REVIEW

HIRSUTISM, VIRILISM AND APPARENT VIRILISM AND THEIR GONADAL RELATIONSHIP

PART II

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THE STEIN–LEVENTHAL SYNDROME

Clinical features

This syndrome, both in its clinical and pathophysiological aspects, is one of the most contentious subjects in medicine. The ovarian changes seem to have been first recognized towards the end of the last century (see Goldzieher & Axelrod, 1963) but it derives its name from the gynaecologists who wrote on it in 1935. They described seven cases with polycystic ovaries and amenorrhoea (Stein & Leventhal, 1935). The syndrome consisted of menstrual irregularities terminating in secondary amenorrhoea, infertility and bilaterally enlarged ovaries with typical histological features. Hirsutism was also frequent. Stein has since regarded the condition as being uncommon—he had only operated on 108 cases in 34 years (Stein, 1964). In 29 years the number of cases seen at the Michael Reese Hospital was 114 (Leventhal, 1958). On the other hand, other workers have found the condition, as defined by them, much more common, seeing cases at least at double this rate (Goldzieher & Green, 1962; Taymor, Clark & Sturgis, 1963; F. T. G. Prunty & P. Rhodes, 1966, unpublished observations).

Review of the literature and personal experience reveals the following clinical features. According to Stein (1964) puberty is usually normal, but others find that it may be delayed (Vignalou, Lemarchal & Plouin, 1965). The onset is usually in the second or third decade and the condition, which is commonly progressive, often exists before it is recognized. Previous pregnancies have been reported in up to one-fifth of the patients. Four examples have been noted of affected sisters (Goldzieher & Green, 1962; Jeffcoate, 1964). The following data are based on over 1300 patients, the figures given being approximations (Goldzieher & Axelrod, 1963; Taymor et al. 1963; Stein, 1964; Smith, Steinberger & Perloff, 1965; Vignalou et al. 1965; Prunty & Rhodes, 1966, unpublished observations). Menstrual function is frequently disturbed, amenorrhoea being present in an average of 55% of cases and dysfunctional uterine bleeding, which is often gross, in 28%. A few patients more severely affected, present with primary amenorrhoea (Prunty, Brooks, Dupré, Hutchinson, London, Mills & Rhodes, 1964; Vignalou et al. 1965). Infertility prior to diagnosis is present
in 75% and evidence of ovulation, such as the finding of corpora lutea at operation, biphasic temperature records or the occurrence of dysmenorrhoea, in about 20%. When it occurs ovulation has, of course, a strong tendency to be intermittent. Ovarian pain or tenderness is occasionally present (Stein & Leventhal, 1935).

In addition to this striking disturbance of ovarian reproductive function 70% of patients show evidence of abnormal hirsutism and up to about 20% of virilization. In extreme cases these changes can be severe (Prunty et al. 1964). The emotional disturbance, which frequently derives from these abnormalities, would seem to be insufficiently stressed by most authors.

A clinical feature which, on the other hand, has been stressed is the enlargement of the ovaries (Stein, 1959) but nevertheless they may vary, as would be expected, from normal to several times normal size; there may be a difference in size of the two ovaries. Evidence of enlargement may be obtained from vaginal examination under anaesthesia, but this may detect only 50% of enlarged ovaries (Leventhal, 1958; Stein, 1964). Useful ancillary techniques are gynaecography and, in some hands, culdoscopy. In 70–80% of patients the ovaries are seen to be enlarged at operation (Goldzieher & Green, 1962; Taymor et al. 1963; Smith et al. 1965). The appearance has also been noted to be typical in 80% by Vignalou et al. (1965) and this is in accord with our own experience (over 95%), in which gynaecography has proved to be a most helpful pre-operative adjunct (Prunty & Rhodes, 1966, unpublished observations).

When reported, the vaginal cytology frequently showed evidence of hypo-oestrogenism (Leventhal, 1958; Vignalou et al. 1965) but, on the other hand, the uterus was hypoplastic in only a minority of patients; endometrial hyperplasia was common and the uterus occasionally enlarged. Cervical mucus has been noted to be thick and scanty (Stein, 1964). Attention has been drawn to reports of endometrial carcinoma (Goldzieher & Green, 1962) which tends to occur in the more prolonged cases with the syndrome (Jackson & Dockerty, 1957). Jeffcoate (1964) has particularly stressed the frequent finding of good mammary development in contrast to the less frequently observed mammary atrophy (Stein, Cohen & Elson, 1949; Chamberlain, 1964).

Although not originally emphasized by Stein & Leventhal (1935), obesity has been regarded as a common feature in this syndrome, being noted in about 40% of cases in the large series mentioned above. It is very doubtful if its presence is of diagnostic significance and both Leventhal (1958) and Stein (1964) have not recently been impressed by its importance, the latter now reporting about 10% only of obese cases.

Comments. The reader will be struck, as have many others (Goldzieher & Green, 1962; Goldzieher & Axelrod, 1963), by the notably variable nature of this clinical syndrome. In the first place a syndrome in which infertility was originally defined as an important feature, and in a more general description of which about 20% of patients have been found to give some indication of ovulation having occurred, might well be questioned. It is apparent from the review of Goldzieher & Axelrod (1963) that the frequency of anovulation, for instance, in patients of different series varied from about 20 to 90%. This high variability must indicate a considerable variation in the acceptable diagnostic criteria of different observers. Nevertheless, it is clear
that at some stage of the condition temporary ovulation can occur. For example, a woman might be sterile for 3 yr. of her marriage, have two children in succession, and then revert to several years of sterility. Another example of variation in the interpretation of the syndrome is the extreme difference in the observed incidence of hirsutism in different series, according to the above authors from 17–83%. In our cases it was as high as 95% (Prunty & Rhodes, 1966, unpublished). This no doubt can be accounted for to a large extent by observer bias and interest. Similar variations are apparent in other features of the syndrome. The proposal has therefore been made that the Stein–Leventhal symptomatology represents only a fraction of a more general 'polycystic ovarian disease' (Goldzieher & Axelrod, 1963). It is for this reason that the latter, wider term has been adopted by many, and even the term 'androgenic ovary' was recently introduced (Jeffcoate, 1964; Short, 1965). Doubts have been raised on other occasions concerning the authenticity of the Stein–Leventhal syndrome by, for example, Roberts & Haines (1960), Taymor et al. (1963) and Jeffcoate (1964). Not only do the clinical features of polycystic ovarian disease vary from patient to patient, and from time to time in the same patient, but it will be seen that the biochemical features observed are also varied.

In spite of the criticisms that have been levelled it appears to the author that recognition of the Stein–Leventhal syndrome serves an important clinical purpose in relation to therapy and also forms the basis of continuing pathophysiological research. It may well transpire in the future that the condition has better defined subdivisions.

Treatment

The most widely practised treatment is ovarian wedge resection, following the observation of its success by Stein & Leventhal (1935). According to Leventhal & Scrommegna (1963) the operation originally followed the observation that ovarian biopsy resulted in improvement. As Stein & Leventhal (1935) recorded, it is not infrequently observed that menstruation occurs within a few days. This bleeding is not merely due to the removal of a corpus luteum. The reason for the effectiveness of wedge resection remains a mystery, although several theories have been advanced. These are, in the main, mechanical and hormonal. It has been suggested that compression permits ovulation to occur (Stein et al. 1949), but it is now known from animal experiments that capsular restriction in itself is insufficient to prevent this (see Goldzieher & Green, 1962). The hormonal theories involve the notion that ovarian steroid production is altered or reduced, possibly by induction of follicular cellular changes and luteinization; this then results in a normal cyclical release of gonadotrophins followed by normal ovarian stimulation (Short & London, 1961; Crooke, Butt, Palmer, Morris, Edwards, Taylor & Short, 1963; Goldzieher & Axelrod, 1963). There is, however, no explanation of the precise way in which these changes are initially induced. Jeffcoate (1964) has gone as far as suggesting that they may be initiated by stimuli to the cerebral cortex.

