, and a radiograph of the spine showed

FIG. 4.—Graph showing the blood-sugar curves in Case I and Case II.

rarefaction in the body of the fifth lumbar vertebra. This information suggested the possibility of a secondary deposit to an adrenal carcinoma. A perirenal air insufflation was performed, but in a person so fat this did not give any material help beyond showing some irregularity of the left kidney. An exploratory laparotomy was then decided upon, which confirmed the absence of adrenal tumour. At a later date, through the kindness of Dr. Payne of Great Ormond Street Hospital, a colour test was performed, and he reported a trace of sterone present in a twenty-four-hour collection of urine.

The patient was then given a course of deep x-ray therapy to his pituitary gland at Charing Cross Hospital. The pain in the back continued to be distressing, and he was seen by Drs. Gordon Holmes and Hamilton, on whose suggestion investigation of the blood calcium was performed. This gave the low figure of 7.9 mg. per 100 c.cm. as against the normal of 9 to 11 mg., suggesting a dysfunction of the parathyroid glands. Four months afterwards there was no improvement; the patient is practically bedridden, and the mother reported that his chest seems to be "bending in," suggesting a further softening of the skeletal structures. I am not aware of any experimental work conclusively establishing the existence of a parathyrotrophic hormone, but I have observed clinically bony hypertrophy and bony overgrowth in association with adrenal tumour and adrenal hyperplasia, and premature ossification in cases of adrenal precocity. It is interesting that this case of pituitary adenoma should reveal such marked secondary changes in other ductless glands.

Case II

Basophilism due to Adrenal Hyperplasia with High Urinary Androgens, lowered by Operation, and a Positive Ponceau-fuchsin Stain

A single woman aged 28 complained of an abnormal growth of hair, irregular menses, and obesity. Her own history and her family history are of no importance. Hair is not a conspicuous feature in her case. At the age of 21 it began to grow under her chin, and, later, on the upper lip and cheeks. There is a slight growth on the chest, the lumbar and suprapubic region, and on the limbs.

Her periods, which started at the age of 12, were normal until she was 14, when they became grossly irregular and painful. At different times there has been amenorrhoea varying from six weeks to eleven months. The period lasts from one to three days, with little loss. Although on the plump side she began to put on weight excessively after the hirsuties appeared, gaining five stone in the last few years, and she is now 15 st. 9 lb. She has also complained of frontal

FIG. 5.

headaches during the last three years, which become worse after she has been to the pictures. Recently she has had pain under the left subcostal margin at intervals. The patient is a stout brown-eyed brunette, fat being confined to the face, neck, breasts, and trunk. Her complexion is ruddy, and the skin round the areola of the breasts is reddish. There are striae distensae in both flanks.

INVESTIGATIONS

The patient's blood pressure was 120/80, the blood urea was 29 mg. per 100 c.cm., and her blood group O. The sella turcica is small and rounded, and the mandible and axillae are well developed. The uroselectan radiograph was normal, but there is a suspicion of a shadow above the left kidney. The urine was normal and the sugar tolerance low, and the pre-operative readings are shown with the post-operative in the accompanying graph. In the out-patient department a diagnosis of Cushing's syndrome was made, but it was decided in the course of routine to have an estimation of her urinary androgens performed, and in two samples taken at a week's interval in May, 1939, Dr. Patterson reported 33.4 and 28.6 mg. of sterone daily on the colour test, a value three times above the average normal in ordinary cases of virilism. On this account she was admitted as an in-patient on July 8 and artificial perirenal insufflation was performed by Mr. Sawyer. A skiagram showed a clear-cut outline of the left kidney surrounded by gas, and above this a circumscribed shadow the size of a golf ball, separate and removed from the shadow of the spleen. A lateral view revealed the same shadow distinctly above and in front of the kidney. In consultation with Dr. Shanks a diagnosis of adrenal tumour was made.

Owing to the war it was not possible to explore this patient until November, 1939. No tumour was found, but the left

adrenal was enlarged and hyperplastic to about three times its normal size, weighing 16 grammes, and Dr. Vines reported that it gave a fairly strong fuchsinophil reaction. Left unilateral adrenalectomy was therefore performed. It was obvious from the skiagram that the "tumour" we suspected was the spleen, although it is difficult to say why it appeared to be surrounded by air. Apart from an unexplained attack of pyelitis about the fourteenth day the patient made an uninterrupted recovery.

