A PERSPECTIVE ON THE HYPERTHECOSIS OVARII SYNDROME

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The study of chromosomes in man and the advances in the biochemical and genetic fields have elucidated stimulating concepts with regard to the hyperthecosis ovarii syndrome. It is felt that a review of the problem at this stage is necessary in order that a perspective be attained.

In 1935 Stein and Leventhal[1] performed wedge biopsies on the ovaries of 7 patients between the ages of 20 and 30 years in order to obtain tissue for histological study. These patients presented with the clinical features of secondary amenorrhoea, sterility, hirsutism and bilaterally enlarged non-tender polycystic ovaries. In the majority of patients menstruation reverted to normal, and pregnancy ensued in some. This dramatic cure aroused their interest in the symptom complex and, since their original paper in 1935, many interesting theories have been postulated. The reasons for cure after wedge resection are still not entirely clear.

The clinical features have been fairly well established. Much interest centres on the pathogenesis and endocrinological and genetic aspects of the syndrome.

PATHOGENESIS

An attempt will be made to review the pathogenesis in a chronological order:

1935—Stein and Leventhal[1] considered that increased anterior pituitary gland secretion accounted for the syndrome and that crowding of the ovarian stroma by cysts prevented follicle development. They felt that the thecal cells might be associated with the production of oestrogens.

1937—Bailey[2] presumed that a pathological change occurred in the ovaries as a result of the presence of a basic pituitary hormone deficiency, resulting in secondary cessation of ovarian function. He reasserted this view in 1959[3] by stating that there was a diminished follicle-stimulating hormone production which led to incomplete follicle development and early atresia, and that there was a relative predominance of luteinizing hormone which led to hyperplasia of the interstitial cell layer. This hypofunction was so slight as to leave unaffected the results of hormone assays, but it manifested itself clinically in the production of menstrual disturbance. He based his beliefs on the following factors:

1. The endometrial development in the majority of cases was below normal.
2. In some cases the uterus had shown some degree of atrophy.
3. The cystic ovarian follicles showed development up to a point only, with early cystic atresia, and an underdeveloped granulosa layer.
4. The theca interna was relatively hyperplastic throughout the phases of retrogression.

These features, enumerated by Bailey, as will be shown later, correspond with the late thecal-dominant phases of Shippel's hyperthecosis ovarii syndrome.

1938—Deanesley[4] thought that the androgenic activity was due to luteinization in the theca interna. This occurred following transplantation of ovaries to abnormal sites in experimental animals.

1939—Greene and Burrill[5] attributed the androgenic activity to excess progesterone production.

1941—Leventhal[6] felt that the disordered pituitary function resulted in marked activity and crowding together of follicles in the ovary, and in some manner also accounted for the thickening and fibrosis of the tunica with the consequent development of a 'mechanical blockade' making ovulation impossible. It was in order to relieve this mechanical blockade that the operation of wedge resection was devised.

1942—Greep et al.[7] showed the effect of luteinizing hormone on hypertrophy of the interstitial cells of the testis.

1948—Gillman,[8] in his paper on the embryology of the ovary, stated that in a foetus of 130 mm. crown-rump length, the large interstitial cells were very similar to that of the thecal cells of atretic follicles in the ovary towards the end of gestation. These 2 cell types were not easily distinguishable on the basis of cell morphology and resembled closely the cortical cells of the foetal adrenal.

If one is to relate function to structure on the basis of cell morphology, it would seem that the androgen-producing interstitial cells are so closely related to the thecal cells that their functions in certain aspects may be concurrent.

1949—Culiner and Shippel[9] suggested that thecal cells have androgenic properties and that virilization may occur in the presence of thecal-cell hyperplasia of one or both ovaries.

1950—Ingersoll and McDermott[10] demonstrated the normal character of the hormone assays in 21 cases, and suggested that the basic disorder might be a collagen infiltration of the ovarian capsules.

1955—Haas and Riley[11] felt that follicle development began normally, but that there was 'something lacking to complete the ovulatory process'.