The clinical indications for wedge resection are becoming well defined, being essentially the promotion of fertility and, less frequently, the need to restore normal menstrual function for the purpose of ameliorating emotional disturbance (Leventhal, 1958; Prunty & Rhodes, 1966, unpublished observations).
The significance of the specificity of the operative results has been justly criticized by Jeffcoate (1964) on the grounds of the absence of controlled observations. Nevertheless, according to the analysis of Goldzieher & Green (1962) regular cycles occurred in 80% of 447 cases, pregnancy in 63% of 640, and decreased hirsuties in 16% of 205. Again there is great variation in these figures, post-operative evidence of ovulation being as low as 6% in some series. However, it seems that in well selected cases the correction of menstrual disturbance and pregnancy rates are in the highest range (Taymor et al. 1963; Stein, 1964; Vignalou et al. 1965; Prunty & Rhodes, 1966, unpublished observations).

Stein (1964) expresses the view that operation in teenage is advisable to prevent sterility, hirsutism and emotional disturbance. On the other hand, in time post-operative relapse sometimes occurs (Vignalou et al. 1965; Prunty & Rhodes, 1966, unpublished observations) and also pregnancy is most likely to occur within a few months of operation, so that prophylactic wedge resection would seem undesirable. Furthermore, in spite of claims to the contrary which are difficult to evaluate, the author's experience, in agreement with Goldzieher (1964) and Shearman & Cox (1965), is that no significant change in hirsuties is induced, even after subtotal ovariectomy (Prunty et al. 1964).

Some events following pregnancy in these patients are of special interest. A high rate of abortions or still births and an abnormally high incidence of twins have been commented upon by Stein (1964). Foetal virilization has not been noted.

Allen & Woolf (1959) claimed that medullary resection of the ovary aimed at reduction of luteinized stromal cells and Leydig cells produced results comparable to wedge resection. Jeffcoate (1964) is notable in his advocacy of conservative treatment, including weight reduction, and claims results, at least as good as those from surgery, by such means. This claim seems clearly related to his somewhat wide diagnostic criteria. It is not an uncommon experience that a number of women with obesity and secondary amenorrhoea will regain normal menstrual function after reduction of their weight.

The effects of some other methods of treatment that have been tried, namely the administration of cortisone, clomiphene and of gonadotrophins, will be discussed below, but it will become clear that wedge resection retains an important place.

The pathological features of the polycystic ovary

The histological pattern observed in ovaries taken from cases of the Stein–Leventhal syndrome diagnosed under the strictest criteria have recently been restated (Leventhal, 1958; Leventhal & Scommegna, 1963). In the classical, well-advanced case the ovaries are enlarged with a pearly white thickened tunica (oyster or sclerocystic ovaries); below this, and sometimes bulging into it are slightly enlarged cystic follicles. The granulosa cell layers are said to be thin with thickening of the theca interna, the latter showing histological evidence of hyperactivity including luteinization and numerous mitotic figures. The ovaries are markedly vascular. These findings are said to be pathognomonic of the condition but, although they must occur in the properly defined case according to Stein and Leventhal, the appearances of the ovary alone are insufficient guide for making the diagnosis (Stein, 1959).
Virilization in the female

This then is the supposedly typical picture, around which controversy exists. Recently studies with the electron microscope and histochemistry have supplemented classical techniques (Dokumov & Dashev, 1963; Green & Goldzieher, 1965; Pesonen, Timonen & Niemi, 1965). There is wide agreement that the histological features can vary, not only between ovaries from the same patient, but within a single ovary, and observer variation has been found to be large (Goldzieher & Green, 1962). In the observations of Jones (1962) and of Green & Goldzieher (1965) comparisons were made with normal ovaries, and in those of Gemzell, Tillinger & Westman (1959) and of Roberts & Haines (1960) with ovaries from patients other than with the Stein–Leventhal syndrome.

With regard to the capsule of the ovary, the comments have been made that there is variation in different parts (Gemzell et al. 1959) and that the thickness is difficult to evaluate. Some agree that capsule thickening is always present (Shippe1, 1955; Goldzieher & Green, 1962; Taymor et al. 1963) and that this is due to fibrosis and increase of collagen (Green & Goldzieher, 1965). Others contradict this view, finding that thickening is not always present (Plate, 1958); Jones (1962) agreed with the latter view after making careful measurements in several cases of our series and in some of whom Short & London (1961) made their classical observations on steroid abnormalities in the cyst fluid.

The occurrence of small subcapsular follicular cysts appears to receive universal acceptance, but the morphology is thought to be normal by Green & Goldzieher (1965) and commensurate with the formation of atretic follicles, the number of which is increased. But it is concerning the theca that the greatest disagreement exists. This tissue is of special interest, for it is widely thought to be the source of abnormal androgen production. Shippe1 (1955) strongly believes in the importance of 'thecal dominance', and hyperplasia with evidence of luteinization in some follicles was also found by others (e.g. Plate, 1958; Gemzell et al. 1959; Jones, 1962; Taymor et al. 1963). The observations of Jones (1962) were carefully made, the follicles in each case in which the theca was widest being selected and the number of cell layers in the theca interna counted. Seventeen cases were examined, the mean thickness being 22 cells compared with ten in normal ovaries. On the other hand, Goldzieher & Green (1962) and Green & Goldzieher (1965) have vehemently opposed the occurrence of hyperthecosis, claiming that their observations only showed thecal changes that were entirely compatible with follicular atresia. They felt that claims of apparent thecal hyperactivity are based on examination of insufficient material from a particular ovary, coupled with the production of artifacts in its preparation. To date these observers seem to hold a minority view, although receiving support from Roberts & Haines (1960) and Chamberlain (1964). Netter (1961) believes that thecal hyperplasia seen in operation specimens may well have been induced if chorionic gonadotrophin has been used for test purposes.

The study of thecal cells by Pesonen et al. (1965) showed them to be sudanophilic and to be normally active with respect to esterase, DNP-diaphorase and 3β-hydroxysteroid dehydrogenase, whilst in this and another study (Dokumov & Dashev, 1963) phosphatase activity appeared to be increased. In addition to the thecal changes it has been suggested that hyperplasia of the stromal cells, which may be luteinized, occurs in some ovaries (Gemzell et al. 1959; Green & Goldzieher, 1965).
It is generally agreed that corpora lutea (and corpora albicantia) occur in these polycystic ovaries, a mean rate of 22% with very wide variation, having been calculated by Goldzieher & Axelrod (1963). Thus Jones (1962) observed a rate of 6% in his series and Gemzell et al. (1959) 35% in theirs. Thus ovulation has almost certainly occurred on a significant number of occasions in these cases.

There are occasional reports of the coincidence of ovarian tumours in patients with the Stein–Leventhal syndrome. Tumours reported are: two hilar cell tumours (Allen & Woolf, 1959; Corral-Gallardo, Acevedo, de Salazar, Loria & Goldzieher, 1966), two arrhenoblastomas (Massachusetts General Hospital Case Records, 1954; Vague, Simonin, Temime-Morhange, Codaccinoni, Lieutaud, Garrigues, Berthet, Ayme & Cadet, 1962) and a granulosa cell tumour (Prunty et al. 1964).