The post-operative assay for male hormone taken on December 13 showed that the amount of sterone was reduced to 6.5 mg. daily, a figure which may be regarded as a low normal. The sugar tolerance shows a decrease, and is charted with the pre-operative result. Within two months the patient had lost a stone and a half in weight, the blood pressure is the same, and her periods have been regular. The present photograph was taken in January, 1940; the pre-operative one was unfortunately lost.

This case of basophilism due to adrenal cortical hyperplasia presents several points of interest. A diagnosis was only arrived at by means of a urinary assay for androgens. The immediate response to unilateral adrenalectomy, both clinically and biochemically, and the corroboration of the diagnosis by histological means, conform to the experience which we have obtained in our work on virilism.

Summary

At the moment it may be said that the subject of basophilism is still *sub judice*. An apparently identical clinical syndrome may result from a lesion in either the pituitary or the adrenal glands. It is a matter of speculation whether the one is primary and the other secondary, or whether both are involved. From the practical standpoint in the treatment of a condition which has hitherto been unsatisfactory, and the study of these two cases, one of each type provides confirmation of the view that estimation of the urinary androgens affords a valuable means of making a differential diagnosis. When these are in excess it points to adreno-cortical overactivity. The ancillary methods of confirming such a diagnosis are discussed in the description of each of the two cases. The important outcome is that unilateral adrenalectomy in suitable cases offers a hope of alleviation, if not cure, in this most distressing condition.

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The printed newsletter which the Central Council for the Care of Cripples has published in the past has been discontinued for reasons of economy. It is being replaced by a quarterly stencilled newsletter, of which the first issue is dated January, 1940. Although the material in such a publication must necessarily be restricted and the circulation has had to be cut down, it is hoped to include in the new publication items of special interest to orthopaedic hospitals and institutions and to all workers for cripples. Those who are in a position to contribute such items may send them addressed to the Editor, News Bulletin, Central Council for the Care of Cripples, 34, Eccleston Square, S.W.1. The fifth International Exhibition of Cripples' Work, which was to have been held at the Seymour Hall, London, W.1, last October, has had to be indefinitely postponed owing to the war.

CARDIAC EXAMINATION IN WARTIME

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The advantage in diagnosis of making the most of symptoms has been well appreciated by the profession in our time, and in no branch of medicine more than cardiology, thanks largely to the influence of Mackenzie. For instance, the diagnosis of angina pectoris can be, and often must be, made solely from what the patient tells us: the patient's story is the foundation of diagnosis. The recognition of slight heart disease in men of military age is to be approached by a very different method. Here physical signs come into their own and become the basis of diagnosis. Unfortunately the signs will often be slight or dubious, and difficult to interpret. A shaky sign is a poor foundation for a weighty diagnosis, though this may rest on a trusty sign supported by others less convincing. It may therefore be useful to recapitulate and examine these signs as they apply to the recognition of the early stage or minor grades of cardiac disease in recruits and soldiers.

The work of a medical examiner in wartime is difficult enough, and constant care will scarcely prevent the occasional acceptance of this type of cardiac subject. The difficulty will be mitigated by knowing that such cases will almost be limited to rheumatic and perhaps congenital heart disease. Even with proper care and reasonable skill, diagnosis may still remain a matter of probability—and yet a decision has to be taken.

The history cannot be neglected, for the candidate may know that his heart has been described as "weak" perhaps from his very early years, or later and maybe from an attack of rheumatism or of chorea. A history of tonsillitis has little value, and of scarlet fever or diphtheria almost none. He may also think or know that he is more short-winded than his fellows. Any such points in history will make the examiner more alert in his search for signs.

The appearance will only help if there happens to be cyanosis and clubbed fingers due to a cyanotic congenital lesion. The coloration of the cheeks is so varied in healthy men that suspicion of mitral disease should not easily be roused by a high colour.

The Pulse

Pulse-response tests (so-called exercise, tolerance tests) can have little value in the recognition of myocardial or valvular disease, or indeed in assessing myocardial efficiency; yet they are valuable in judging the nervous control of the heart rate. An examiner soon learns to overlook the natural tachycardia of nervousness, especially when it dwindles as the interview proceeds and during the recumbency which is essential to every cardiac examination. Where a high rate persists—for example, over 100—a thermometer may explain it, or the state of the throat or the lungs. Re-examination after an interval may be indicated if the rate persists well over 100 throughout the interview and after recumbency. A high grade of persistent tachycardia can be one expression of a neurosis, and judgment as to fitness may have to depend on the state of the nervous system more than that of the heart.