THE PITUITARY—ADRENAL—GONADAL COMPLEX.*

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Until some few years ago the following conceptions summarized our knowledge of the clinical evidence of the influence of the pituitary and adrenal glands on sex :

Pituitary : (1) In Fröhlich's syndrome, there was hypogonadism, with infantile primary and secondary sexual characteristics.

(2) With a chromophobe adenoma or cranio-pharyngioma or other para-pituitary cysts, there resulted (through destruction of the chromophil cells) a condition of hypogonadism.

(3) In Simmonds's cachexia, with destruction of the anterior lobe (usually atrophy), hypogonadism developed.

(4) In acromegaly (eosinophil hyperplasia or adenoma), amenorrhœa and impotence were early features, but a preliminary hypergonadal activity might occur.

Adrenal Cortex : (1) Tumours (adenoma or carcinoma) produced sexual precocity in both girls and boys, but in girls this was associated with hirsutism and enlarged clitoris (pseudo-hemaphroditism).

(2) Tumours produced virilism in adult females, with inhibition of homosexual function.

(3) Virile females, with adrenal tumours, might be spare and muscular, or adipose. The latter type might have in addition lineæ distensæ on the abdomen, diabetes mellitus, and hypertension, etc.

(4) Removal of a tumour produced a complete return to normal in adults, complete or incomplete in children.

(5) Hyperplasia of the adrenal cortex appeared to produce similar clinical pictures to those resulting from tumours.

Cushing⁽⁶⁾ drew attention to a syndrome called "Basophilism," which was associated with, and which he believed to be due to, a basophil adenoma of the anterior lobe of the pituitary gland. The main features were (in women) virilism, amenorrhœa, involution of breasts, hypertension, adiposity, red lineæ distensæ on the abdomen, diabetes mellitus, plethora, with or without polycythæmia, and sometimes osteoporosis. By virilism is meant the loss or diminution of primary and secondary feminine characteristics, and growth of hair on the face and trunk of masculine distribution; the hair of the head tends to fall out, the voice to become hoarse, and the clitoris to enlarge.

Cushing's basophilism syndrome had many features in common with that due to an adrenal cortical tumour, and many words, and more ink, were used in pointing out the clinical differentiation. Accumulated knowledge showed that the clinical manifestations might be identical and indistinguishable. It was further shewn that the syndrome of "Basophilism" might occur in the absence of a

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basophil adenoma or of an increase in the number of basophil cells (basophilia) e.g. with adrenal or thymus tumours (the latter being associated with adrenal cortical hyperplasia). Also a basophil adenoma of the pituitary might be present without endocrine manifestations.

Crooke⁽⁴⁾ shewed that whether the basophilism syndrome was associated with an adrenal tumour or hyperplasia, a thymus tumour, or a basophil adenoma, one constant histological feature was present, namely the hyalinization of the basophil cells of the pituitary. He concluded therefore that this change indicated an altered function, and that this change was the cause of the basophilism syndrome. Since virilism could occur in the absence of such a change, it was not caused by the pituitary, and, as previously conceived, was the result of an adrenal cortical hyperfunction. This hyalinization does not affect the cells of any pituitary basophil adenoma that may be present. This evidence⁽⁴⁾ suggests that there is little to support Cushing's theory as to the ætiological significance of a pituitary basophil adenoma. It has also been pointed out that if the basophil cells influence the gonads, they are apparently inhibitory, and doubt has been thrown on an association of any kind between these cells and sex function.

Supplementary Clinical and Pathological Knowledge.

The occurrence of virilism in the female, and the absence of feminization in the male, was ascribed to the difference in embryological development, the ovary being said to be a potentially bisexual organ, with a feminine cortex, and a rudimentary masculine medulla. The latter was thought to undergo hyperplasia, when the former had been inhibited and caused to involute⁽¹⁴⁾. Actually, feminization does occur, although it is a rarity. Impotence and atrophy of the male sex organs are associated with gynæcomastia and breast secretion, adiposity of feminine distribution, higher pitched voice, but an increase of bodily hair. Removal of an adrenal cortical tumour has resulted in a return to normality.

If the basophilism syndrome occurs in childhood it may cause sexual precocity. Cushing⁽⁶⁾ has described such a case, and the author has seen two.

Virilism may be superimposed upon acromegaly, and this may not occur for some years after the initial acromegalic manifestations. It is due to adrenal hyperplasia, or neoplasm, secondary to pituitary overactivity. In one such case (to be published) an excess of pituitary adrenotropic hormone was present in the serum. Adrenal cortex hyperplasia, with or without adenomata, is a common finding in acromegaly. Such adenomata may become malignant, as is evidenced by a case of acromegaly in which carcinoma of both adrenal glands was present⁽¹⁰⁾. It would appear that adrenal hyperplasia may be secondary to pituitary eosinophil or basophil hyperactivity, and that both types of cell may give rise to an excess of the adrenotropic hormone. It would also follow that what may appear as a primary adrenal cortex carcinoma may have had its origin from a pituitary stimulus (adrenotropic). On the other hand, in some cases of adrenal cortex carcinoma, the opposite gland is atrophied rather than hypertrophied.