Hormonal abnormalities

Excretion of gonadotrophins

Since, in the opinion of many, one of the basic defects in the Stein–Leventhal syndrome is a disturbance in the secretion of gonadotrophins, review of the data on this point is important. Assays of total gonadotrophin excretion give little due to the secretion of the constituents, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), but those investigations that have been done have not revealed any abnormality, even when acceptable quantitative assays have been performed (Prunty, Brooks & Mattingly, 1958; Taymor & Barnard, 1962; Charles, Barr, Bell, Brown, Fotherby & Loraine, 1963).

That LH excretion was elevated was first suggested by Keettel, Bradbury & Stoddard (1957) who, observing proliferation of the theca in the rat ovary on a qualitative basis, concluded that excess LH occurred in ten out of eleven patients. Later Ingersoll & McArthur (1959), using the rat ventral prostate assay, found irregularly fluctuating levels, with a mean value above that of the normal female. Taymor & Barnard (1962) went into the matter in greater detail with careful assays, but these suffered from the disadvantage that parallelism with the standard response was not established. They also found that LH excretion fluctuated and was raised in half their cases. They attempted to distinguish, on the basis of 17-oxosteroid excretion, patients with and without evidence of adrenal hyperplasia. The results in the two groups were similar. They did, however, find a correlation of LH excretion with duration of anovulation and thus postulated that the rise in LH was a secondary effect arising from ovarian progesterone deficiency. Soffer & Fogel (1964) claimed that a substance they had obtained from human urine, with an inhibitory action on LH activity, was present in reduced amount in Stein–Leventhal patients. The existence of such a substance is at present controversial (Hahn & Albert, 1965; Soffer, Fogel & Rudavsky, 1966; Krishnamurti & Bell, 1967).

Data on FSH excretion are also scanty. Using the ‘augmentation’ technique, Butt, Crooke, Cunningham & Palmer (1963) found normal excretion in four patients.

The present data on gonadotrophin excretion cannot therefore be regarded as fully adequate. It may be that there is an increased excretion of LH but further observations are clearly required and observations on the response to treatment would also be valuable.
Steroid metabolism

Steroids in the ovary and their biosynthesis in vitro. In a search for abnormal androgen production in the Stein–Leventhal syndrome, the ovary must be highly suspect. It has long been known that the ovary is the site of oestrogen and progesterone synthesis, but it was not until 1958 that a C-19 steroid, androstenedione, was first demonstrated in the human ovary (Zander, 1958). Short & London (1961) then showed that follicular fluid obtained from patients of the author contained abnormally large amounts of androstenedione and reduced amounts of oestradiol, oestrone and progesterone. These findings were confirmed and extended by Short (1962), Giorgi (1963) and Mahajan, Shah & Eik-Nes (1963). It was, however, noted that the clinical, pathological and biochemical correlations were not good. The results suggested that there might, in general, be a deficiency in the rate of conversion of androstenedione to oestrogen in these ovaries. It was later observed that dehydroepiandrosterone could be present in follicular fluid (Short, 1965).

Other workers were isolating steroids from polycystic ovarian tissue with similar results (Mahesh & Greenblatt, 1964a). It was clearly established that some polycystic ovaries contained excessive quantities of dehydroepiandrosterone (Mahesh, 1965) and, perhaps surprisingly, Kecskés, Mutschler, Thán & Farkas (1962) found unusually large quantities of oestrogen in their specimens.

Meanwhile Lanthier & Sandor (1960) had initiated the study of biosynthesis of androgens and oestrogens by polycystic ovarian tissue in vitro. They found that progesterone and pregnenolone could both be converted to androstenedione, the latter the more readily, and that androstenedione could be converted to testosterone (Sandor & Lanthier, 1960). There is general agreement that androstenedione and testosterone are synthesized in polycystic ovaries in increased amounts, originally from acetate, by way of progesterone (Warren & Salhanick, 1961; Leon, Neves & Castro & Dorfman, 1962; Dorfman, 1963; O'Donnell & MacArthur, 1965; Brooks, 1967). In addition it is clear that dehydroepiandrosterone also accumulates to a greater or lesser extent when pregnenolone is used as substrate. It has been suggested that this is due to a deficiency of 3β-hydroxydehydrogenase required for the conversion of dehydroepiandrosterone in the pathway pregnenolone → 17-hydroxypregnenolone → dehydroepiandrosterone → androstenedione → testosterone (Axelrod & Goldzieher, 1962; Mahesh & Greenblatt, 1964a).

Recent evidence indicates that the synthesis of androgens predominates in the thecal and stromal elements, that possibly the dehydroepiandrosterone pathway is the major one, at least in some ovaries, and that this androgen synthesis is excessive in polycystic ovaries (Rice & Savard, 1966; Ryan & Petro, 1966). Still further work on the role of the ovarian components is required however, for Pesonen et al. (1965) observed that the presence of tissue from the corpus luteum or corpus albicans seemed to be required for converting dehydroepiandrosterone to androstenedione.

Whilst there is general agreement that polycystic ovarian tissue synthesizes more C-19 steroids than normal, unanimity has not been reached, not only on the ovarian oestrogen content, but also on the amount of oestrogen synthesized. No oestrogen was found in most of the specimens of Axelrod & Goldzieher (1962). Mahesh & Greenblatt (1964a) found poor conversion of dehydroepiandrosterone to oestrogens
in ovaries rich in this steroid or poor conversion of androstenedione to oestrogen in ovaries in which androstenedione predominated. Some synthesis of oestradiol-17β and of oestrone was also observed, for example, in the experiments of Kase (1964) and Rice & Savard (1966). Axelrod & Goldzieher (1962) agreed that the relative failure of oestrogen synthesis might be due to a 3β-hydroxydehydrogenase deficiency causing a lack of conversion of dehydroepiandrosterone to androstenedione in one type, and suggested a deficiency of aromatization of ring A in the conversion of androstenedione to oestrogens in the other. The necessity for postulating such enzymatic deficiencies has now however been questioned. Kase (1964) believes that the increased C-19 steroid production is a consequence of increase in mass of synthesizing tissue, which, according to Rice & Savard (1966), is of thecal origin and likely to be under continuous gonadotrophin stimulation.

Apart from the variation in behaviour of tissue from different ovaries, the results in vitro generally correlate poorly with the clinical circumstances and this doubtless may be due to fluctuation from time to time of events in vivo.

**Urinary steroid excretion.** Much interest has centred around the metabolism of C-19 steroids for the reason that nearly every investigator agrees that the adrenal cortex may make a contribution to the clinical abnormalities, at least in a proportion of cases. It was therefore hoped that changes in steroid metabolism would help to elucidate this problem but in practice the results have frequently been equivocal. The excretion of 17-OS is higher than normal, up to about 30 mg./day, in about one-third of cases (Brooks & Prunty, 1960; Goldzieher & Axelrod, 1962; review of Goldzieher & Green, 1962). Here once again the results of different observers vary widely and the correlations with clinical severity are poor. The component C-19 steroids have also been studied (see Lanthier (1960) for review until that time), and showed variation between patients and in some individuals from day to day. Although the steroid pattern is often normal it is agreed that in some patients there is increased excretion of androsterone, etiocholanolone, dehydroepiandrosterone and, to a lesser extent, components of the 11-oxy-17-OS (Brooks & Prunty, 1960; Lanthier, 1960; Goldzieher & Axelrod, 1962; Goldzieher & Green, 1962; Mauvais-Jarvis & Baulieu, 1962; Baulieu, Mauvais-Jarvis & Corpéchot, 1963; Cassano, Conti, Forchielli, Capone & Sorcini, 1964; Mahesh, 1965). In the light of present knowledge the only steroids to which an adrenocortical origin can be ascribed are in the 11-oxy fraction, elevations of which are the least convincing. It will be seen, however, that the effects of adrenal suppression on the 11-deoxy fraction may provide further information concerning an adrenal in contrast to an ovarian component.

