BILATERAL POLYCYSTIC OVARIES

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The writing of an article about this condition presents considerable difficulties. It is found in a number of separate disorders and is not therefore an entity in itself, though a common final mechanism may be typically involved. Moreover, a number of matters are involved about which knowledge is confused, fragmentary or uncertain. It is proposed to consider various aspects of the subject separately and then to attempt some synthesis of ideas in the final section on aetiology.

Control of the Menstrual Cycle

Much is uncertain about the mechanism of the menstrual cycle, despite the vast amount of research which has gone into this field. It is proposed to present some commonly accepted views on matters relevant to the present paper. For critical reviews of the subject the reader is referred to writings by Hisaw, Harris and Velardo.^{19, 20, 55}

Experiments with pure gonadotrophins have shown that FSH is responsible for the early stages in follicular development. Cyst formation, theca cell luteinization and ovulation, however, require the additional presence of LH. Timing and dosage of FSH in relation to LH appears critical, an abnormal balance between the two leading to various histological abnormalities and failure of ovulation. The formation of progesterone may depend upon a further pituitary hormone—luteotrophin.

It seems likely that a centre for the initiation and regulation of the menstrual cycle resides in the hypothalamus, influenced by feed-back mechanisms from the ovary. There is evidence, for example, that oestrogens stimulate the production of LH and that progesterone inhibits that of FSH.

Clinical Associations and Pathology

Polycystic ovaries are found in a variety of conditions. These fall into several distinct groups.

Multiple cysts with luteinization of theca cells have been reported in conditions of raised intracranial pressure,²⁶ hydatidiform mole and chorion-epithelioma,³⁵ basophil adenomata of the pituitary,^{5, 33} and following injections of gonado-

trophins. Multiple cysts have also been found in the ovaries of newborn infants⁴⁶ and in experimental hypothalamic lesions.⁴⁰ Abnormal secretion of gonadotrophins is known, or is likely, to be associated with all these conditions.

Polycystic ovaries have been reported in a small but important group of cases with virilizing adrenal adenomata.^{1, 16, 30, 37} Typical polycystic changes with luteinization of theca interna cells and thickening of the capsule have been observed. The ovarian changes in congenital adrenal hyperplasia, however, appear different;²⁴ generally speaking, follicular activity is depressed, though multiple small cysts were observed on occasions.

Multiple cysts with predominating granulosa cell activity are found in some patients with menorrhagia.³⁵ Multiple cysts are also found in association with pelvic inflammatory disorders.

In 1935 Stein and Leventhal⁴⁷ reported on the association of oligomenorrhoea with anovulatory cycles, infertility and polycystic ovaries. Numerous reports from Stein and his colleagues and others have appeared since on this subject.^{3, 7, 10, 21, 28, 31, 41, 43, 44, 48, 49} Hirsuties has been present in about half the reported cases and in such cases the clitoris is occasionally enlarged. Somewhat characteristic histological changes are found in the ovary. The capsule is commonly thickened and there is a tendency to hyperplasia of the theca interna, with the appearance of clumps of theca-like cells in the stroma. The theca and theca-like cells may or may not be luteinized. Wedge resection of the ovaries has led to improvement in menstrual function and relief of infertility, but not of hirsuties, in a considerable proportion of cases, though not in all. Stein⁴⁷ has followed many of his cases for 25 years and reports apparently permanent relief from symptoms and ovarian enlargement. The author thinks it possible that the cases in this group with and without hirsuties may have different causes. It would, at any rate, help in clarifying a complicated situation if observations on the two types were clearly distinguished in future reports.

Before leaving this section it is worth noting the

limitations on our investigation of the pathology of polycystic ovaries. The ovary is not readily accessible to inspection, information being largely restricted to findings at operation and autopsy. Serial observations are largely non-existent and our knowledge of any evolution in the histological picture which occurs with time is therefore extremely meagre. Gynaecography has been helpful, but its value is limited, since the information it provides relates only to ovarian size.

