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Pathogenesis of polycystic disease of the ovary

by

F. CAROLLO *

INTRODUCTION

Polycystic disease of the ovary constitutes an extensive chapter in gynaecological pathology, comprising a set of pictures, different on the clinical, biological and anatomo-pathological planes, but which physiologically have in common: deficient ovulation, constant luteinic insufficiency and frequently sterility.

Ovarian polycystic disease is also called ovarian dystrophy.

Within ovarian dystrophy two forms are classically distinguished: macropolycystic dystrophy, commonly called oophoritis or « sclerocystic ovariopathy » and micropolycystic dystrophy.

Macropolycystic ovarian dystrophy is secondary to numerous dysfunctional conditions in which recurrent anovular cycles are found, either with a central origin or with a local cause. The ovaries are increased in volume, have a lumpy, asymmetrical surface, of variable volume at different periods of the cycle, painful either spontaneously or on palpation, irregular in shape and dimensions, present scars of the corpus luteum, with a thin capsule of variable thickness, and histologically follicles are found in various stages of development, some follicles being atresic (Fig. 1).

Included among the micropolycystic dystrophies, on the other hand, are ovaries upon whose surface no apparent cyst follicles can be seen; these only become evident when a section is made. These have a smooth surface, a mother-of-pearl colour and hard consistency, with an inspissated and sclerotic, sometimes leathery, cortex. They are indolent and painless, of variable dimensions but bilaterally constant in each individual case; their volume may be normal, but is more often 2 to 5 times greater than normal (Fig. 2); they are never less than normal in volume, and show hypertrophy of the stroma and hyperplasia of the internal theca of the follicles, with diffuse interstitial thecomatosis.

The standard description given to these ovaries is that of Stein-Leventhal's syndrome (abbreviated S-L in this paper).

We shall not consider macropolycystic dystrophy in this study, since its pathogenesis is already well known.

This is not so in the case of micropolycystic dystrophy, still today defined as of obscure ([6, 40]) or enigmatic ([39]) pathogenesis. We shall consider the most recent views and our own.

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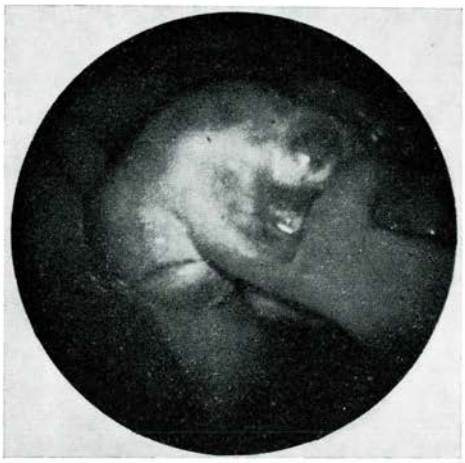

FIG. 1 - Macropolycystic ovarian dystrophy. Large follicles are seen, deforming the surface of the ovary.

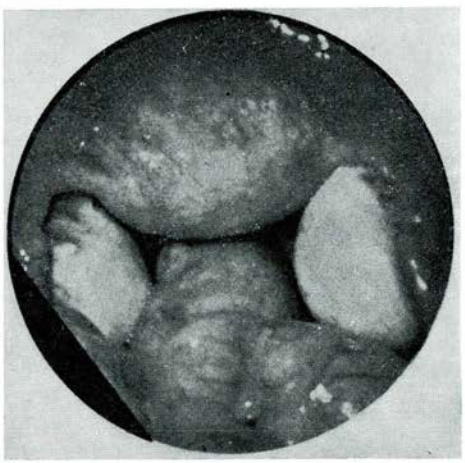

FIG. 2 - Micropolycystic ovarian dystrophy. Both ovaries alike are increased in volume, with a smooth surface.

In 1962, in critical review of the existing literature on the subject, and of our own experience ([8]), we wrote: « . . . we are inclined to distinguish two classifications of the primary condition described as the S-L syndrome: the disease and the syndrome. Factors of a probably genetic origin can be seen as being pathogenetically responsible for S-L disease; they are expressed by the abnormal production of substances with an androgenic activity on the part of the ovary, due to enzymatic block acting at various levels upon the chain of reactions in the biosynthesis of the oestrogens.

Since this biosynthetic alteration determines the abnormal presence in the circulation of androgenic substances, it could be responsible for all the phenomena encountered in S-L disease.

The S-L syndrome, although characterized by phenomena almost identical with those found in the disease, also seems to be determinated by the abnormal presence in the circulation of androgenic substances, and its pathogenetic cause can be recognized as an abnormal production of androgens by the suprarenals, due either to congenital or acquired causes.