In all of six patients urinary excretion of testosterone glucuronide was elevated (Futterweit, McNiven, Guerra-Garcia, Gibree, Drosdowsky, Siegel, Soffer, Rosenthal & Dorfman, 1964; Ibayashi, Nakamura, Murawaka, Uchikawa, Tanioka & Nakao, 1964; Lim & Dingman, 1965).

Certain importance also is attached to the urinary excretion of oestrogens, especially in the light of the suggested deficiency of oestrogen biosynthesis. A number of reliable assays of the excretion of oestrone, oestradiol and oestriol are now available and show that, apart from isolated instances, these are essentially normal for the follicular phase (Brown & Matthew, 1962; Charles et al. 1963; Giorgi, 1963; Cassano et al. 1964; Prunty et al. 1964; Shearman & Cox, 1965, 1966).
Virilization in the female

Progestrone metabolism has not been studied in detail; the use of progesterone as a substrate in vitro and its occurrence in low concentration in cyst fluid have been described. The absence of gross metabolic abnormalities is suggested by the finding of normal pregnanediol excretion during the follicular phase (Shearman & Cox, 1966).

Patients with the Stein–Leventhal syndrome often excrete increased quantities of pregnanetriolone (Leventhal & Scommegna, 1963; Shearman & Cox, 1966) and, according to some, of $\Delta^5$-pregnenetriol (Stern & Barwell, 1963; Shearman & Cox, 1966) but not according to others (Wilson, Lipssett & Ryan, 1961; Mahesh & Greenblatt, 1964a). It has been proposed by Shearman & Cox (1966) that $\Delta^5$-pregnenetriol originates from increased ovarian synthesis of 17-hydroxyprogrenolone, and that pregnanetriolone, because of the presence of an 11-oxo group, originates from the adrenal, possibly from 21-deoxycortisol. There seems no reason to suppose that the adrenal may not contribute to the $\Delta^5$-pregnenetriol from its 17-hydroxyprogrenolone (Prunty, 1964). In any event it remains difficult to explain the normal excretion of pregnanetriol (Brooks & Prunty, 1960).

The excretion of metabolites of cortisol is most often within normal limits (Brooks & Prunty, 1960; London & Prunty, 1960; Mahesh, Greenblatt, Aydar, Roy, Puebla & Ellegood, 1964; Shearman & Cox, 1966). There are occasional high values (Chamberlain, 1964) and these may perhaps be associated with obesity (Giorgi, 1963) or ‘adrenocortical hyperfunction’ (Goldzieher & Axelrod, 1962). It would seem that insufficient quantities of $\Delta^5$-pregnenetriol or pregnanetriolone are likely to be excreted to raise significantly 17-oxygenic steroids or 17-hydroxycorticosteroids determined by oxidative techniques.

Steroids in blood, their secretion and production. In theory the best evidence of the secretion of a particular steroid by the ovary is its concentration in ovarian vein blood but such specimens are not easy to obtain in women and, in any case, the ovarian veins do not always drain only the ovary. Hence steroid secretion rates cannot be determined by this method. The concentrations of androstenedione and/or dehydroepiandrosterone are elevated, the ratio of C–19 steroid to oestrogen being high (Mahesh, 1965). Testosterone concentration has been found to be considerably greater than in peripheral blood (Goldfien & Jones, 1966; Lloyd, Lobotsky, Segre, Kobayashi, Taymor & Batt, 1966).

In peripheral blood, assays of total 17-oxygenic steroids (17-OS) and dehydroepiandrosterone and androsterone sulphates appear to show that these steroids are elevated (Seeman & Saracino, 1961; Mahesh & Greenblatt, 1964a). The level of the last of these can be higher than in ovarian vein blood (Baulieu et al. 1963). Testosterone is above normal in most, but not all, patients (Dorfman, Forchielli & Gut, 1963; Cassano et al. 1964; Dignam, Pion, Lamb & Simmer, 1964; French, Baggett, Van Wyk, Talbert, Hubbard, Johnston, Weaver, Forchielli, Rao & Sarda, 1965; Korenman, Kirschner & Lipshtet, 1965; Lloyd et al. 1966; Prunty & Lim, 1966; Surace, Luisi, Moneta, Marescotti & Polvani, 1966). Lloyd et al. (1966) emphasized the poor correlation of plasma testosterone with clinical conditions or 17-OS excretion.

The rate of testosterone production was raised in two of three patients in one study (Prunty, 1966), but not in another (Korenman et al. 1965). During dexamethasone suppression it was also elevated in six out of 11 patients (Prunty, 1966) and dehydroepiandrosterone and androstenedione plus testosterone productions were
high in the majority of the patients of Macdonald, Vande Wiele & Lieberman (1963). In three patients with normal testosterone production the whole of this appeared to originate from other C-19 steroids, predominantly androstenedione (Brooks, Jeffcoate, London, Prunty & Smith, 1966).

The concentration of oestrogens in ovarian vein blood was found to be normal (Mahesh, 1965), but in spite of this and the normal urinary excretion, Ichii, Forchielli, Perloff & Dorfman (1963) observed slightly elevated peripheral concentrations although French et al. (1965) for the most part did not do so. The production rate of oestrogen (Mahesh, 1965; Brooks et al. 1966; Goering & Herrmann, 1966) was essentially normal (Goering, Matsuda & Herrmann, 1965).

*The adrenocortical contribution in the Stein–Leventhal syndrome*

It has already been suggested that, in some cases at least of the Stein–Leventhal syndrome, there is an adrenocortical abnormality in steroid metabolism. The problem of a subtle interplay between the ovaries and the adrenal cortex has been realized for many years by experimental workers (Parkes, 1945) and by numerous clinical observers. An androgenic potential in the ovary was shown by Deanesly (1938) with transplants to be associated with the theca interna, and a physiological androgenic function in relation to ovulation was proposed by Gaarenstroom & de Jongh (1946). In a review Parkes (1950) realized that pathological androgenic activity of the ovary, like that of the adrenal cortex, may be regarded as the expression of a latent potentiality rather than as a new separate endocrine activity. Some good evidence that the ovary is a source of abnormal androgen production has also been reviewed above. What is the evidence that the adrenal is involved in the Stein–Leventhal syndrome? This problem may be related to histological, therapeutic and biochemical observations.