1955—Shippel[12] set out to show that: (*a*) the syndrome of secondary amenorrhoea, hirsutism and masculinization, as first described by Stein and Leventhal,[1] was merely the end-result of a very much larger syndrome; (*b*) many conditions associated with menorrhagia, endometrial hyperplasia, and cystic glandular hyperplasia, which are considered separate entities, are merely phases of this syndrome; and (*c*) the theca cell has androgenic function.

Shippel felt that an abnormality of one of the endocrine glands, e.g. pituitary, thyroid or pancreas, may result in a state of anovulation. This occurs in patients in their teens in whom endocrine adjustment is taking place. An associated prolonged period of anovulation will result in thecal proliferation and excess androgen production. Subsequently, the primary endocrine abnormality may be corrected, but the pathological changes within the ovary persist and can only be corrected by either prolonged cyclical therapy or wedge resection.

The absence of ovulation is associated with continuous, rather than fluctuant, levels of either FSH or LH with concomitant persistent stimulation of: (*a*) the ovarian stroma, transforming prothecal to thecal cells; (*b*) the thecal cells; and (*c*) the tunica with resultant thickening. Pregnancy may stimulate thecal cells, and if postpartum involution of ovaries is deficient, hyperthecosis may result.

1957—Keetel et al.[13] demonstrated an excess of LH in 10 out of 11 patients with polycystic ovaries.

1959—Falck[14] isolated by microdissection techniques granulosa cells, theca interna cells, interstitial and corpus luteum cells from ovaries of the mature rat. These were then transplanted into the anterior chamber of the eye separately and in combination with a contiguous piece of vaginal epithelium as indicator of oestrogenic activity.

He found that oestrogen secretion was never recorded in transplants of pure cell systems but only in transplants containing theca interna cells or interstitial cells combined with granulosa cells or corpus luteum cells. The production of hormone depended on a joint action of 2 principal ovarian systems: the system of theca interna and interstitial gland cells and the system of granulosa and corpus luteum cells.

1959—Ingersoll and McArthur[15] showed that the elevated excretion of LH was greater in patients who had the largest ovaries and the longest period of amenorrhoea. They also found raised LH excretion in adrenal hyperplasia. This is not surprising as it has been suggested that LH acts on the adrenal as well. In the normal female there are two peaks of LH excretion, one at midcycle and the other in the luteal phase. With the Stein-Leventhal syndrome the LH excretion is constant without any significant peak, but at a higher level.

1960—Gemzell, Diczfalusy and Tillinger[16] administered pure human pituitary follicle-stimulating hormone (HP—FSH) to amenorrhoeic patients and found that ovulation did not occur unless human chorionic gonadotrophin (HCG) was administered. However, in the Stein-Leventhal syndrome ovulation occurred without the use of HCG, indicating the presence of LH in this syndrome.

Two other observations can be deduced: (*a*) that when properly stimulated, the polycystic ovary is capable of ovulation without wedge resection; and (*b*) that the instigating cause of the ovarian pathology might be found in the pituitary gland.

1961—Barraclough and Gorski[17] 'masculinized' the hypothalamus of immature rats by injecting them with testosterone and found that electrical stimulation, which normally does produce ovulation, failed to do so. It is postulated that LH secretion becomes masculine in character, that is, continuous and non-fluctuating levels are produced. It is possible that in the Stein-Leventhal syndrome a similar mechanism of 'masculinization of the hypothalamus' might be operating due perhaps to excess androgenic secretion by either the maternal or foetal adrenal during the period of gestation.

That HP-FSH[18] and clomiphene[19] can stimulate ovulation is further evidence in favour of the 'masculinization of the hypothalamus' theory.

1961—Warren and Salhanick[20] observed that fluid from polycystic ovaries contained a very high concentration of androstenedione, with no detectable amount of oestrogen, whereas fluid from the follicle cysts of a control group contained significantly lower levels of androstenedione and definite levels of oestrogens. These findings were confirmed by Short and London.[21]

1962—Giorgi's results[22] performed on the cyst fluid of 30 patients are in agreement (Fig. 1). These results strongly suggest a block in the production of oestrogen from androstenedione in the ovary with Stein-Leventhal syndrome.