The Association of Polycystic Ovaries, Oligomenorrhoea, Infertility and Hirsuties

It is now desirable to consider certain matters which bear on an understanding of the above syndrome.

Congenital Bilateral Adrenal Hyperplasia

This condition is classically manifest in the female by gross virilization. External genitalia are masculinized. Hirsutism develops early. The breasts do not develop and the menses fail to appear.

The condition is caused by an enzyme defect in the synthesis of cortisol from cholesterol in the adrenal cortex. This synthesis takes place in a series of steps which include pregnenolone, progesterone and 17-hydroxyprogesterone. Stemming off along this pathway other substances are produced, including such androgen-derived ketosteroids as dehydroepiandrosterone, androsterone, aetiocholanone, and 11 β -hydroxyandrosterone, and pregnanediol and pregnanetriol, all of which normally appear in small amounts in the urine. Metabolites of cortisol of a 17-ketosteroid nature also appear normally in the urine, including 11 β -hydroxy-aetiocholanone and 11-oxo-aetiocholanone. In congenital bilateral adrenal hyperplasia there is a defect in the conversion of 17-hydroxyprogesterone to cortisol. Corticotrophin production by the pituitary increases in an attempt to step up the production of cortisol. As a consequence there is a considerable over-production of androgenic 17-ketosteroids and pregnanetriol. The ratio of these substances to cortisol metabolites is greatly increased and the ratio is not significantly lessened following stimulation by injected corticotrophin.

Corticoid therapy has proved remarkably effective in this condition. A considerable improvement in the hirsuties takes place. Breasts develop and regular ovulatory menstruation appears. There are even records now of pregnancies.^{2, 53, 54, 56}

Constitutional Virilism

In 1940 Sheldon, Stevens and Tucker⁴² suggested that there was an interplay of masculine and feminine characteristics in every individual.

Secondary sex characteristics certainly show quantitative variations between individuals of the same sex and considerable quantitative overlap between the two sexes. This has been demonstrated very clearly for hair growth,^{8, 9, 52} and for shoulder and hip widths.^{29, 45, 50} Similar features are shown by 17-ketosteroid excretions.

It has been suggested that there is a constitutional variant in women in which the deviations from normal are in a masculine direction.^{4, 27} A significant tendency to increased shoulder width in hirsute women has been observed.¹¹ An increased 17-ketosteroid excretion has been found in hirsute women compared with controls.^{11, 37, 39} A significant correlation has been shown between the degree of hirsuties and 17-ketosteroid excretion in males.⁵¹

That this constitutional variant may be associated with disturbance of the menstrual cycle, and possibly with infertility, is suggested by a significantly greater incidence of oligomenorrhoea in hirsute subjects found during an investigation of some 350 women.¹¹

Results of Steroid Assays

FSH excretion appears to lie within normal limits.^{10, 18, 21} It has been claimed that LH excretions are raised, but methods for the assay of LH are doubtfully reliable at present and these reports must be accepted with reserve.

Increased pregnanediol excretions have frequently been reported in the past; significant series are reported by two authors.^{10, 15} Unfortunately the methods employed have been insufficiently specific, estimating pregnanetriol among other substances. More specific methods have been employed, however, in two series^{32, 34} where a tendency to raised excretion was observed; unfortunately these workers were concerned with hirsutism alone and ovarian pathology was not recorded. Very little work has been done on oestrogen excretions, but no abnormalities have been reported. The results of pregnanetriol and androgen assays will be described later.

Aetiology

Disturbance in the secretion of gonadotrophins would appear adequate to explain the appearance of polycystic ovaries in conditions of raised intracranial pressure, basophil tumours of the pituitary, hydratidiform mole and chorion-epithelioma, and experimental lesions of the hypothalamus.

Nothing would appear to be known about the aetiology of multiple follicular cysts associated with menorrhagia.

A primary hyperplasia of ovarian theca cells has been postulated for the group of non-hirsute Stein-Leventhal cases. The beneficial effect of wedge

resection is advanced in favour of this explanation. The present author considers that it would be wise to keep an open mind on the matter for the present.