*Histological evidence*

This could be derived from ovarian changes in adrenal disease or adrenal changes in ovarian disease. With respect to the former, statements are sometimes made (e.g. Goldzieher & Green, 1962; Goldzieher, 1964) implying that in virilizing adrenal disease, and other conditions, ovaries of the Stein–Leventhal type are found. A description of the occurrence of polycystic ovaries in congenital adrenal hyperplasia can be found in the *Massachusetts General Hospital Case Records* (1952), but doubts were expressed by the observers as to the true nature of the ovarian changes. An active theca has also been described in three cases by Goldberg (1954) and Fehér, Györy, Less & László (1958). Apart from the reports of the occasional occurrence of an active theca, or of hilar cell proliferation (Landing, 1954), the changes do not otherwise suggest a convincing similarity to polycystic ovaries as described in the section above (Blackman, 1946; Goldberg, 1954; Jones & Jones, 1954; Morris & Scully, 1958; Perloff, Channick, Hadd & Nodine, 1958; Milcou, Pitis, Stanescu, Serban, Leiba, Nedelniuc & Opran, 1960). The two patients of Geist & Gaines (1942), which are sometimes quoted in this connexion, appear to have had polycystic ovaries but there was no anatomical or other good evidence of adrenal disorder. In Cushing’s syndrome the ovaries are not large and have a few small cortical cysts (Iannaccone, Gabrilove, Sohval & Soffer, 1959). Hence, the occurrence of polycystic ovaries with adrenal hyperplasia remains not proven.
The question of adrenal changes in the Stein–Leventhal syndrome remains uncertain. Leventhal (1962) found no adrenocortical hyperplasia in two biopsies in the Stein–Leventhal syndrome, and Benedict, Cohen, Cope & Scully (1962), likewise, were not sure of adrenal hyperplasia. Hence the occurrence of adrenal hyperplasia in the Stein–Leventhal syndrome is also not proven. Its absence does not necessarily imply that there is no increase of adrenal androgen production.

**Therapeutic studies: effect of corticosteroids**

The successful use of cortisone in treating congenital adrenal hyperplasia prompted its trial in hirsute patients with menstrual disturbance. Reports are difficult to interpret as there is little indication of the number of true Stein–Leventhal patients included, and controlled studies are lacking. Greenblatt, Barfield & Lampros (1956) observed improvement in ovarian function and in hirsutism in a large proportion of patients. Occasionally ovulation continued after treatment ceased, but this might sometimes be expected to occur spontaneously. Jeffries & Levy (1959) reported similar results in 'ovarian dysfunction', irrespective of the initial level of 17-OS, which was depressed by treatment in most cases. Smith et al. (1965) thought that prednisone treatment compared favourably with wedge resection but Greenblatt et al. (1956) and Ferriman, Purdie & Tindall (1961) noted many abortions when Stein–Leventhal patients became pregnant. The use of corticosteroids (de Mowbray, Spence, Medvei & Robinson, 1959), even combined with ethinyl oestradiol (Mattingly, Mills & Prunty, 1960), was not felt justifiable as far as the responses in hirsutism were concerned.

Sometimes it is found that corticosteroid treatment fails but wedge resection succeeds (Taymor et al. 1963). Conversely the situation may be reversed (Shearman & Cox, 1965) and interpreted to indicate an adrenal component in the symptomatology (Greenblatt, 1958). The therapeutic evidence for adrenal hyperactivity might therefore seem moderately strong, but it should be borne in mind that corticosteroids can increase gonadotrophin and FSH excretion (see Barlow, 1964; Shearman & Cox, 1966) so that an indirect action on the ovary is also possible.

From the practical point of view it appears that to maintain normal menstrual function long-term corticosteroid therapy is necessary and, in view of the possible side effects, less desirable than wedge resection.

**Biochemical observations: adrenal suppression and stimulation**

Since in the literature on the Stein–Leventhal syndrome the term 'adrenal hyperplasia' is frequently loosely used it would be valuable also to understand what is sometimes meant by this expression in biochemical terms. It does not include patients with true congenital adrenal hyperplasia (Prunty et al. 1958; Brooks & Prunty, 1960); according to Leventhal (1958) and Taymor et al. (1963) it is present on the sole criterion of elevated 17-OS excretion, a concept supported by Stein (1959); Jones & Jones (1954) accept increased excretion of 17-OS when the ovaries are of normal size, and a favourable response to cortisone treatment as criteria.

The presence of adrenal hyperplasia is also generally implied when the 'adreno-genital syndrome' is diagnosed (Prunty, 1964b). But Beck, Grayzel, Young & Kupperman (1966), for example, distinguish this entity from the Stein–Leventhal syndrome.
too, merely by the presence of raised 17-OS which are readily suppressed by corticosteroids.

In the author's view the above criteria are inadequate for the diagnosis of adrenal hyperactivity, which might or might not be accompanied by adrenal hyperplasia. It is of some interest that Cassano et al. (1964) did not detect adrenal enlargement by pneumography, admittedly an insensitive technique, in their cases with polycystic ovaries. More detailed investigation of patients in the above categories might reveal some with mild post-pubertal congenital adrenal hyperplasia, and others with the Stein–Leventhal syndrome.

Adrenocortical suppression. There is now an extensive literature on attempts to provide evidence of an adrenal component by suppression and stimulation tests. For the former various corticosteroids including prednisone, and recently dexamethasone in varying dosage, have been used. Suppression of the various cortisol metabolites is usual, but it is the metabolism of C-19 steroids that is of special interest.

Although 17-OS excretion is depressed, irrespective of the initial level, in many patients (see Goldzieher & Green, 1962; Goldzieher & Axelrod, 1963; Lloyd et al. 1966) this alone does not indicate whether normal or abnormal adrenal function is involved, but fractionation studies throw some light on this. Thus Baulieu et al. (1963) observed that dexamethasone suppressed 11-oxy 17-OS to a greater extent than 11-deoxy 17-OS, suggesting that much of the latter originated from the ovary. Mahesh et al. (1964) found two kinds of Stein–Leventhal patients; one kind showing good suppression of 11-deoxy 17-OS (Lanthier, 1960; Netter, Jayle, Lambert & Mauvais-Jarvis, 1960; Jayle, Scholler, Mauvais-Jarvis & Szper, 1962) and the other poor suppression. The latter showed marked suppression when given additional stilboestrol, further suggesting that in this group the 11-deoxy 17-OS were mainly of ovarian origin.

Suppression of plasma testosterone is variable, occasionally being fairly good, and suggesting a partly adrenal origin (Korenman et al. 1965; Lloyd et al. 1966; Prunty, 1966; Surace et al. 1966), but in some cases depression was poor in spite of good adrenal suppression as shown by a fall in the plasma level of dehydroepiandrosterone and androsterone sulphates (Dignam et al. 1964). Dexamethasone suppressed the rate of testosterone production (Korenman et al. 1965; Prunty, 1966); norethindrone acetate given with dexamethasone caused lower production rates of dehydroepiandrosterone and androstenedione plus testosterone than those when dexamethasone was given alone, presumably substantiating an ovarian contribution (Macdonald et al. 1963).

An apparently paradoxical finding is the increased excretion of oestriol in response to dexamethasone administration. This may be due to an increased secretion of gonadotrophin (Butt et al. 1963; Crooke et al. 1963). The phenomenon was not observed by Mahesh & Greenblatt (1964a).

Further evidence of adrenal involvement has been provided by the observation that, in biosynthetic experiments in vitro there is a deficiency of 3β-hydroxydehydrogenase in both adrenal cortex and ovary (Axelrod, Goldzieher & Ross, 1965).

Stimulation with corticotrophin (ACTH). It was thought that evidence of adrenal involvement might also be obtained by hyper-responsiveness to ACTH stimulation. Brooks & Prunty (1960) and Lanthier (1960) observed a somewhat greater response
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of 17-OS than normal with a tendency to a predominance of 11-deoxy 17-OS. Lloyd et al. (1966) did not confirm this finding but they gave ACTH for a shorter period. ACTH also induced some increase of pregnanetriol excretion (Brooks & Prunty, 1960).