This distinction is not imposed only for the purpose of more precise and scientific classification of the condition, but has its own *raison d'être* due to the different therapeutic direction required by the diverse aetiological factors upon which the conditions themselves are based. Treatment is in fact exclusively surgical (ovarian resection) in S-L disease, but can be either medical (suprarenal inhibition therapy) or surgical (removal of adenomas or suprarenal carcinomas) in the S-L syndrome. »

A few years later ([10]), in an attempt to classify all the ovarian dystrophies, we outlined a classification of the micropolycystic dystrophies, distinguishing between: 1) Ovarian dystrophies of S-L disease; 2) Ovarian dystrophies of S-L syndrome; 3) Ovarian dystrophies of the S-L type (Fig. 3).

We can now add that the ovarian morphology of all three types of condition here considered constitutes the exceptional expression of a number of aetiological

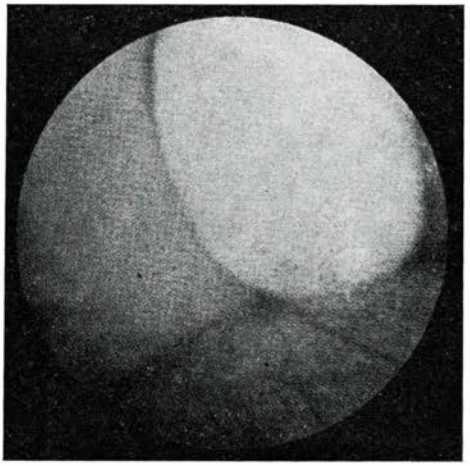

FIG. 3 - Stein-Leventhal type of ovarian dystrophy. One ovary only is seen, with a smooth surface and almost normal dimensions. This belonged to a woman who had an arrhenoblastoma of the contralateral ovary.

factors, which as regards the disease are of a genetic nature and operate within the ovarian structure itself, giving rise to an anomalous biosynthetic process in the chain of reactions that leads to the formation of the oestrogens. As regards the syndrome, the aetiological factors must be searched for in extra-ovarian factors (hereditary and acquired), which secondarily induce an ovarian morphology similar to that of S-L disease.

In the ovary of the S-L type, aetiological factors responsible for the anomaly generally reside in the changes present in the contralateral ovary.

The ideas we are now putting forward have made a world tour, and the many contributions that have appeared in the international literature during the past 15 years have in many respects stated and scientifically demonstrated the pathogenesis of the disease and the syndrome of the microcystic ovary.

In the international literature, in fact, it has recently been common to find the phraseology: polycystic disease of the ovary, type I (to indicate the true S-L disease) and polycystic disease of the ovary, type II, or atypical (referring to the ovary of the S-L syndrome) ([6]), or ovarian polycystic disease type Ia, type Ib, type IIa and type IIb ([39]).

AETIOLOGY OF STEIN-LEVENTHAL'S DISEASE

It was already suspected that polycystic disease of the ovary might have a genetic cause, after several cases of this disorder were found to exist clinically in several members of the same family: sisters, twins, mother and daughters.

Various authors ([12, 13, 14, 20, 21, 23, 30]) have demonstrated the familial and hereditary nature of ovarian polycystic disease.

Quite recently, Cohen ([14]) studied 18 families of negroes through 5 generations, and was able to establish a genetic basis for ovarian micropolycystic disease, with dominant autosomal transmission (Fig. 4).

Givens *et al.* ([18]) also studied two families in which the incidence of ovarian

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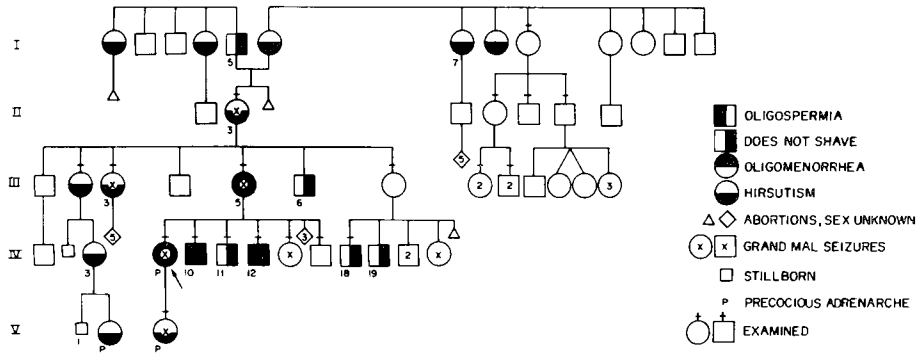

FIG. 4 - (From Cohen *et al.*, Fertility and Sterility (1975), 26, 12, 1228). Shows the genetic transmission of polycystic disease of the ovaries, of oligospermia and other pathological conditions known in 18 families of 5 generations of negroes.

polycystic disease suggested a dominant mode of hereditary transmission.

The data in Cohen's possession suggest the possibility of dominant heredity linked to the X chromosome. In order to explain the great variety and degree of gravity of this condition the Lyon hypothesis was put forward, according to which the casual inactivation of the X chromosome which carries the mutant gene, is responsible for ovarian polycystic disease.