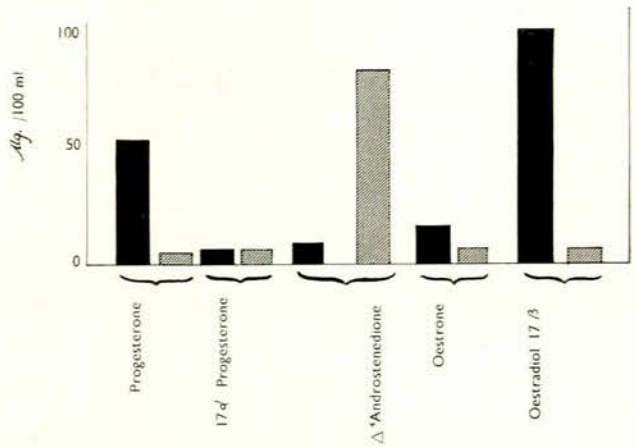

Fig. 1. Steroid analysis of cyst fluid.
■ = patients without Stein-Leventhal syndrome.
▨ = patients with Stein-Leventhal syndrome.

1962—Gemzell[18] reported pregnancies resulting from HP-FSH administration in 2 patients with Stein-Leventhal syndrome. It is interesting to note that both patients had twins.

1962—Greenblatt et al.,[19] using an analogue of the non-steroidal Tace (MRL 41 or clomiphene), were able to induce ovulation in 18 out of 22 patients with the Stein-Leventhal syndrome; one of these became pregnant. Leventhal and Scommegna[23] also describe such a case. Greenblatt thought that clomiphene might work on a hypothalamic-pituitary level.

1962—Mahesh and associates[24] described 2 types of Stein-Leventhal syndrome with regard to steroid secretion. In one they found that the polycystic ovaries contained a large amount of $\triangle^4$ androstenedione and 17-α-hydroxyprogesterone. In the other they found predominantly dehydroepiandrosterone.

In the biosynthesis of steroids in the ovary (Fig. 2) the normal pathway (illustrated on the right side of the figure) is acetate → cholesterol → pregnanelone → progesterone → 17-α-hydroxyprogesterone and androstenedione, which by aromatization of ring A produces oestrogens. If the failure of

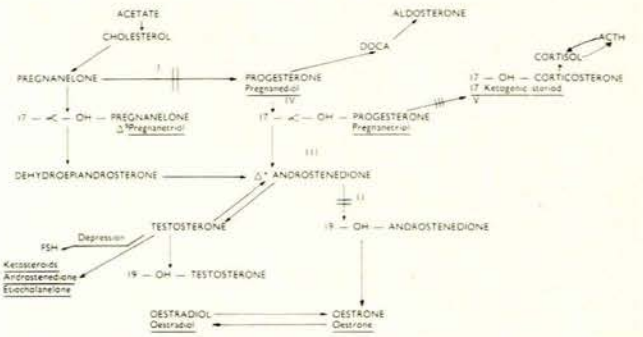

Fig. 2. Biosynthesis of steroids in the ovary. Underlined words = breakdown products in the urine.
I = defect in 3 ol-dehydrogenase
II = defect in 19-hydroxylase
} Defects in Stein-Leventhal syndrome
III = desmolase
IV = 17-hydroxylase
V = defect in adrenogenital syndrome

enzymes that convert $\triangle^4$ androstenedione to oestrogens occurs, then large amounts of precursors accumulate, namely 17-α-hydroxyprogesterone and androstenedione. This represents one type of Stein-Leventhal syndrome.

1962—Smith and Ryan[25] described a minor route of oestrogen synthesis, bypassing progesterone and producing 17-α-hydroxypregnanelone and dehydroepiandrosterone (see left side of Fig. 2). In the normal ovary this is a minor route, but if there is a deficiency in the enzyme system which converts pregnanelone to progesterone, namely 3-β-ol dehydrogenase, then there will be a shift of steroid production towards the alternate route and dehydroepiandrosterone will be increased. This is the pathway which is predominant in the second type of polycystic ovary described by Mahesh.