Plasma testosterone levels have in general shown an unimpressive response to ACTH (Prunty & Lim, 1966; Surace et al. 1966) as have also testosterone production rates (Korenman et al. 1965; Lloyd et al. 1966).

Stimulation with gonadotrophins

The formation of big follicular cysts in Stein–Leventhal ovaries was first noted in response to porcine or ovine FSH (Keettel et al. 1957). Later, human pituitary (HP) FSH was found to produce ovarian enlargement and ovulation (Gemzell, Diczfalussy & Tillinger, 1960). Subsequently FSH and chorionic gonadotrophin (CG) have been given sequentially, with (Crooke et al. 1963; Mahesh & Greenblatt, 1964b) or without (Vande Wiele & Turksoy, 1965; Goering & Herrmann, 1966) corticosteroid suppression. The FSH preparations derived either from human pituitaries or from post-menopausal urine (HMG). In 22 cases ovulation was frequently induced, occasionally also when HMG was given alone (Vande Wiele & Turksoy, 1965), and several pregnancies occurred but the abortion rate was high. Current opinion is that considerable risk is entailed in the treatment of Stein–Leventhal syndrome with gonadotrophins (B. Lunenfeld, 1966, personal communication; R. P. Shearman, 1966, personal communication).

There is abundant evidence that human FSH, both with and without CG, can cause profound ovarian stimulation, but the data on the detailed effects produced both in vivo and in vitro are conflicting. This may be partly due to the fact that all FSH preparations to date contain varying proportions of LH. Biopsy studies soon after injections of HP-FSH and CG have shown multiple follicular cysts and intracystic haemorrhage (Crooke et al. 1963; Short, 1965). In the cyst fluid there was more progesterone and oestradiol-17β, and less androstenedione, than in the fluid of untreated patients.

In vitro, HMG increased the biosynthesis of testosterone from acetate and HP-FSH, that of androstenedione from progesterone, but oestrogen production was not increased (O’Donnell & MacArthur, 1965). This has been partly confirmed by Rice & Savard (1966). They obtained variable results and observed that the effects of gonadotrophin were difficult to interpret. Mahesh (1965) showed that, in vivo, HP-FSH did not raise the ratio of oestrogen to androgen in the ovarian vein blood in the Stein–Leventhal syndrome although it did so in normal women.

One preparation of HP-FSH with dexamethasone, but not another, raised the rate of testosterone production whilst HMG alone did not raise the plasma testosterone level until CG was also given (Brooks et al. 1966; Prunty & Lim, 1966, unpublished observations). However, CG alone, or with dexamethasone, produced a variable rise of plasma testosterone (Dignam et al. 1964; Korenman et al. 1965; Lloyd et al. 1966; Surace et al. 1966); moreover the concentrations of androsterone and dehydroepiandrosterone conjugates (Dignam et al. 1964), of androsterone only, increased (Baulieu et al. 1963). Goering & Herrmann (1966) found oestrogen production rates rose in response to HMG in combination with CG.
In some instances urinary 17-OS excretion rose with pregnant mare serum gonadotrophin (PMS) (Koettel et al. 1957); HP-FSH given with (Prunty, 1966) and without (Gemzell et al. 1960; Gemzell, 1965) dexamethasone can also have this effect. Mahesh & Greenblatt (1964b) using HP-FSH with dexamethasone found an increase of 11-deoxy 17-OS in patients who showed poor suppression with the corticosteroid. On the other hand, CG alone also increased this steroid fraction (Lanthier, 1960) or with dexamethasone produced a pronounced rise of 17-OS (Lloyd et al. 1966) due to increase of the androsterone and etiocholanolone components (Jayle et al. 1962; Mauvais-Jarvis & Baulieu, 1962; Baulieu et al. 1963). There is a solitary observation of an increase of 17-OS with CG after oophorectomy was performed, suggesting the possibility of an adrenal contribution to the response in the Stein–Leventhal syndrome (Perloff & Jackson, 1963).

Pregnanetriol and pregnenetriol excretions have been reported to increase after PMS (Shearman & Cox, 1965) and with HP-FSH given with dexamethasone (Jayle et al. 1962; Baulieu et al. 1963; Brooks et al. 1966) but Lanthier & Sandor (1964) were unable to confirm this.

Urinary oestrogen excretion was increased by HP-FSH (Gemzell et al. 1960) and also when dexamethasone was given (Crooke et al. 1963). Although Mahesh & Greenblatt (1964b) found a variable increase under the latter regime, Shearman & Cox (1966) noted Stein–Leventhal patients to be over-responsive to FSH given alone. Cassano et al. (1964) noted that oestrogen excretion, particularly oestradiol, was very sensitive to the administration of CG.

In summary then, leaving some anomalous features aside, the overall effects of gonadotrophins would appear to be as follows. Increased biosynthesis of androgen is induced by FSH resulting in increased excretion of 11-deoxy 17-OS. Although oestrogen synthesis was not increased in vivo, urinary excretion in vivo has been demonstrated, as has increase of pregnanetriol and of pregnenetriol, presumably by way of the biosynthetic intermediates 17-hydroxyprogesterone and 17-hydroxyprogrenolone.

On the other hand, plasma testosterone and 11-deoxy C-19 steroid levels increase in response to CG, with increased excretion of 11-deoxy 17-OS. There also appears to be increased excretion of pregnanetriol and pregnanediol, the latter presumably derived from progesterone.

The effects of wedge resection

The therapeutic results of wedge resection are unrelated to the level of 17-OS excretion or to its suppressibility with corticosteroids. The operation causes a fall in 17-OS excretion in about half the cases but quite frequently this effect is transitory (Goldzieher & Axelrod, 1962; Goldzieher & Green, 1962; Shearman & Cox, 1965).

Zander, West & Ober (1962), like others, observed that ovarian tissue removed after wedge resection converted [14C]progesterone to androstenedione to a greater extent than normal tissue. No difference was, however, observed with tissue obtained by biopsy at a later time, so that the effect of the resection was apparently limited to that of removal of some of the functioning tissue.

Plasma 17-OS levels have been found to fall for periods up to 2 months (Seeman & Saracino, 1961) and the testosterone level fell consistently (Dorffman, 1963; Prunty &
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Lim, 1966, unpublished; Surace et al. (1966). Lloyd et al. (1966) found that this fall continued up to 21 months postoperatively, but it was not correlated with therapeutic success. The rates of production of testosterone and androstenedione fell and oestrogen production was slightly increased (Brooks et al. 1966; Prunty, 1966).

When it occurs, the overall fall in 17-OS excretion is due to a decrease of the 11-deoxy rather than of 11-oxo 17-OS (Lanthier, 1960; Baulieu et al. 1963; Mahesh et al. 1964). The normal cyclical behaviour of pregnanediol excretion was restored and some increase in pregnanetriol excretion was apparent (Lanthier & Sandor, 1964). Persistence of abnormal excretion of pregnanetriolone has been noted (Shearman & Cox, 1965).

The effects of clomiphene

The first findings were that clomiphene citrate (1-\([p-(\beta\text{-diethylaminoethoxy})\text{-phenyl}]-1,2\text{-diphenyl}-2\text{-chlorethylene}\) had anti-ovulatory properties. It was surprising, therefore, to find that in women it stimulated ovulation (Greenblatt, Barfield, Jungck & Ray, 1961). Many reports of ovulation and of pregnancies following its use in the Stein–Leventhal syndrome have now been published (Roy, Greenblatt, Mahesh & Jungck, 1963; Hoekenga, 1964; Vorys, Gantt, Hamwi, Copeland & Ullery, 1964; Seagar Jones & Moraes-Ruehsen, 1965; Wall, Franklin, Kaufman & Kaplan, 1965).

