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DEFECTIVE BIOSYNTHESIS OF OVARIAN STEROIDS IN THE STEIN-LEVENTHAL SYNDROME

BY

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Although the Stein-Leventhal syndrome was first described in 1935 (Stein and Leventhal, 1935), its aetiology is still obscure and its treatment empirical. There can be little doubt that the associated hirsutism is due to an increased production of androgens, and there has been much discussion on whether they are of adrenal or ovarian origin. The studies of Gallagher *et al.* (1958), Prunty *et al.* (1958), Perloff and Channick (1959), and Shearman *et al.* (1961) have all suggested that the adrenals may be involved. On the other hand, there is much circumstantial evidence to implicate the ovaries; for example, the condition responds successfully to such varied surgical procedures as ovarian wedge resection (Stein, 1955), ovarian eversion (Ingersoll and McDermott, 1950), or ovarian medullary resection (Allen and Woolf, 1959).

With the recent elucidation of the pathways of oestrogen biosynthesis in the ovary (Meyer, 1955; Solomon *et al.*, 1956), it became apparent that at least

one androgen, androstenedione, is normally produced by the ovary as an intermediate in the synthesis of oestradiol-17 β from progesterone (see Formulae).

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A method has recently been described for the simultaneous determination of progesterone, 17 α -hydroxyprogesterone, androstenedione, oestrone, and oestradiol-17 β in small samples of follicular fluid (Short, 1961). Since each of these five steroids has been identified in human ovarian tissue (Zander, 1958; Zander *et al.*, 1959; Smith, 1960), it seemed important to establish the levels of these compounds in the cyst fluid of patients with the Stein-Leventhal syndrome, and to compare them with the levels found in a control group of subjects.

Material and Methods

Cyst fluid was obtained at operation from the ovaries of five patients exhibiting the characteristic features of the Stein-Leventhal syndrome; seven additional samples were obtained from women in whom ovarian cysts or follicles were an incidental finding at laparotomy. After collection the fluid was stored in the deep-freeze until it could be assayed.

Four of the five Stein-Leventhal patients were shown by pelvic radiography after pneumoperitoneum to have enlarged ovaries before submitted to laparotomy. In addition, a number of routine urinary hormone assays were carried out on these patients as further aids to the diagnosis of the syndrome. 17-Ketosteroids were determined by the method of Gibson and Norymberski (1954), and 17-ketogenic steroids by minor modifications of the method of Norymberski *et al.* (1953). Pregnanetriol (5 β -pregnane-3 α :17 α :20 α -triol) was determined by the method of Bongiovanni (1954). "Total gonadotrophins" were measured by the method of Loraine and Brown (1956a, 1956b). The atlas of Greulich and Pyle (1950) was used for the determination of bone age. Progesterone, 17 α -hydroxyprogesterone, androstenedione, oestrone, and oestradiol-17 β were measured by the method of Short (1961).

Case Reports

Case 1.—Aged 24, menarche at 13; her periods were infrequent, and eventually she became completely amenorrhoeic, with a history of three years' infertility. On examination she was minimally hirsute, with a male distribution of pubic hair. The biochemical findings in the urine were: 17-ketosteroids, 8.8 mg./24 hr.; 17-ketogenic steroids, 13.2 mg./24 hr.; gonadotrophins, 21.5 and 16 units HMG/20A/24 hr. Laparotomy revealed bilateral polycystic ovaries with thickened capsules, the right ovary measuring 6 by 3.5 by 2.5 cm., and the left 6.5 by 3 by 2.5 cm. A bilateral wedge resection was carried out. Histologically the ovaries revealed a thickened theca interna layer; there was no corpus luteum present. Post-operatively she had regular monthly periods and the temperature chart showed evidence of ovulation; she has recently become pregnant.

Case 2.—Aged 20, menarche at 14; her periods lasted five days every two months initially, but eventually they occurred only once a year. There was a history of four years' infertility. On examination she showed minimal facial hirsuties, with a male distribution of pubic hair; the clitoris was normal. The biochemical findings in the urine were: 17-ketosteroids, 14.7 mg./24 hr.; 17-ketogenic steroids, 5.6 mg./24 hr.; gonadotrophins, 9.5 and 8.5 units HMG/20A/24 hr. Laparotomy revealed bilateral polycystic ovaries, the right ovary measuring 6 by 6 by 3 cm., and the left 5 by 5 by 3 cm. A bilateral wedge resection was carried out; histologically the ovaries showed a thickened capsule and follicular cysts with a prominent theca interna. Post-operatively she had regular monthly periods.