Many explanations have been suggested for the group of hirsute Stein-Leventhal cases. Two in particular require consideration. The first postulates a primary hyperplasia of ovarian theca cells, the second a primary adrenal anomaly associated with excessive excretion of an androgen.

Hirsutism is explained on the former hypothesis as being due to the secretion of an androgen by the luteinized theca cells. There is no theoretical objection to this, since androgens are normally secreted in small amounts by the ovary and masculinizing thecomas are well known. The failure of wedge resection to relieve hirsuties may be due to removal of insufficient ovarian tissue; it is a little surprising, however, that no improvement whatever had taken place three years after bilateral oophorectomy in a case reported by Geist and Gaines.¹⁴ The beneficial effect of wedge resection is advanced in favour of this hypothesis; it is not proof, however, any more than the good effect of partial thyroidectomy proves the primary thyroidal origin of thyrotoxicosis.

The primary ovarian hypothesis cannot be dismissed, but evidence has been accumulating about the importance of an adrenal factor in many of these cases. The finding of polycystic ovaries in virilizing adrenal adenomata indicates the possibility of such an explanation. The work of Pfeiffer in 1936³⁸ suggests a possible mechanism. Female rats were castrated at birth and testes implanted; ovaries were re-implanted at puberty. Many of these animals showed a state of constant oestrus with ovarian changes indicative of a constant acyclic production of FSH, and these abnormalities persisted after removal of the testes. Even among those animals with cyclic behaviour menstrual cycles were prolonged, recalling the oligomenorrhoea of clinical practice. It was suggested that androgens have a masculinizing effect on hypothalamic centres, leading to an acyclic production of FSH characteristic of the male in contrast to the cyclic production of FSH and LH which occurs in the normal female.

Two lines of evidence support the importance of adrenal androgens in hirsute Stein-Leventhal cases. These arise from the results of steroid assays and the effects of administered cortisone on clinical disturbances. Clinically it is impossible to distinguish between cases with hirsutism alone and those with hirsutism and polycystic ovaries. Indeed, there may be no aetiological difference, though certain clinical differences were noted in one series of cases.³⁹ Much of the reported data relates to both groups and it will be necessary,

therefore, to consider evidence concerning the two groups at the same time.

Assays of 24-hour excretions of total 17-ketosteroids in hirsute patients, with and without polycystic ovaries, usually show normal or high normal figures only, but assays of individual steroids after chromatographic separation tell a different story. Androgen-derived 17-ketosteroids, such as androsterone and aetiocholanone, are abnormally high and the ratio of these to cortisol metabolites is raised above normal.^{6, 10, 12, 13, 23, 36, 39} This similarity in kind, though hardly in degree, to the findings in congenital adrenal hyperplasia is shown also by the results of pregnanetriol estimations. Several authors^{15, 34, 39} report cases in which 24-hour excretion rates are above normal. The two former groups find, however, that the pregnanetriol/cortisol metabolite ratios after corticotrophin stimulation approximate to normal. Another group⁶ found the same in regard to the ratio of androgen/cortisol metabolites. It would seem, therefore, that the *capacity* for production of cortisol is within the normal range and the anomaly, if similar in kind to that found in congenital adrenal hyperplasia, is certainly less in degree.

Cortisone has led to the correction of menstrual disturbances, and of infertility in hirsute subjects with and without polycystic ovaries.^{15, 17, 22, 24, 25, 39} One group³⁷ report considerable relief of hirsuties (ovarian pathology not stated), but this is doubtfully the experience of other workers, including the present writer.

It is hard to resist the conclusion that an adrenal anomaly is important, perhaps primary, in many hirsute Stein-Leventhal patients. This may be of the kind found in congenital adrenal hyperplasia, but, if so, is certainly much milder in degree. Alternatively, it may be due to a constitutional variant in which either androgen production is greater than normal and/or end organ sensitivity to circulating androgens higher.

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