Occasionally normal spontaneous menstrual cycles follow treatment (Charles et al. 1963; Seagar Jones & Moraes-Ruehsen, 1965). Patients have been successfully treated who had previously responded to gonadotrophins (Vande Wiele & Turksoy, 1965) and after previous failure of wedge resection (Charles et al. 1963; Whitelaw, Grams & Stamm, 1964; Beck et al. 1966). In early work doses up to 200 mg. daily were used. A major complication, thought to be related in part to high dosage, is ovarian enlargement due to follicular or luteal cyst formation (Smith, Smith & Kistner, 1963; Charles et al. 1963; Beck et al. 1966), Stein–Leventhal patients being particularly sensitive (Kistner, 1965; Pildes, 1965). Large cysts may take up to 2 weeks to reach full size and can rupture (Roy et al. 1963; Vorys et al. 1964; Seagar Jones & Moraes-Ruehsen, 1965).

It has been pointed out that a rise of basal body temperature, endometrial changes and even progesterone secretion can occur in the absence of ovulation (Kistner, 1965; Seagar Jones & Moraes-Ruehsen, 1965; Beck et al. 1966). This is thought to be due to thecal luteinization associated with cystic proliferation which has been seen histologically (Pildes, 1965). The anti-oestrogenic effect of the drug interferes with the expected changes in cervical mucus and vaginal epithelium and leads to atypical endometrial appearances (Charles et al. 1963; Roy et al. 1963; Kistner, 1965; Pildes, 1965; Thompson & Mellinger, 1965; Wall et al. 1965; Beck et al. 1966).

No one has claimed that clomiphene has any effect on hirsutism. Some feel that the drug is ideal for patients with the Stein–Leventhal syndrome with amenorrhoea (Kistner, 1965), but others consider that wedge resection is preferable (Beck et al. 1966).

Apart from its therapeutic properties clomiphene is in the centre of interest in connexion with its mode of action. Most observers find that oestrogen excretion increases but there are differences of opinion on details (Greenblatt, Roy & Mahesh, 1962; Riley & Evans, 1964; Beck et al. 1966). The oestrogen increase includes all three classical fractions, oestrone, oestradiol and oestriol (Charles et al. 1963; Loraine,
1966) and the finding of an ovulatory peak and the normal luteal phase pattern (Charles et al. 1963; Roy et al. 1963). However, Dickey, Vorys, Stevens, Beech, Hamwi & Ullery (1965) think that there was a fall in the ‘oestradiol’ fraction due to a decrease of compounds other than oestradiol. Bishop (1965) observed the most pronounced rise of oestrogen excretion in the oestrone and oestriol fractions, without evidence for a decreased conversion of oestrone to oestriol.


Whilst there is considerable evidence of increased urinary oestrogen excretion, the situation regarding gonadotrophin responses is less clear. There are two main theories of the action of clomiphene. These are that the drug acts by causing a release of gonadotrophin, the ovarian phenomena being secondary, or, secondly, that its primary action is on the ovary in connexion with oestrogen synthesis.

In support of the first of these theories are the reports on increased gonadotrophin excretion in response to clomiphene. FSH and LH excretion tended to rise together (Riley & Evans, 1964; Thompson & Mellinger, 1965) or sequentially in one case studied (Roy et al. 1963). Dickey et al. (1965) observed increased FSH excretion but LH changes were difficult to interpret. Total gonadotrophin showed a modest and variable rise in the cases of Beck et al. (1966) and in about half the cases of Naville et al. (1964). Hence Riley & Evans (1964) subscribe to the view that clomiphene acts directly by stimulating the pituitary whilst Roy et al. (1963) believe that it stimulates the pituitary by virtue of its antioestrogenic properties. This is further supported by the finding of the probability of a competitive uptake, by uterine and pituitary tissue, of clomiphene and oestradiol-17β. Thompson & Mellinger (1965) also support the theory of pituitary stimulation in one or other form. Dickey et al. (1965) consider that the decrease in ‘oestrogen’ components is responsible for pituitary stimulation.

On the other hand, Pildes (1965) could only find unconvincing increases of total gonadotrophin excretion, whilst Charles et al. (1963) and Loraine (1966) failed to find any. They therefore contend that the action of clomiphene is primarily on the ovaries and even adrenals, a view held by Whitelaw et al. (1964) who have supporting evidence that ovulation can be blocked in the normal woman, presumably by stimulation of oestrogen release. Smith et al. (1963) also found a rise in oestrogen excretion but not of gonadotrophin, supporting the view that clomiphene acts by stimulating ovarian enzyme systems or possibly as a potentiator of gonadotrophin stimulation in the ovary.

It is clear from the above discussion that more information using specific techniques, particularly in Stein–Leventhal patients, is required before the controversy can be resolved. There is no available information on changes in androgen metabolism induced by clomiphene.

Theories of origin of the Stein–Leventhal syndrome

On the basis of the abnormalities of the steroid metabolism in the ovary discussed above it was thought likely that enzymatic deficiencies of at least two types might
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exist, analogous to those in congenital adrenal hyperplasia. These involved deficiency of ring A aromatization in the conversion of androstenedione to oestrogen and 3β-hydroxydehydrogenation (Short & London, 1961; Axelrod & Goldzieher, 1962; Mahesh & Greenblatt, 1964a). However, the fact that stimulation by FSH with CG could overcome these defects makes it unlikely that genetically determined enzyme deficiencies are involved. It has hence been suggested that the aromatization step may be rate-limiting owing to some deficiency in gonadotrophin stimulation (Short, 1962).

It has been seen that there is some evidence in vivo of abnormal LH secretion probably causing a more or less continuous ovarian stimulation, but with an absence of the normal ovulatory stimulus. In rats normal cyclic gonadotrophin release has been experimentally prevented by androgen administration (Barradough & Gorski, 1961) and it seems possible that the cyclic behaviour is similarly disturbed in the Stein–Leventhal syndrome (Goldzieher & Axelrod, 1963). The cause responsible is not identified. Taymor & Barnard (1962) think that deficiency of ovarian progesterone could be involved. In spite of the above objections the possibility of excess androgen production for genetic reasons is not entirely ruled out and there exist reports of chromosomal abnormalities. There are two suggesting the occurrence of a male chromosome pattern (see Short, 1962) and also reports of two cases probably with mosaics involving X chromosome abnormalities (de Grouchy, Lamy, Yaneva, Salomon & Netter, 1961; Netter, 1961). Alternatively it is possible that hypothalamic imbalance is promoted by abnormal stimuli from other parts of the central nervous system.

These considerations leave aside the role of the adrenal cortex. Leventhal & Scommegna (1963) ingeniously suggest that in accordance with the observations of Dorfman, Sharma, Menon & Forchielli (1966) there might be some inhibition of 11β-hydroxylation in the adrenal by ovarian androgens, resulting in impaired cortisol synthesis, secondary adrenal stimulation by ACTH and increased output of 11-deoxy C-19 steroids. This does not seem in accord with the observations of increased excretion of 11-oxy 17-OS or with the lack of evidence for decreased cortisol synthesis. On the other hand, if there is abnormal hypothalamic activity, the pituitary factor, involved in C-19 steroid production by the adrenal, postulated by Prunty (1956), Mills, Brooks & Prunty (1962) and Segre, Klaiber, Lobotsky & Lloyd (1964) might be implicated.