Case 3.—Aged 16, menarche at 10; her periods lasted five days every six months, and she had been hirsute for four years. On examination she was obese, grossly hirsute, and

had an enlarged clitoris; her bone age was 20 years. The biochemical findings in the urine were: 17-ketosteroids, 13.5 mg./24 hr.; 17-ketogenic steroids, 10.3 mg./24 hr.; pregnanetriol not detectable; gonadotrophins, 28 and 21.5 units HMG/20A/24 hr. Laparotomy revealed bilateral polycystic ovaries with thick white capsules, the right ovary measuring 5 by 2.5 by 3 cm. and the left ovary 6 by 3 by 2.5 cm. A bilateral wedge resection was carried out; histologically the ovaries showed multiple follicular cysts with thecal proliferation. A post-operative follow-up has not yet been made.

Case 4.—Aged 18, menarche at 12; her periods had always been irregular, lasting for four days every 6–16 weeks. On examination she showed gross hirsuties of the face and legs, with a male distribution of pubic hair; the clitoris was normal, and there was no obesity. The biochemical findings in the urine were: 17-ketosteroids, 14.8 mg./24 hr.; 17-ketogenic steroids, 16.3 mg./24 hr.; pregnanetriol, 2.5 mg./24 hr. The gonadotrophin excretion was not determined. Laparotomy revealed bilateral polycystic ovaries, the right ovary measuring 5.5 by 2.5 by 3 cm. and the left ovary 6 by 2 by 3 cm. A bilateral wedge resection was carried out; histologically the ovaries showed thecal proliferation. There has not yet been a post-operative follow-up of this patient.

Case 5.—Aged 18, menarche at 14; her periods lasted for three days every six months, and the menstrual flow was scanty. She had been hirsute for three years. On examination she showed gross hirsuties of the face, legs, and sacral region, with a male distribution of pubic hair; her bone age was normal, and the clitoris was not enlarged. The biochemical findings in the urine were: 17-ketosteroids, 14 mg./24 hr.; 17-ketogenic steroids, 4.3 mg./24 hr.; pregnanetriol, 0.8 mg./24 hr.; gonadotrophins, 4.5 units HMG/20A/24 hr. Laparotomy revealed bilateral polycystic ovaries about twice the normal size. A bilateral wedge resection was carried out; histologically the ovaries showed follicular cysts and some thecal hyperplasia. A post-operative follow-up has not yet been made.

Comment

All these patients conform to the clinical pattern of the Stein-Leventhal syndrome (Stein, 1959). They all had oligomenorrhoea or amenorrhoea, were hirsute, and had enlarged polycystic ovaries with thickened capsules. The histological sections all showed follicular cysts and thecal hyperplasia. The two women who were operated on long enough ago for there to have been an adequate follow-up both developed regular monthly periods, and one of them has since become pregnant.

There was no suggestion that any of these patients might have been suffering from the adrenogenital syndrome or a virilizing adrenal carcinoma. Although the urinary pregnanetriol of Case 4 was slightly elevated, subsequent investigation (Brooks and Prunty, 1961) showed that the 17-ketogenic-steroid/pregnanetriol ratio was not similar to that found in cases of adrenal virilism. Even though the gonadotrophin levels are usually normal in the Stein-Leventhal syndrome, they are occasionally elevated (Prunty *et al.*, 1958; Stein, 1959; Ingersoll and McArthur, 1959), as they were in Cases 1 and 3.

Controls

The case histories of the seven patients who served as controls are given below. Care was taken to select women who did not show any of the physical manifestations of the Stein-Leventhal syndrome.

Case 6.—Aged 34. A total hysterectomy was performed for menorrhagia 12 days after the commencement of her

last menstrual period; histologically the uterus showed a normal proliferative endometrium. Fluid was obtained from numerous small follicles in both ovaries.