Cushing's basophilism syndrome may occur in an incomplete form with artificial or menopausal castration⁽¹⁶⁾.

Do the Basophil Cells Secrete the Gonadotropic Hormone?

The chromophobe cells of the pituitary give rise to basophil and eosinophil cells, and although the reverse process may occur, there is no evidence of

transformation of basophil into eosinophil, or *vice versa*. Although an average percentage of these cells can be worked out, their proportion is a dynamic figure which, at any rate in the smaller animals, varies with the physiological state, *e.g.*, oestrous, dioestrous, pregnancy, castration. Similar changes may occur in man.

The chromophobe cells are not known to give rise to any hormones, the eosinophil cells secrete the growth hormone, and the basophil cells were believed to secrete the gonadotropic hormone. This latter supposition has been severely criticized largely on the ground that with Cushing's basophilism, the gonads are inhibited. It is dangerous to conclude too much from a clinical syndrome, and in my opinion there is good evidence for believing that the basophil cells do give rise to the gonadotropic hormone. Thus:—

(1) Castration gives rise to an increase in the number of basophil cells, and a coincident increase in the gonadotropic potency of the pituitary gland (when implanted).

(2) At the menopause there is an increase in the number of basophil cells, and an increase in the amount of Prolan A. excreted in the urine.

(3) Adrenalectomy results in a diminution in the number of basophil cells, and a decrease in the gonadotropic activity of the pituitary, together with an atrophy of the gonads (after some weeks).

(4) In animals, oestrin injections cause a degranulation, and destruction of the basophil cells, with a decrease in the gonadotropic potency of the pituitary, and a decrease in the size of the gonads.

Biological Investigation of Virilism and Feminization due to Adrenal Cortex Hyperplasia or Neoplasm.

In virilism of the female it has been shewn that there is a considerable excess of male comb-growth (or testicular like) hormone in the urine⁽¹⁴⁾. In feminization of the male, there is a considerable excess of oestrogenic hormone (to be published). In one such case this hormone disappeared after removal of the tumour, and returned when metastases made their appearance. Further, both oestrogenic and male comb-growth hormones have been obtained from the normal adrenal gland. It is therefore probable that an adrenal cortex hyperplasia or neoplasm may give rise to oestrogenic hormone in the male, and comb-growth hormone in the female. It will remain to be explained why the hyperplasia or neoplasm appears the same in both sexes on ordinary histological examination.

That the hyperplasia of the adrenal cortex in virilism is not due to the hyperplasia of cells responsible for the life maintaining hormone "cortin" is suggested by the following facts:—

- (1) Such patients often have symptoms of Addison's disease, *e.g.*, weakness and pigmentation⁽¹⁴⁾.
- (2) "Cortin" potent for adrenalectomized animals, does not influence the primary or secondary sex organs (most species).
- (3) The cells are said to have a special affinity for a fuchsin stain (Vines and Broster).
- (4) Indirect evidence favours the androgenic zone (of the inner layer of the cortex), that normally involutes at birth, as the one that undergoes hyperplasia.

Discussion.

Cases of basophilism (Cushing's syndrome) have been described, which were due to an adrenal adenoma, but, what is more important, is that in at least one woman all the symptoms of basophilism disappeared after removal of the adrenal growth.⁽¹²⁾ This would appear to suggest that—

(1) we cannot accept the view that basophilism is due to a basophil adenoma of the pituitary⁽⁶⁾;

(2) we cannot accept the view that basophilism is due to a hyalinization of the basophil cells⁽⁴⁾, or

(3) that an adrenal tumour may produce changes in the adrenal gland in the direction of basophilia, and that removal of such a tumour causes the disappearance of such basophilia. This was a view that appealed to me⁽¹⁴⁾ (especially as the opposite occurs in Addison's disease⁽⁵⁾), and I would add that, in addition to, or instead of, an increase in the number of basophil cells, one must also postulate the possible qualitative change of hyalinization of basophil cells.

Whether the hyaline change in the basophil cells is the immediate and direct cause of the symptoms of basophilism (excluding virilism) is perhaps less definite than some would have us believe. One must remember that the adrenal cortex is known to have a profound influence on carbohydrate metabolism and adiposity, and part of the syndrome may have to be explained *via* an adrenal change. Against this theory is the fact that adrenal hyperplasia is not constant (Crooke)⁽⁵⁾, but since virilism (hirsutism and amenorrhoea) was present in three of these cases where hyperplasia was said to be absent, and since it is agreed⁽⁵⁾ that virilism results from adrenal hyperfunction, the gross criteria of cortical hyperplasia cannot be readily accepted.