In the families studied by Cohen, not only various women who were carriers of S-L disease were found, but also some males who carried gonadal anomalies such as hypogonadism, a spermatic maturation defect, absence ofbeard and other concomitant pathology. Neither in the males nor in the females of various generations were low levels of FSH found. This fact has been interpreted as the expression of the existence of arrested spermatogenesis, and in the females as S-L disease, due to inadequate follicular maturation.

On the basis of knowledge acquired up to the present time we can say that not all cases of polycystic disease of the ovary can be explained aetiologically on a genetic basis; only true S-L disease can be so explained.

PATHOLOGY OF STEIN-LEVENTHAL'S DISEASE

The genetic anomaly encountered in S-L disease seems to be responsible for a partial enzymatic block which is expressed at different levels of the biosynthesis chain reaction of the ovarian oestrogens.

Netter ([30]) accepted that various kinds of enzymatic block could exist within S-L disease, depending on the individual genotype. In some cases the block is found at the level of 17-α-hydroxyprogesterone; in others, at the level of androstendione.

Goldzieher & Axelrod ([19, 20]) have supposed the existence of a deficit at aromatization level (Fig. 5). In this case, together with hyperproduction of androgens, an almost normal level of circulating oestrogens may be found, since androgens in large quantity may be converted into oestrone.

Mahesh & Greenblatt ([25]) accepted the existence of a deficit of 3-β-ol-dehydrogenase, which would give rise to an accumulation of dehydroepiandrostendione, a steroid normally produced by the suprarenal, but which in pathological cases may derive from the ovary.

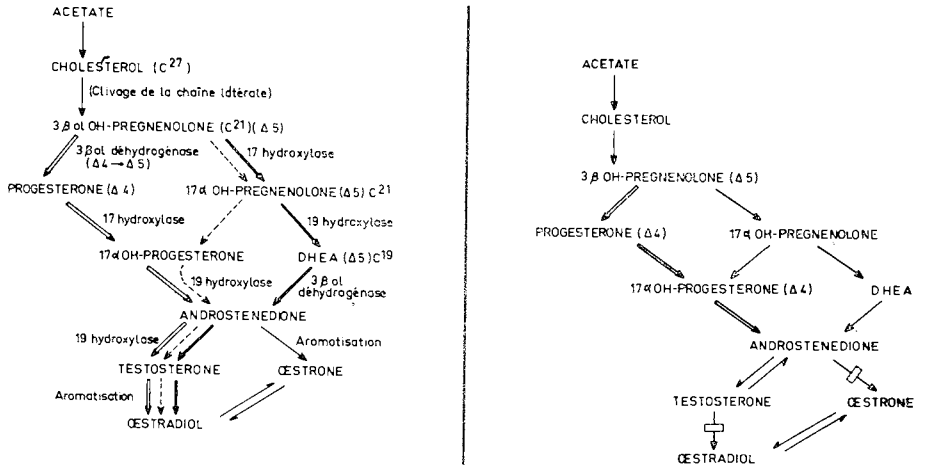

FIG. 5 - (From Vokaer: Rev. Franc. Gynec. [1973] 68, 4, 221). On the right is a scheme of normal ovarian steroid biosynthesis. On the lefts, the scheme proposed by Goldzieher and Axelrod to support their hypothesis.

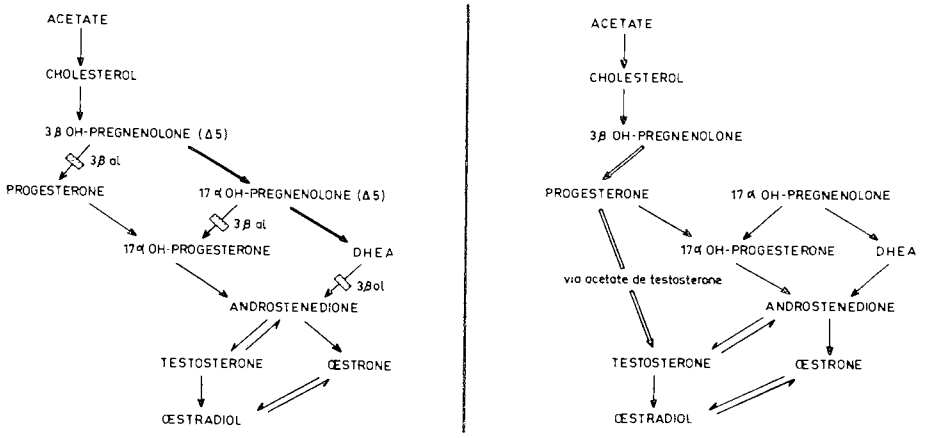

FIG. 6 - (From Vokaer: Rev. Franc. Gynec. [1973] 68, 4, 221). On the right, the scheme suggested by Mahesh and Greenblatt to explain their hypothesis. On the left, the scheme proposed by Forchielli to support his hypothesis.