Stimulation of the ovary with human pituitary FSH in the latter type of patient results in an increase in dehydroepiandrosterone, suggesting faulty synthesis by the alternate pathway. Estimation of $\triangle^5$ pregnanetriol, the breakdown product of 17-α-hydroxypregnanelone, has been shown to be increased in the Stein-Leventhal syndrome by Cox and Sherman.[26]

1963—Leventhal and Scommegna[23] point out that testosterone can be synthesized by human ovarian tissue obtained from patients with or without hirsutism. The amount produced from polycystic ovaries is greater than that from normal ovaries.

1961—Netter[27] discusses 2 typical cases of Stein-Leventhal syndrome in which he found a mosaic of 46 normal chromosomes and of 47/XXX chromosomes. In the second case he found a mosaic of 46 chromosomes in which deletion of the major part of the long arm of one chromosome occurred. He felt that the enzymatic blocks were related to the chromosomal defect.

1964—Bishun and Morton[28] found their patient to have 40% of cells with a Barr body, and a mosaic of cells containing 46/XX and 45/XO chromosomes. The missing chromosome belonged to group C, 6 - 12.

1965—Hargrave[29] studied the karyotype of a typical female with this syndrome and found the cells to contain less than 20% Barr bodies. The patient was a mosaic, the cells containing 46/XX and 45/XO chromosomes. The cells with 45 chromosomes showed a loss of a chromosome from the 6 - 12 group.

PATHOLOGY

The ovaries in the classical case are enlarged, with a thickened tunica albuginea, multiple cysts showing a striking hyperplasia of theca interna with luteinization, many mitotic figures and marked vascularity.

Shippel[12] described an early, intermediate and late thecal-granulosal synergistic phase, which was followed by the early, middle and late thecal-dominant phases. Each phase is associated with certain clinical features, and a definite histological pattern in both the ovary and the endometrium (Table I). The table represents features originally described by Shippel[12] and modifications by virtue of added experience.[30] The clinical features mentioned are those which are frequently seen in association with the pathological findings in the ovary and endometrium in our university. A more accurate correlation will be attempted in the future.

DIAGNOSIS AND MANAGEMENT

The diagnosis in the classical case is not difficult, as the patient presents with most of the features as originally described by Stein and Leventhal. In addition, 10 - 20% are obese and some may have hypertension.

The earlier phases of the hyperthecosis ovarii syndrome may be more difficult to diagnose. Whatever the basic cause of anovulation might be, this feature initiates diagnostic criteria in the endometrium, revealing a hyperplastic picture as described under pathology (Table I). In the absence of oestrogen medication, persistent follicular cysts, or a hormone-producing ovarian tumour, the diagnosis must be strongly considered when taken in conjunction with abnormal menstruation, either from the menarche or within 3 years of the onset of menstruation. Early virilizing features may be present, especially in patients under the age of 25 years. This, however, does not mean that wedge resection should be immediately performed. On the other hand the patient may not have virilizing features, as the thecal cells are probably not producing sufficient androgens.

Differentiating a mild case of congenital adrenal hyperplasia may be difficult. This syndrome has been well documented and a recent review is given by Speroff.[31] The presenting features of the post-pubertal form that may lead to confusion are virilizing features, abnormalities of menstruation and infertility. A genetic block due to a deficiency of both the 21- and 11 - hydroxylase enzymes is the cause (Fig. 2), so that cortisol production is greatly diminished. The pituitary gland attempts to compensate for the deficiency by secreting excess ACTH, which overstimulates the zona reticularis of the adrenal, resulting in excess androgen production.