Case 7.—Aged 36. She had a history of irregular cycles with occasional prolonged menstrual periods. A total hysterectomy was performed, and at the time of operation she had been menstruating for 13 days; histologically the uterus showed a normal proliferative endometrium. Fluid was obtained from a large cyst in the left ovary. Histological examination of the cyst revealed normal granulosa and theca interna layers.

Case 8.—A total hysterectomy was performed for severe menorrhagia 24 days after the commencement of her last menstrual period. Histologically the uterus appeared normal, and it was lined by a late secretory endometrium. The fluid was obtained from a cyst in the left ovary.

Case 9.—Aged 29. This patient had a history of continuous vaginal bleeding for six weeks, and at laparotomy an unruptured ectopic pregnancy was discovered in the right fallopian tube. Her last menstrual period had occurred 51 days prior to the operation. Fluid was obtained from several small follicles in the right ovary.

Case 10.—Aged 28. A laparotomy was performed for sterilization by tubal ligation 11 days after the beginning of the last menstrual period. A complete Graafian follicle 1.5 cm. in diameter was removed intact from the right ovary. Fluid was subsequently aspirated from the excised follicle.

Case 11.—Aged 34. This patient complained of abdominal pain, and a laparotomy was performed 14 days after the beginning of the last menstrual period. Fluid was obtained from a large follicular cyst in the right ovary.

Case 12.—Aged 35. A total hysterectomy was performed for severe dysmenorrhoea two days after the commencement of the last menstrual period. Both the uterus and the ovaries appeared normal. Fluid was obtained from numerous small follicles by multiple incisions in both ovaries.

Results

The results of the steroid assays on the samples of cyst fluid are shown in the Table. It was necessary to combine the material from Cases 4 and 5 in order to obtain sufficient fluid to assay.

Concentration of Steroids in the Fluid from Human Ovarian Cysts and Follicles

Case No.	Diagnosis	Vol. of Fluid (ml.)	Progesterone (µg./100 ml.)	17 α -Hydroxyprogesterone (µg./100 ml.)	Androstenedione (µg./100 ml.)	Oestrone (µg./100 ml.)	Oestradiol-17 β (µg./100 ml.)
1	Stein-Leventhal	2.5	< 10	32	88	< 2	< 2
2	"	1.4	7	36	196	< 2	< 2
3	"	3.2	13	39	156	< 2	< 2
4 and 5	"	2.6	< 12	23	134	< 2	< 2
6	Menorrhagia	2.8	109	55	32	7	156
7	"	25.0	54	31	5	< 1	36
8	"	8.5	9	13	19	2	24
9	Ectopic pregnancy	7.6	310	58	23	< 1	4
10	Normal	2.0	95	85	78	68	70
11	Ovarian cyst	17.0	47	36	38	2	22
12	Dysmenorrhoea	1.7	15	21	35	18	44

The most striking finding in the patients with Stein-Leventhal syndrome was the very high concentration of androstenedione present, coupled with a complete absence of detectable amounts of oestradiol-17 β or oestrone. In the control group of patients, on the other hand, the levels of androstenedione are significantly lower, and oestradiol-17 β was detected in every sample. These oestradiol values are within the range of those reported by Granjon *et al.* (1958), Zander *et al.* (1959), and Smith (1960) for normal and cystic follicles. However, most of the oestrone values seem to be somewhat lower than the ones found by these authors.

The results in the Table therefore strongly suggest that in the Stein-Leventhal syndrome there is a defect in the conversion of androstenedione to oestradiol-17 β within the cystic follicles. The resultant build-up of androstenedione could possibly account for the clinical signs of virilism in these cases. However, although androstenedione is a potent androgen when administered locally, it has only a very weak androgenic activity when administered systemically (Dorfman and Shipley, 1956; Mann *et al.*, 1960).

It can also be seen from the Table that some of the control patients had very high concentrations of progesterone in their cyst fluid. In some instances—for example, Case 9—this may have been due to the fact that luteinization changes were taking place in the follicles (Short, 1961).

In addition to steroids listed in the Table, an attempt was made to identify a number of other compounds. Zander *et al.* (1958) reported the presence of 20 ξ -hydroxypregn-4-en-3-one in human ovaries, but there was no evidence of either the 20 α or 20 β epimer in any of the samples assayed in this study (<1 μ g./sample). This is in agreement with observations on the mare's ovary (Short, 1961), where 20 α -hydroxypregn-4-en-3-one was found in the corpora lutea but not in the follicular fluid.