Forchielli has demonstrated the possibility of the direct passage of progesterone into testosterone (Fig. 6).

That these anomalous metabolic routes really exist has been demonstrated by two groups of facts: 1) when ovarian tissue from patients with S-L disease was incubated *in vitro*, conversion of progesterone into androgens was obtained. This was not found in normal ovarian tissue. 2) When the ovary affected by S-L disease was stimulated, there was hyperproduction of androsterone and etiocholanolone (metabolites of androstendione), as well as an accumulation of dehydroepiandrostendione.

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It should be said, however, that the enzymatic blocks, as is the case with congenital suprarenal hyperplasia, were never complete.

Various investigators ([16,25,27,33,34,37]) have also demonstrated the presence in the ovary in S-L disease of an aberrant 11-ß-hydroxylase, as a result of which these patients eliminate pregnantriolone. Production of this substance ceases if the ovaries are removed bilaterally.

As in congenital suprarenal hyperplasia, the genetic anomaly gives rise to enzymatic blocks at different levels of the steroid biosynthesis chain reaction, so that in S-L disease a genetic anomaly may give rise to enzymatic blocks at different levels of the oestrogen biosyntesis chain reaction.

It is well known that the suprarenals and the ovary derive from a common primordial rudiment of the mesodermal coelomic epithelium, and therefore either gland may run up against entirely superimposable pathological conditions.

Cases of ovarian hyperplasia in prepubescent girls have been reported; they subsequetly developed the typical symptomatology of S-L disease.

Since abnormal biosynthesis of the oestrogenic steroids at ovarian level will induce a high circulating concentration of androgens, it will produce unsuitable feedback at hypothalamic-pituitary level ([26,41]), with maintenance of chronic anovularity ([39,40]).

More particularly, the enzymatic blocks at various levels of ovarian steroid biosynthesis will from time to time produce accumulations of: androstendione, dehydroepiandrostendione, dehydroepiandrostendione sulphate and oestrone, but not oestradiol ([15,31,40]) (Fig. 7).

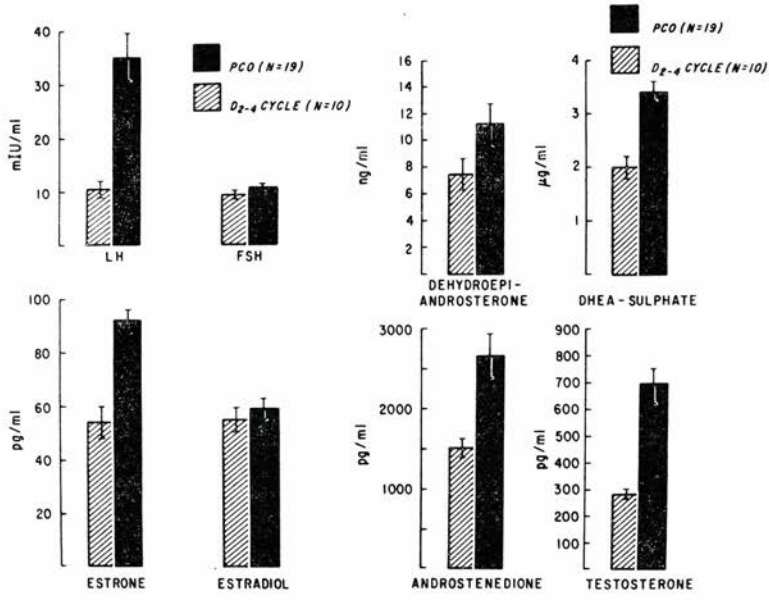

FIG. 7 - (From Yen, S.S.C. *et al.*: « The endocrine function of the human ovary », Acad. Press, London, 1976). On the right, the mean concentrations of LH, FSH, oestrone, oestradiol, in 19 patients with ovarian polycystic disease and in 10 normal women between the 2nd and 4th day of the menstrual cycle. On the left, the mean concentrations of testosterone, androstendione, dehydropiandrostendione sulphate, in the same patients during the same period.

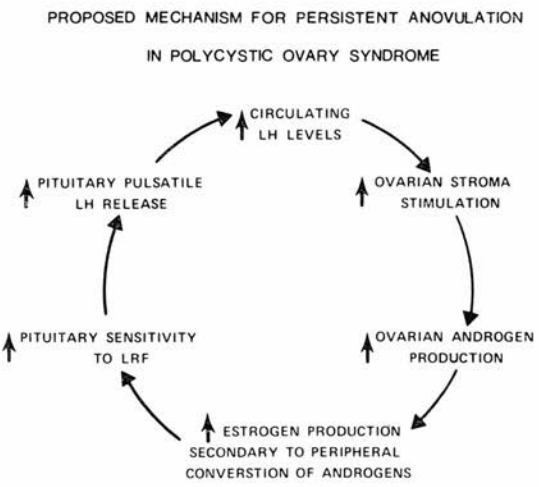

FIG. 8 - (From Yen, S.S.C. *et al.*: « The endocrine function of the human ovary », Acad. Press, London, 1976). Scheme proposed by Yen to esplain chronic anovularity in ovarian polycystic disease.