Anovulation occurs, so that ultimately the histologic features of the endometrium and the ovaries may be similar to the hyperthecosis ovarii syndrome. (We have seen a case of an adrenal rest tumour of one ovary, by virtue of its androgenic activity, produce 'hyperthecotic' histologic changes in the endometrium as well as a polycystic contralateral ovary.) However, the 17-ketosteroids other than the

TABLE I. CLINICAL FEATURES IN HYPERTHECOSIS OVARII SYNDROME

		Endometrium	*Ovary*	*Clinical features*
Granulosal-thecal synergistic phase	I Early	1. Hyperplastic endometrium showing: (*a*) back-to-back phenomenon of glands (*b*) psuedo-stratification of nucleii (*c*) intralumenal papillary-inclusions 2. No cystic glands	1. Thickened tunica 2. Zones of atretic follicles 3. Normal amount of granulosa and luteinized theca 4. Broad theca externa (protheca) with active mitoses 5. Little thecal proliferation	1. Menorrhagia initially 2. Irregular menses or 3. Oligo-amenorrhoea 4. Hirsutism in some cases 5. Ovary usually slightly enlarged, but may be normal or small
	II Intermediate	Tendency for glands to become cystic and features mentioned in I	1. Luteinized theca is increased in amount, in some follicles, granulosa cells are present 2. Broad zones of theca externa	
	III Late	Typical 'Swiss cheese' endometrium	Further progression of intermediate phase	Long periods of amenorrhoea, followed by severe bleeding. This phase is rare
Thecal dominant phase	IV Early	May be I, II or III, with perhaps decreased mitotic activity. However, only valid if endometrium obtained not during a bleeding phase, because during bleeding, as a result of oestrogen withdrawal, the mitotic index will be very low	As above, but in addition, islands of luteinized theca appearing in stroma	Virilizing features more marked. Longer periods of amenorrhoea. Ovarian size—usually large, or may be normal
	V Intermediate	Mitotic index low	Broad zones of luteinized theca surrounding atretic follicles and extending into prothecal zone	Further progression
	VI Late	Atrophic endometrium	Islands of luteinized theca more prominent in stroma. Atretic follicles present	Fully developed Stein-Leventhal syndromes with all clinical features as described. Ovaries usually large, cystic, non-tender

etiocholanelone and androstenedione fractions are raised. The cortisone suppression test is positive.

It is possible that cases of Stein-Leventhal syndrome formerly diagnosed as having responded to cortisone therapy might well have been cases of mild adrenal hyperplasia. Proper pre-operative investigation will eliminate this error.

Gynaecography

Kelling[32] first introduced pneumoperitoneum to facilitate the inspection of abdominal viscera at peritoneoscopy. Alvarez[33] introduced the use of carbon dioxide in visualizing the pelvic organs with the patient in the Trendelenburg position. Stein induced a pneumoperitoneum through the tubes in a series of 1,000 cases. Later in 1935 Stein and Leventhal demonstrated enlarged ovaries by pneumoroentgenography in patients with amenorrhoea, hirsutism and anovulatory cycles. The term gynaecography was first introduced in 1958 by Stein,[35] and the use of gynaecography has been reviewed by Bonham *et al.*[36]

Premedication for this investigation is indicated only in nervous patients. The bowel is cleansed the previous evening and on the morning before the X-ray. The usual sterile precautions are observed. Between 1,000 - 2,000 ml. of nitrous oxide are injected into the peritoneal cavity and X-rays are taken with the tube centred through the coccyx and the patient in the prone position with a head-down tilt of 45°.

Excellent visualization of the pelvic organs is obtained. Side-effects are so minimal as to be almost negligible. The size of the ovaries can be accurately measured, and in obese and nervous patients this can be invaluable as a diagnostic procedure. We feel that this investigation should be done as a routine part of the investigation in a suspected case of hyperthecosis ovarii syndrome. Bimanual palpation of the ovaries does not give a conclusive result, whereas accurate visualization and measurement by pneumoroentgenography is a scientific approach to the problem. A more detailed report on gynaecography will be published at a later date.

Culdoscopy or Peritoneoscopy

These procedures allow for direct visualization of the ovaries: culdoscopy is contraindicated in the presence of vaginal infection, fixed retroversion of the uterus and masses in the pouch of Douglas. It may be done under local, spinal or general anaesthesia. It is felt that these investigations are a refinement which are not indicated if the facilities for good pelvic pneumograms are available.