Zander *et al.* (1959) were unable to identify any oestriol in human ovaries, although Smith (1960) reported finding large amounts (24 μ g./100 ml.) in a pool of secretory-phase follicular fluid; more recently, however, Ryan and Smith (1961a, 1961b) failed to demonstrate any *in vitro* conversion of acetate or progesterone to oestriol by the linings of human follicular cysts. In the present study, oestriol was not detected in any of the 12 samples assayed (<0.1 μ g./sample).

With the recent identification of dehydroepiandrosterone in testicular tissue (Neher and Wettstein, 1960), it seemed possible that this androgen might also be produced by the ovary; however, it was not detected in any instance in the present study (<2 μ g./sample).

Since the ovary is capable of producing androstenedione, it is also possible that it could produce testosterone. There is some evidence for testosterone production by pathological human ovarian tissue *in vitro* (O'Donnell and McCaig, 1959; Mills *et al.*, 1959), but as yet testosterone has not been isolated from human ovaries *in vivo*. In the paper chromatographic system used in the present study, it is not possible to separate testosterone from 17 α -hydroxyprogesterone. Therefore the 17 α -hydroxyprogesterone eluates from Cases 3, 4, and 5 were pooled, treated with acetic anhydride and pyridine, and rechromatographed. No testosterone acetate could be detected, indicating that there must have been less than 1 μ g. of testosterone in the original pooled sample. The 17 α -hydroxyprogesterone eluates of Cases 6, 7, 8, and 9 were treated in the same way, with similar negative results. This is in agreement with the findings in another study (Short, unpublished observations) in which <0.1 μ g. of testosterone was present in 6.5 μ g. of 17 α -hydroxyprogesterone isolated from a pool of human ovarian cyst fluid.

A number of other steroids have been isolated from the follicular fluid of the mare—namely *epitestosterone* (Short, 1960a), 6 α -hydroxyoestradiol-17 β (Bush *et al.*, 1960), and 19-norandrostenedione (Short, 1960b); however, none of these steroids was detected in this

study (<1 μ g./sample). No attempt was made to look for 19-hydroxyandrostenedione, the postulated intermediate in the conversion of androstenedione to oestrone (Meyer, 1955; Ryan, 1959), since this steroid has never been detected in large pools of human, equine, or bovine follicular fluid (Short, 1960a, 1960b, and unpublished observations).

Discussion

In interpreting the results of this study it has been assumed that the steroid concentrations in follicular fluid are a valid index of the *relative* amounts of each hormone secreted by the cells lining the follicle (Short, 1961). However, it is important to remember that such estimations do not necessarily provide any information about the secretion rates of the hormones concerned. Thus, while the results presented here strongly suggest that there is a defect in steroid biosynthesis in the ovary, resulting in a build-up of androstenedione and a decreased production of oestrogens, it is not possible to determine the quantitative significance of the defect.

Studies of endometrial histology (Stein, 1955; Leventhal, 1958) and urinary oestrogen excretion (Evans and Riley, 1960; Shearman *et al.*, 1961) in the Stein-Leventhal syndrome have indicated that oestrogens are being produced in amounts comparable to those found in the middle of the proliferative phase of the normal menstrual cycle. In view of the fact that the theca interna cells are probably responsible for oestrogen synthesis in the ovary (Brambell, 1956; Falck, 1959; Pinkerton, 1959), one might have expected the hyperthecosis found in the Stein-Leventhal syndrome to result in a greatly increased production of oestrogens. The fact that this is not so lends some support to the concept of a block to oestrogen synthesis in these thecal cells.

The residual oestrogens that are produced could be coming from the remaining normal tissue in the ovary; or it may be that the defect is not an absolute one, and that even the cystic follicles can produce small amounts of oestrogen. Evans and Riley (1960) briefly reported finding oestrogenic activity in some Stein-Leventhal follicles, while none was detected in others. It should also be remembered that the adrenals are apparently capable of producing at least as much oestrogen as the ovaries (Brown *et al.*, 1959), and there is evidence (Gallagher *et al.*, 1958; Prunty *et al.*, 1958; Shearman *et al.*, 1961) to suggest that the adrenals may be hyperactive in the Stein-Leventhal syndrome.