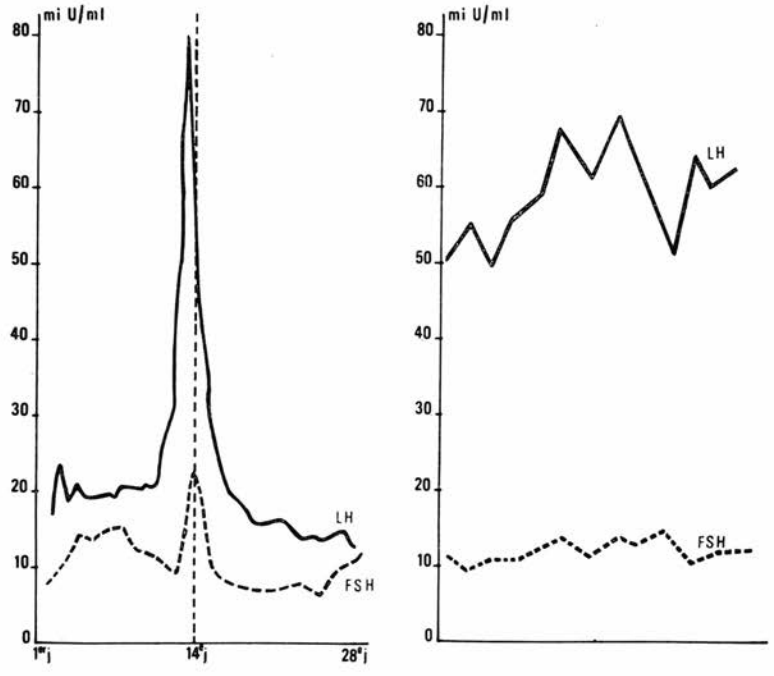

FIG. 9 - (From Barrat, J. and Kutten, F.: « Dystrophie ovarienne. Encyclopédie Médico-Chirurgicale, Gynécologie », 133 A 10-12, 1974). On the right, normal curve of plasma level of FSH and LH during the cycle. On the left, values obtained in a case of micropolycystic ovary.

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Siiteri & MacDonald ([36]) had demonstrated that more than half of the production of oestrone is derived from the peripheral conversion of androstedione into oestrone. Yen ([41]) supposed that this extraglandular source of oestrogens was extremely important in maintaining chronic anovularity (Fig. 8).

These steroids, in their turn, seem to have an adverse influence upon the centre of the anterior pituitary which controls the gonadotrophin release cycle, while stimulating the tonic centre. In fact, analyses carried out with the most modern techniques agree in disclosing high levels of LH and low production of FSH ([6, 15, 31, 40]) (Fig. 9).

More particularly, the gonadotrophic outline of S-L disease discloses levels of LH that are maintained on the basis of high values and little variation without the typical ovulatory peak, while the FSH values are maintained with low tonicity (Fig. 10).

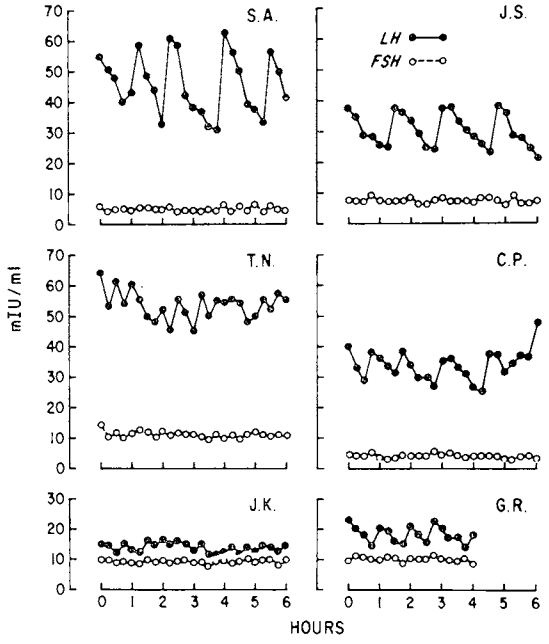


FIG. 10 - (From Yen, S.S.C. *et al.*: « The endocrine function of the human ovary », Acad. Press, London, 1976). Shows the variable and exaggerated behaviour of the release of pulsatile LH, but not of FSH, in 6 patients affected by ovarian polycystic disease.