Hormone Studies

Follicle-stimulating hormone, oestrogens and 17-hydroxycorticosteroids are normal. Androstenedione and etiocholanelone fractions of the 17-ketosteroids may be raised. This investigation is at present unfortunately not available for general use in our laboratories. Pregnandiol estimations are low in the advanced case in which there is anovulation. Pregnanetriol, the breakdown product of 17-α-hydroxyprogesterone, is normal but may be raised if the ovary is stimulated by chorionic gonadotrophin. The basal metabolic rate is normal. Thyroid gland studies may reveal hypothyroidism in those patients in whom this is a cause for the anovulation.

Netter's Dynamic Suppression Test

In principle the adrenal cortex is inhibited by the administration of 3 mg. of dexamethasone orally, daily for 12 days, followed, while the inhibition is still maintained, by stimulation of the ovaries with chorionic gonadotrophin (HCG), 5,000 units on the 6th, 7th and 8th days. Urine is collected on the day before starting the test, and subsequently on the 5th and 12th days of the test.

The androstenedione and etiocholanelone fractions of the 17-ketosteroids rise in spite of the adrenal suppression in the Stein-Leventhal syndrome, while the 17-hydroxysteroids remain normal. This would localize their origin to the ovary after stimulation with HCG. Pregnandiol levels remain low, proving the absence of corpus luteum. The oestrogen levels rise. Initial high levels of 17-ketosteroids not depressed by dexamethasone indicate benign or malignant adrenal tumours, whereas a moderate level which responds by falling to normal or lower levels indicates congenital adrenal hyperplasia. This is a valuable test if properly conducted and if the HCG used is potent enough to really stimulate the ovaries.

Other Investigations

Diagnostic dilatation and curettage is always indicated to reveal the type of endometrium. Endometrial biopsy on the first day of the menses will determine a state of anovulation.

Vaginal smears to assess the presence or absence of cornification may be helpful.

Basal temperature charts are monophasic in the latter stages of the syndrome.

The Place of Wedge Resection

The patient with large polycystic ovaries and the classical clinical picture does not present a problem with regard to the management since bilateral wedge resection will cure the majority of cases. Stein[35] reported that 95% of patients had normal menstruation, and 85% of cases became pregnant following bilateral wedge resection. Bailey[3] found that regular menstruation occurred in 40 out of 50 patients and 15 had full-term pregnancies.

Wedge resection, however, does not give uniformly good results in patients with normal or small ovaries, and it is not uncommon for complete amenorrhoea to follow removal of wedges from small ovaries. The removal of wedges from the ovaries of a mildly myxoedematous hirsute patient with abnormal menstruation, would have obvious disastrous results, unless she was treated for myxoedema at the same time. Cases of mild adrenal hyperplasia are sometimes subjected to the same operation with equally poor results. Again proper pre-operative investigation will eliminate these errors.

If the abnormality is a dysfunction in the hypothalamic-pituitary-ovarian axis, then prolonged cyclical therapy for a period of 6 - 9 months may correct the disorder. (This aspect is under investigation and will be reported later.) This is indicated in patients with the early features of the hyperthecosis ovarii syndrome in their late teens and early twenties in whom the ovaries are still probably normal in size. Wedge resection may be considered subsequently if conservative therapy fails, for once a wedge is removed, it can never be replaced. It is interesting to speculate whether such a patient with normal-sized ovaries following

wedge resection may well have a premature menopause, as the total number of oestrogen-producing follicles will have been greatly reduced.