Some objections to Cushing's theory of a basophil adenoma or hyperplasia being responsible for his syndrome are:—

(1) The syndrome occurs in the absence of such pituitary changes.

(2) A basophil adenoma may be present without any symptoms.

(3) The gonads are inhibited, whereas basophil cells are probably gonadotropic.

(4) The only constant change is hyalinization of the basophil cells.

In consideration of these objections let us assume three things, for which there is much evidence:—

(a) Hyalinization of the basophil cells is the cause, direct or/and indirect, of the basophilism syndrome.

(b) Hyperactivity of the adrenal cortex is the cause of virilism, which latter may or may not be associated with the basophilism syndrome.

(c) Adrenal hyperplasia (adenoma) can cause changes in the basophil cells (hyperplasia and/or hyalinization)—evidence based on result of operation (see above); also gradual transition of some cases of virilism to basophilism.

Now, to return to the four objections:—

(1) The presence of the syndrome in the absence of pituitary changes does not mean that a basophil adenoma may not be a cause of the basophilism syndrome.

(2) Eosinophil adenomata occur in the absence of gigantism and acromegaly, but no one disputes the relationship.

- (3) Since adrenal hyperplasia (or neoplasm) produces excess of male comb-growth hormone (in female) and oestrogenic hormone (in male) this may explain inhibition of gonads. Further, in the young or adolescent, clinical basophilism may be associated with sexual precocity. Also, prolonged outpouring of gonadotropic hormone may (? by antibodies) produce ultimate inhibition—compare the myxoedema that may occur in acromegaly. No one has yet explained why the adrenal cortex produces sexual precocity in the young, and sexual inhibition in the adult, but no one doubts its relationship to sex.
- (4) A basophil adenoma might be a cause of hyalinization of the basophil cells, indirectly through secondary adrenal hyperplasia.

Apart from the frequency of the association of a basophil adenoma with basophilism, the fact that the syndrome occurs in varying degrees of completeness after artificial or physiological castration (menopause)⁽¹⁴⁾ is in favour of Cushing's theory, since castration results in an increase of the basophil cells, and adenoma formation may be an expression of hyperplasia. One must also admit that castration causes degranulation of basophil cells in the direction of vacuolization (castration cells).⁽¹³⁾

In view of all these considerations I do not agree with those who would discard Cushing's theory of the ætiology of the basophilism syndrome, although it is quite evident that a basophil adenoma is not the only cause. The tale is incomplete, but we still need to walk warily.

Summary.

I would summarise the conclusions of this review as follows.

- (1) Virilism (and feminization) results from adrenal hyperplasia or neoplasm, either of which may be primary or secondary to pituitary hyperfunction (adrenotropic).
- (2) Clinical basophilism (adiposity, hypertension, plethora, diabetes, etc.) results from hyalinization of the basophil cells, but the immediate cause of some of the symptoms may be adrenal.
- (3) Hyalinization and/or hyperplasia (with or without adenoma formation) may result from primary adrenal cortex neoplasm or hyperplasia, and may disappear after removal of an adrenal neoplasm.
- (4) A pituitary basophil adenoma may be insecurely established as a prior cause of clinical basophilism, but there is insufficient evidence to discard this attractive hypothesis.

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Hunterian Society Gold Medal.

Dr. L. J. A. Parr of Sydney, Australia was awarded the Medal for 1936 for an essay on "Rheumatoid Arthritis."

The subject selected for 1937 is "The Prognosis and Care of Heart Disease in General Practice," and for 1938 "The Management of Inoperable Malignant Disease in General Practice."

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A copy of the Rules and any further information can be obtained on application to the Honorary Secretary, Mr. Arthur E. Porritt, 27, Harley Street, W.1.

Fellowship Coronation Dinner-Dance.

We should like to remind our members that the above function takes place on Friday, May 28th, at Claridges Hotel. Reception of guests commences at 8.30 p.m., dinner at 9 p.m. and dancing afterwards till 3 a.m. There will be a cabaret entertainment at midnight. Tickets, one guinea each (inclusive of dinner and running buffet during dancing), may be obtained from the Secretary, The Fellowship of Medicine, 1, Wimpole Street, W.1, or from any member of the Ladies' Committee.

Erratum.

Dr. Levy Simpson has asked us to draw the attention of our readers to a typographical error in his article "The Pituitary-Adrenal-Gonadal Complex," which appeared in the March issue of the Journal. On page 99, line 9 should read "that an adrenal tumour may produce changes in the pituitary gland in."