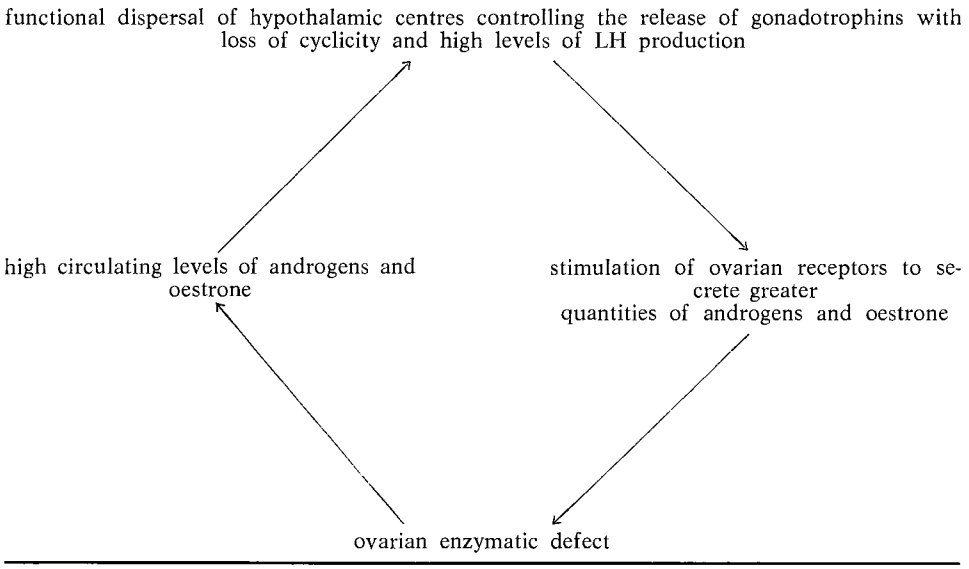
The disparity between the levels of LH and FSH in S-L disease has been explained in various ways: 1) the preferential inhibition of FSH has been found to be greater than that of LH, brought about by the high level of oestrone. Naftolin *et al.* ([29]) claim to have demonstrated that the rat hypothalamus may convert androstendione into oestrogens. Berger *et al.* ([6]) claim to have demonstrated a differentiated action of oestrone in preferentially suppressing the liberation of FSH and stimulating that of LH. 2) Yen ([41]) has postulated the existence of relative insensitivity of FSH to LHRF.

Thus the abnormal secretion of gonadotrophin is due to functional dispersal

consequent upon a chronic unsuitable feedback of the oestrogens at hypothalamic level.

It seems from what we have said that a vicious circle would be set up, of which the most obvious result is the perpetuation of chronic anovularity. Ovarian enzymatic defect→high levels of androgens and circulating oestrone→functional dispersal of the hypothalamic centres that control the release of gonadotrophins with loss of cyclicity→high levels of production of LH→which in their turn stimulate the receiving ovarian structures to secrete an increased quantity of androgens and oestrone. In this way the circle is closed (Fig. 11).

FIG. 11 - Scheme proposed to explain the pathogenesis of S-L disease.



The absence of follicular maturation in the ovary in S-L disease is a consequence of the relative deficiency of FSH and of the inhibitory process, in the ovaries themselves, brought about by the circulating androgens ([7, 8, 9, 10, 41]).

Numerous experimental investigations, recent and less recent, have confirmed that the androgens produced by enzymatic defects encountered from time to time in individual cases are responsible for all the phenomena encountered in S-L disease.

Barraclough ([3]) has demonstrated that by injecting testosterone into rats during the first few days of life (i.e., during the period of sexual maturity), chronic anovularity is found, with the presence of polycystic ovaries, much resembling the anovularity of S-L disease. Animals treated in this way lose the cyclic nature of the normal oestrus cycle.

In addition, by injecting androgens into young monkeys, a clinical and anatomical picture is obtained as regards the ovary that is similar to that found in S-L disease ([22]).

Anovularity is also obtained by injecting dehydroepiandrostendione for a long period into immature rats, and this is comparable to the typical ovaries in S-L disease ([4, 32]).

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Thus, from the data given above it seems evident that the abnormal ovarian production of androgens may give rise to characteristic clinical and morphological ovarian changes, typical of S-L disease. The experimental data, then, confirm that high doses of androgens, when administered for a long time, may give rise to micropolycystic ovarian dystrophy with hyperplasia of the stroma and inspissation and sclerosis of the cortex.

Therefore the thickness and sclerosis of the ovarian capsule, once considered fundamental pathogenetic factors in the aetiology of polycystic disease, should be though of purely as secondary endocrine effects. And even this exceptional occurrence due to androgenic action should be considered a clinical symptom of S-L disease.

The anatomic changes encountered in the ovaries in this disease thus constitute the morphological expression of a double pathogenetic factor: 1) production of steroids with androgenic activity and a direct action on the ovarian structures; 2) indirect action on the ovaries by means of the functional dispersal that they produce on hypothalamic-pituitary activity.

The hyperproduction of androgens explains the hirsutism and its diverse aspects; these depend on the degree of endocrine disorder, the quality of the androgens and the reactions of the pilar system of the androgens themselves (Fig. 12).