DISCUSSION

The incidence of the typical syndrome is low. Blewitt[37] found 10 cases in 611 patients (1·6%) complaining primarily of infertility. Stein and Leventhal[1] have only collected 114 cases in 29 years, an average of 3·9 cases per year. Yet the diagnosis is fairly often made and confusion exists with regard to certain cases which do not present all the features of the original syndrome. Roberts and Haines[38] reported on 21 cases at the Chelsea Hospital for Women and divided their patients into 3 groups: (*a*) those with a typical histology and clinical syndrome; (*b*) those with a typical histology and clinical syndrome, but with the presence of a corpus luteum; and (*c*) those with typical histology, but clinical features unlike the classical syndrome. They did not find hyperplasia of the theca in any case, and half of their cases with clinical features of the syndrome were ovulating. In fact, Roberts and Haines[38] doubted that such a well-defined clinical entity really existed.

Further confusion is added by the state of the endometrium. According to Bailey,[4] it may be atrophic in the fully advanced case, or a picture of cystic glandular hyperplasia may occur, as found by Kauffman *et al.*[39]

Acceptance of the broader aspect of the syndrome as postulated by Shippel[12] will eliminate confusing variants of the Stein-Leventhal syndrome, such as normal-sized ovaries, hyperplastic endometria, frequent ovulations, or the other incongruous features mentioned above. The problem becomes much simplified if these cases are classified as falling into one of the subgroups of the hyperthecosis ovarii syndrome of which the Stein-Leventhal syndrome is merely the end-result of thecal, and therefore androgenic, dominance.

In the granulosa-thecal synergistic phase, a predominance of oestrogen will produce hyperplastic endometria. The patient may not yet be hirsute, as the amount of androgen produced is not excessive. As the syndrome advances the granulosal elements atrophy, whereas the thecal cells, having a better blood supply and not being subjected to pressure atrophy, remain viable and are able to continue with the biosynthesis of steroid hormones.

It may be that the synthesis of testosterone from cholesterol occurs in the thecal cell and that the enzymes necessary for the conversion to oestrogens are present or produced in the granulosal cell. With the atrophy of these cells in the latter phases of the syndrome, the metabolism of androgens is brought to a halt in the thecal cell and virilization of the female occurs.[20]

The stranglehold that the thecal cells have on the pituitary prevents further ovulation, until such time as they are removed by wedge resection. This allows the pituitary to regain a normal relationship with the ovary and so ovulation occurs. This concept was put forward by Shippel in 1955.

It is difficult to evaluate the practical results of wedge resection with genetic blocks. If the Stein-Leventhal syndrome is caused by a genetic block previously determined by a chromosomal abnormality, then it should not be cured by a wedge resection, as this operation cannot remove a genetically determined enzymatic abnormality. However, it may ultimately be found that there are many aetiological pathways which end with the clinical picture of the hyperthecosis ovarii syndrome. In other words, the basic aetiology may be diverse, but the end-result is the same.

Furthermore, if the basic pathology is solely within the pituitary, then the syndrome should recur following wedge resection. This was not the case in 75 patients followed up for over 15 years by Stein *et al.*[40]

Whether Shippel's theory is acceptable or not, it would be wise to classify these cases within the hyperthecosis ovarii syndrome to avoid confusion. Prolonged cyclical therapy at an early phase of the hyperthecosis syndrome should then prevent progression with the ultimate development of the frank Stein-Leventhal syndrome.

SUMMARY

1. The Stein-Leventhal syndrome is defined and a chronological review of the pathogenesis is given, bringing into perspective Shippel's hyperthecosis ovarii syndrome.

2. Secretion of LH is thought to be continuous, as in the male, rather than at intermittent or fluctuating levels; the levels of androstenedione and etiocholanelone are raised in this syndrome.

3. The theories of genetic blocks are presented, and chromosomal abnormalities are discussed. A 'masculinized hypothalamus' might be in an abnormal anatomical site.

4. Emphasis is laid on accurate diagnosis before attempting wedge resection. Mild cases of myxoedema, congenital adrenal hyperplasia and virilizing tumours should be differentiated.

5. Pelvic pneumography is a valuable procedure in the diagnosis.

6. Hormone studies of the urine, diagnostic curettage and the dexamethasone suppression test are some of the investigations used.

7. The place of wedge resection is discussed. Removal of wedges from small ovaries may result in complete amenorrhoea.

8. The relationship of the thecal cell to the syndrome is discussed.

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