The hypothesis that gonadotrophins are involved in the abnormal ovarian steroidogenesis would be compatible with the effects, not only of the administration of gonadotrophins, but perhaps also of cortisone and of clomiphene.

Diagnosis of the Stein–Leventhal syndrome

Diagnosis of this syndrome becomes difficult when account is taken of the great variability in the features that have been described. To the author a middle course seems desirable rather than rigidly adhering to the criteria of Stein & Leventhal (1935). Thus the occasional presence of ovaries of normal size and of temporary ovulatory menstrual cycles may be acceptable; the occurrence of hirsutism is helpful but marked degrees of virilization should be unusual (Prunty et al. 1958); the demonstration of a typical ovarian histology is an important feature.
The condition needs to be differentiated from post-pubertal congenital adrenal hyperplasia (Brooks & Prunty, 1960), sometimes from Cushing's syndrome (Leventhal, 1958; London & Prunty, 1960), ovarian tumours (see above) and virilizing adrenal tumours (see Prunty, 1964c). Other less well defined conditions which may resemble the Stein-Leventhal syndrome are simple hirsutism, adrenal hyperplasia other than the congenital type, hyperthecosis and other types of cystic ovarian disease (Leventhal, 1958; Vignalou et al. 1965).

Summarizing the available data, it is clear that the biochemical features in the Stein–Leventhal syndrome are of limited specific value, but the tendency for some ovarian and adrenal tumours to cause high 17-OS excretion, often containing much dehydroepiandrosterone in the latter condition, can be helpful differential points. Likewise, the excessive pregnanetriol excretion and the relative ease of adrenal suppressibility in congenital adrenal hyperplasia may assist. In Cushing's syndrome there are numerous specific biochemical features.

The degree of the adrenal contribution in individual Stein–Leventhal cases is not easy to assess. Current data suggest that the adrenal contributes about 20 mg./100 ml. to the plasma testosterone level (Prunty & Lim, 1966, unpublished) so that falls greatly in excess of this in response to dexamethasone might be regarded as indicative of a significant adrenal contribution. Further study of the 11-oxy metabolites, pregnanetriol and pregnantriolone may also be helpful in this connexion.

Other suggestions, based on the stimulating properties of gonadotrophins, are also worthy of further study in the diagnosis of the Stein–Leventhal syndrome. French workers (e.g. Jayle et al. 1962) suggest stimulation with CG under dexamethasone suppression to increase urinary steroid excretion. This suggestion might more usefully be adapted to an investigation of changes in plasma testosterone levels, but is likely to remain unhelpful in differentiating some ovarian tumours. When standardized, the excessive oestrogen response to FSH stimulation observed by Shearman & Cox (1966) could be of interest.

THE PATHOLOGICAL IMPORTANCE OF THE THECA CELL-INTERSTITIAL CELL-HILAR CELL SYSTEM

The evidence of a close relation in origin and function between theca, interstitial and hilar cells is compatible with persuasive evidence of their predominant pathological role in the production of excess androgens. Thus virilizing ovarian tumours may be classified into three groups, each with a medullary component: those originating from both cortical and medullary elements, those primarily of medullary origin and those in which secondary stimulation by the tumours of theca-luteal elements in the stroma seems to occur. There is also the general view that thecal tissue is of importance in the production of excess androgen in the Stein–Leventhal syndrome, which would be in accord with the hypothesis of the presence of a constant stimulation of this tissue by LH. In addition, prominence of thecal tissue in abnormal androgen biosynthesis has been noted. Furthermore, glucose-6-phosphate dehydrogenase and isocitric dehydrogenase activities have been found to be similar in certain enzymically active normal stromal cells, some luteinized, and in stromal cells in primary and secondary ovarian tumours (Seully & Cohen, 1964).
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Apart from the pathological changes already described, there remains the condition of 'hyperthecosis' which has been given prominence by Shippel (1955) and Scully (1963), both of whom discern a close relation to the Stein–Leventhal syndrome. The condition is evidenced by abnormal islands of thea cells, often luteinized, in the stroma. As these authors have pointed out it can accompany changes in the ovary of the Stein–Leventhal type (Massachusetts General Hospital Case Records, 1952). It has been seen in pregnancy (Lynch, Kyle, Raphael & Bruce-Lockhart, 1959). In this connexion a recent observation by the author of the rapid appearance of hirsutism in early pregnancy subsequent to the development of large luteal cysts following the administration of FSH plus CG is pertinent, as is the not infrequent observation of the occurrence, or exacerbation, of hirsutism in pregnant women.

'SIMPLE' OR 'IDIOPATHIC' HIRSUTISM

There is a large number of hirsute women in whom obvious ovarian or adrenal lesions can be excluded. There is some difficulty in deciding how far they depart from normal. Racial features need considering, for example Caucasian women have much more facial and axillary hair than Japanese (Hamilton, 1958). Women originating in the Mediterranean region are more hairy than other Europeans. According to Ferriman & Gallwey (1961) significant hirsutism occurs in about 10% of young women who have no endocrine disease or menstrual irregularity. This condition was defined as 'constitutional'. In other white women the incidence has been as high as 28% (Hamilton, 1958). Although Japanese women have the same plasma testosterone levels as occidentals (Kobayashi, Lobotsky & Lloyd, 1966), some hirsute women have been presumed to have hair follicles abnormally sensitive to a normal androgenic stimulus, but it is pertinent that Ferriman, Page & Newnham (1962) found a tendency for another masculine feature, increased biacromial diameter, in such individuals. On the other hand, the reverse situation of decreased sensitivity to a normal androgenic stimulus has been well documented in testicular feminization.

Bearing in mind the above considerations many studies have been made of hirsute women so that the descriptive terms used could be examined. 'Simple' hirsutism, according to Bishop (1954), included a hirsute face, extremities, abdomen and chest, possibly with acne, irregular menses or amenorrhoea. Goldzieher & Laitin (1960) included a number of patients with gross menstrual irregularities and even some with additional virilization. Segaloff, Gordon, Horwitt & Weed (1955) defined the condition in terms of familial and racial characters, unassociated with increased 17-OS excretion, and apparently due to increased sensitivity of the follicles.

'Idiopathic' hirsutism is a term generally used in a similar sense, but applied in different ways. Lloyd, Moses, Lobotsky, Klaiber, Marshall & Jacobs (1963) did not define menstrual status but excluded palpably large ovaries. Others have accepted varying degrees of irregular and infrequent menstruation without reference to ovarian size (Wieland, Maynard & Hamwi, 1966), with ovaries that were 'not large' (Mauvais-Jarvis & Baulieu, 1962), not palpably large (Lloyd et al. 1966; Nichols, Nugent & Tyler, 1966), or normal by gynaecography or culdoscopy (Korenman et al. 1965). Lloyd et al. (1966) had also a group of patients with normal menstruation and palpably normal ovaries.
The hirsute subjects studied by Mahesh et al. (1964) had varying degrees of menstrual irregularity and classification of these patients on biochemical grounds proved difficult.

Hence the patients described in the literature in the above categories are somewhat heterogeneous. Some could conceivably belong in the Stein–Leventhal category (Prunty et al. 1958). On the whole the general feeling appears to be that in many of these patients some degree of adrenal abnormality is present.

REFERENCES
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