The other systems associated with the standard ovarian pathology may likewise be explained by the action exercised upon the hypothalamic-pituitary system and on the other sexual effectors by the various quantities and quality of the androgens, deriving from the primary ovarian endocrine disorder.

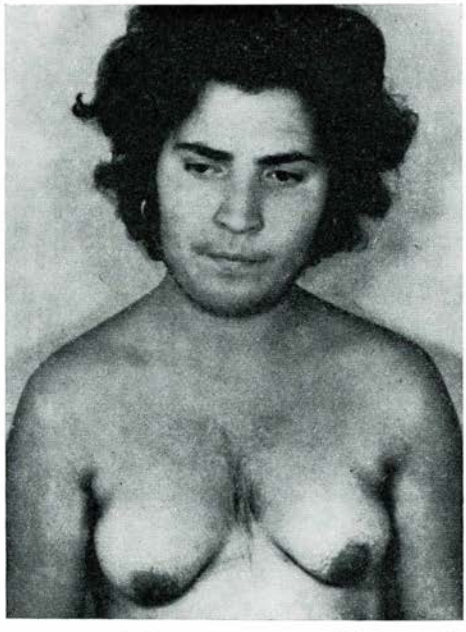

FIG. 12 - Shows the appearance of the arrangement of hair on the back and breast of a patient aged 28, affected by Stein-Leventhal disease.

AETIOLOGY OF THE STEIN-LEVENTHAL SYNDROME AND OF THE STEIN-LEVENTHAL TYPE OVARIES

The aetiological factors that may give rise to the S-L syndrome are manifold; they may be congenital or acquired, endogenous or exogenous, and are nearly always of extra-ovarian origin.

They have to be sought for among the substances with androgenic action produced directly by the female body or administrated to it.

Among the former may be enumerated: congenital suprarenal hyperplasia; suprarenal virilizing tumours; Cushing's syndrome or disease; suprarenal hyperfunction with hyperandrogenic endocrine disorder; sometimes ovarian masculinizing tumours (arrhenoblastoma).

Among the second, perhaps more numerous, are all the substances with androgenic action that are administered from outside.

The administration of exogenous androgens to the mother during the period of gestation may not only give rise to feminine pseudohermaphroditism, but may cause a true S-L syndrome in the daughter. Thus even the administration of androgens or substances with an androgenic action (oral anabolizers) to young children or to pre-pubescent or para-pubescent girls may have this effect.

A wide spectrum of aetiological factors, of which those mentioned make up only a very small part, may give rise to the S-L syndrome, whose clinical picture may be superimposed upon that of the disease, though it may sometimes be more obscure. Only the appearance of the ovary, which is generally not increased in volume nor in weight, is reminiscent of that of S-L disease.

A great many other factors of endocranial and cranial origin, functional or acquired and sometimes exogenous may give rise to ovarian conditions typical of those found in the S-L disease and syndrome. To name only a few: hypophyseal adenomas; acromegaly; hydrocephalus; cerebral gliomas; hypothalamic changes; endocraniosis; same contraceptive pills when given in insufficient doses (the « mini-pill ») or composed of progestational agents alone.

PATHOGENESIS OF THE S-L SYNDROME AND OF S-L TYPE OVARIES

After what has been said by way of explanation of S-L disease, the pathogenetic mechanism of the syndrome will easily be understood, since it exactly imitates it.

As we have seen, various aetiological, genotypical and paratypical factors may give rise to the syndrome.

This has been confirmed by the experimental data on animals in which ovarian changes have been produced similar to those found in the human S-L syndrome after the administration of androgens; and by the clinical finding of the existence of ovarian polycystic disease in congenital suprarenal hyperplasia, in Cushing's syndrome and disease, and in women with virilizing tumors either of the ovary or the suprarenals ([1,19,20,21]).

In all these cases the hyperandrogenic endocrine disorder, whether already present or brought about, interferes with the normal cyclic release of LH and produces a block in the maturation of the ovarian follicles ([16]) (Fig. 13).

If we accept the pathogenetic theories outline above in order to explain S-L disease, the ovarian conditions encountered in the S-L syndrome, described as typical Stein ovaries, might also be considered as the morphological expression of the androgenic action upon the hypothalamo-pituitary axis primarily, and secondarily upon the ovary.

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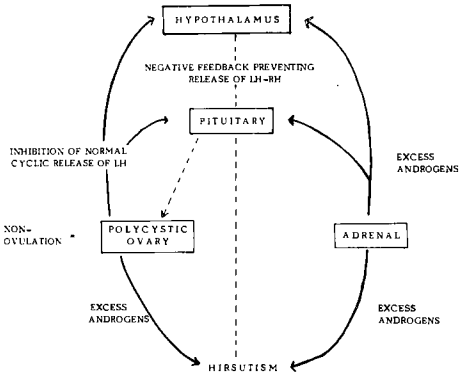

FIG. 13 - (From Duignan, N. H.: Brit. J. Obst. Gyn. [1976], 83, 8, 593). Scheme according to which the androgens, however present, induce the formation of ovarian polycystic disease by means of hypothalamic repercussions.