From the results presented in this study it is not possible to locate the exact site in the biosynthetic sequence at which the block occurs, except that it appears to be somewhere between androstenedione and oestrone. It is generally believed that androstenedione is converted to oestrone via 19-hydroxyandrostenedione (Meyer, 1955; Ryan, 1959); hence the defect could possibly be in the 19-hydroxylating enzyme system. It is well known that similar hydroxylation disorders occur in the adrenal cortex in congenital adrenal hyperplasia, when the 11- or 21-hydroxylating enzyme systems appear to be at fault.

It has been postulated by Hollander and Hollander (1958), on the basis of *in vitro* experiments with dog ovaries, that the conversion of C₁₉ steroids like androstenedione to oestrogens is a rate-limiting reaction, which is under the control of follicle-stimulating hormone. If this theory is correct, then the defect in

the Stein-Leventhal ovaries could result from a decreased secretion of follicle-stimulating hormone by the pituitary. However, more recent *in vivo* evidence (Short, 1961) strongly suggests that there are no such rate-limiting reactions under gonadotrophic control in the conversion of androstenedione to oestradiol-17 β by the ovary.

One of the most puzzling features of the Stein-Leventhal syndrome has been the success of such a wide variety of surgical procedures for its treatment; the only factor they apparently have in common is trauma to the ovary. It is known that, in some animals, artificial rupture of large follicles will bring about luteinization changes indistinguishable from those that normally follow ovulation (Harrison, 1946). The essential biochemical difference between a follicle and a corpus luteum seems to be that luteal tissue is relatively deficient in the enzyme systems responsible for hydroxylation at position 17, side-chain cleavage, and aromatization. Thus the corpus luteum is forced to produce mainly progesterone, and little 17 α -hydroxyprogesterone, androstenedione, or oestrogens are formed (Short, 1961, and unpublished observations). It therefore seems possible that the trauma involved in the surgical correction of Stein-Leventhal ovaries could provide the stimulus for luteinization of the defective cystic follicles. Many of the thecal cells would then regress in the normal way, and the granulosa cells would luteinize and start secreting progesterone.

Summary

An analysis of the steroids present in cyst fluid from the ovaries of five patients with the Stein-Leventhal syndrome revealed a very high concentration of androstenedione, and no detectable amounts of oestradiol-17 β or oestrone. In seven control patients, on the other hand, in whom normal or cystic follicles were an incidental finding at laparotomy, the concentrations of androstenedione were significantly lower, and oestradiol-17 β was detected in every instance.

On the basis of this evidence it is therefore postulated that in the Stein-Leventhal syndrome there is a defect in the biosynthesis of oestrogens within the cystic follicles. This defect takes the form of a block in the conversion of androstenedione to oestrogens; the resultant increase in androstenedione production could possibly account for the virilism seen in some patients. A tentative explanation is also offered for the success of such a wide variety of non-specific surgical procedures in curing the condition.

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The Hong Kong Government recently accepted a report by Dr. L. T. HILLIARD, formerly consultant psychiatrist and superintendent of the Fountain Hospital, London, as a guide to policy for dealing with the problem of mental deficiency in the Crown Colony. Dr. Hilliard went to Hong Kong last year to examine the problem of mental deficiency there and to advise on measures for dealing with the problem. The Acting Colonial Secretary has told the Hong Kong Legislative Council that it was proposed to proceed in three different but interrelated fields. Under the Medical Department would come the diagnosis of all mental defectives and the provision of separate hospital accommodation for severe-grade mental defectives. The provision of residential and day-training institutions for medium-grade mentally defective children and adults would be the responsibility of the Social Welfare Department. The Education Department would deal with the provision of special facilities for teaching minor-grade mental-defective children. In his report Dr. Hilliard said most of the existing tests of intelligence were inappropriate and inaccurate when applied to races or countries for which they had not been devised. He emphasized that it would be useful if a clinical psychometrist undertook some research into this matter in Hong Kong, and he suggested that this might be provided through Unesco.