The above has been confirmed by the fact that in patients who before the syndrome arose, had regular menstrual cycles, sometimes followed by one or more pregnancies, the characteristic morphological and structural ovarian changes, typical of S-L disease, have been observed.

The clinical picture of the S-L syndrome represents the point of arrival at which various kinds of progressive pathological conditions of androgenic type converge, no matter how unrestrained.

In order to understand the pathogenesis of the ovarian type of micropolycystic disease it should be remember that the hypothalamus integrates information not only of a hormonal kind but also that relating to the central nervous system.

Therefore, both hyperandrogenous endocrine disorders and abnormal stimuli deriving from the central nervous system may give rise to tonic secretion of FSH-LH, bringing into being the picture of ovarian micropolycystic disease, whose origin is at the nervous control centre of the hypothalamus.

When the cerebral centres that control the development of the gonadotrophic hormones come to maturity in a girl at age X, these may have been made inert or at any rate virilized due to unsuitable androgen therapy administered to the mother during pregnancy, or to the child in the pre-pubescent or para-pubescent period, losing (perhaps definitively) their functional capacity in the gonadotrophin release cycle.

Experimentally, in rodents, a pattern has been set up that is comparable with the polymicrocystic ovary, chemically or physycally destroying the anterior pituitary centre responsible for the cyclic liberation of LH ([28]).

The same effect of functional dispersal of the cyclic centre can be obtained by administering androgens to subjects who have already menstruated normally or with the occurrence of spontaneous pathological virilization. In the latter cases the effect is temporary and limited to the period of persistence of the androgenic action.

To sum up, we think it can be accepted that it is possible to distinguish, within the framework of the condition originally described by Stein and Leventhal ([31]), three separately classified entities, which though they have in common

the anatomical picture of the ovary (and in some cases the clinical picture), differ with regard to the aetiological agent.

The first of these entities (the disease) comprises pathological manifestations occurring in young women and due to primary involvement of the ovary, brought about by an abnormal genetic constitution.

In the disease, the hyperandrogenism occurs at the first menstruation and progressively increases. Rarely, it has the character of hyperandrogenism with modifications of the android type; very often it is merely hypertrichosis, characterized by excessive proliferation of pubic hair and on the inner sides of the thighs.

The clinical picture of S-L disease, in which the fundamental factor found is marked ovarian hyperplasia, should be seen as the homologue of that found in congenital suprarenal hyperplasia. In fact, just as there exists in the suprarenals a pathological condition of enzymatic blocks, found at different levels of the steroid biosynthesis chain reaction, due to genetic factors, so in the ovary there exists a pathological condition due to genetic factors with enzymatic blocks in the ovarian steroid genesis chain reaction, and consequent ovarian hyperplasia.

S-L disease, as we defined it, is circumscribed, of rare occurrence, and not susceptible of spontaneous cure.

Patient affected by this disease remain sterile throughout life if they are not treated, and the course of the clinical symptoms becomes gradually worse.

In the syndrome, on the other hand, should be included the group of conditions which, although they present the anatomical ovarian symptoms and to some extent the clinical symptoms of S-L disease, are brought about by different aetiological factors. Their common denominator is hyperandrogenism.

The group of patients affected by the S-L syndrome is very heterogeneous and of frequent occurrence, as indeed are the « S-L type ovary » patients.

We need hardly say that a considerable role in the epidemiology of the S-L syndrome is played by the unsuitable administration of androgens, either to the mother during pregnancy (progestational agents with androgenic action) or to the child in the pre-pubescent or para-pubescent period.

In conclusion, the present criteria for the classification of the pathological conditions that we have considered, hinge upon the aetiological factor, seeing that neither the clinical nor the anatomo-pathological criterion, nor the endocrine outline, are sufficient to differentiate the various forms, thus making them easier to define.

Taking only into account the causes that have from time to time given rise to the individual clinical pictures, we have an excellent guide to the execution of correct therapeutic procedure.

SUMMARY

The author, on the basis of a critical review of the literature and his own experience, distinguishes three classificatory entities within the condition originally described by Stein-Leventhal: the disease, the syndrome and the Stein-Leventhal type of ovary.

Each of these has its own aetiological factor.

The disease is brought about by genetic factors and constitutes an entity analagous to congenital suprarenal hyperplasia.

The syndrome, occurring more commonly, is brought about by a large number of factors, endogenous and exogenous.

The Stein-Leventhal type of ovary seems to be caused by functional dispersal of

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the brain centres deputed to control the gonadotrophins, and is due to abnormal stimuli deriving from the cranial and pericranial structures.

This classification of ovarian polymicrocystic disease on an aetiological basis offers a guide to correct therapeutic procedure.

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