Summary

Two types of L.E. cell factors—transferable and non-transferable—were found in experiments in which plasma from patients with systemic lupus erythematosus was transfused into dogs.

Identical results were obtained in human subjects and in dogs with transfusions of transferable and non-transferable L.E. plasma factor.

The amount of transfused L.E. plasma appears not to be responsible for the production of two types of L.E. cell factor.

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IS THERE A STEIN-LEVENTHAL SYNDROME?

BY

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During the past twenty years much attention has been paid to the pathological findings in cases of multiple small cysts in ovaries with thickened capsules. Stein and Leventhal (1935) first described a group of cases with such findings and have recently reiterated their conception of what has become known as the Stein-Leventhal syndrome. Stein (1959) defines it as "sterility accompanied by secondary amenorrhoea, hirsuties in 50–75%, and consistently enlarged symmetrical ovaries with a definite pathological pattern." The ovarian changes, he says, may also be found in cases of the adrenogenital syndrome. Leventhal (1958) describes the ovarian pathological findings. The tunica is thick, tough, and pearly white. There are multiple small cysts. The follicles may or may not have layers of granulosa cells. The most consistent finding he describes is hyperplasia of the theca interna with frequent luteinization. The absence of corpora lutea or corpus luteum cysts is noted, and he states that when secretory endometrium is found there is again no evidence of corpora lutea, but marked luteinization of the theca

Present Investigation

The findings at Chelsea Hospital for Women have been quite different from any reported so far, and are therefore worthy of note.

The clinical features are correlated with the histological findings in two groups, while a third group acts as a control.

Group 1: Typical histology + clinical syndrome of infertility, irregular periods, and hirsutism.

Group 2: Typical histology + clinical syndrome and corpus luteum.

Group 3: Controls; patients in the same age-group, seen during the same period of time, but with varying indications for operation.

The main findings, histologically, are recorded in Table I. All the histological preparations which provide the material for this analysis were examined "blind," and no indication was given of the group to which the section belonged. It will be noted that histological changes in the ovarian capsule are not included in the table, and this is because we have not found it possible to decide a "normal" for each age, owing to the wide variation in the thickness of the capsule. The clinical features are recorded in Table II.

It will be seen that our findings approximate fairly closely as regards the large number of cystic follicles, while the operation notes mention the tough fibrous capsule. A layer of granulosa cells is present in all but one of our cases, but hyperplasia of the theca interna is not as evident as Leventhal has found. In fact, though the theca interna has been present, hyperplasia has not been noted in a single case (Table I).

Luteinization of the theca interna has not been a feature in the cases studied, though it is thought by Shippel (1955) and by Plate (1958) to constitute the principal finding. This hyperthecosis is reported as affecting the theca externa as well, but in our series no cases have come to light where the theca externa has shown hyperplasia. Leclercq (1958) in a series of 51 cases reports very similar findings to those of Leventhal, but we are unable to find the same degree of specificity described by them.

Ovulation has been reported by Stein *et al.* (1949) as occurring very rarely, at long intervals, or not at all; and Kaufman *et al.* (1959) refer to a characteristic lack of recent corpora lutea. Shippel mentions ovulation as a freak occurrence; Ingersoll (1955) says that all the patients are anovulatory, the only common finding being the ovarian pathology; while Prunty *et al.* (1958) also note the absence of ovulation in this syndrome. Bailey (1959) found no corpus luteum in 63 cases. The striking thing about our cases is the comparatively large number showing corpora lutea.

The question of ovulation is obviously of prime importance, since the object of treating these patients is to enable them to ovulate and thus become pregnant. The operation of wedge resection, detailed by Leventhal (1958), may produce regular menstruation in a patient who was previously ovulating with an irregular cycle. It is doubtful whether the operation is indicated in such cases.

Wedge resection may also produce normal ovulatory cycles in patients who were previously suffering from amenorrhoea. The continuance of normal cycles, with or without ovulation, is not necessarily permanent after the operation (Table II).

Groups 1 and 2 show the same features except for the evidence of recent ovulation in group 2. It will also be seen that there is no typical histological pattern of the ovaries which serves to distinguish either of these groups from the controls.

Hirsuties was considerable in three cases in group 1 while the other four showed slight excess of hair. In group 2 (patients who were ovulating) there was considerable hirsutism in four, and two showed a slight excess of hair. The other case in this group was interesting, because, though there was hirsuties of the face and trunk, the hair on her head was absent and she needed to wear a wig. Hirsuties was present in one case in the control group.

Lynch *et al.* (1959) noted a direct relationship between the degree of masculinization and the extent of luteinization of the theca cells. The present series of cases shows that there can be a marked degree of masculinization coincidental with ovulatory menstruation.

It will be seen from Table II that the operation of wedge resection has had no effect on the hirsuties of these patients, only one suggesting that she felt she was growing less hair after the operation, though there was no objective proof of this.

Obesity is no longer considered to be of importance in this syndrome (Stein, 1958), and it has not been a feature in our series of cases.

Hormone estimations were carried out on eight of the patients in groups 1 and 2. No abnormalities were found in the levels of the urinary 17-ketosteroids or the pituitary gonadotrophins.

Endometrial biopsies were taken in 11 cases. Of these, one showed no endometrium, and two showed a proliferative and one a secretory endometrium in the presence of a corpus luteum. The other seven showed cystic glandular hyperplasia. This is in contrast to Stein (1955), who found predominantly early proliferative endometrium, as did Ingersoll (1957) and Leclercq (1958). Jackson and Dockerty (1957) found mainly proliferative endometrium in a non-neoplastic group of

TABLE I.—*Histological Findings*

Case No.	Follicles			Lining of Follicles			Corpus Luteum	Endometrial Biopsy
	Cystic	Position	Atretic	Granulosa	Theca in Cystic Follicle	Theca in Stroma		
Group 1								
1	Many	D/B	Many	Present	+ in cystic + „ atretic	No	No	C.G.H.
2	Few	D	„	Scanty	No	„	„	Nil
3	Many	D	Few	Present	± in cystic	„	„	C.G.H.
4	„	D	„	„	+ „ „	„	„	C.G.H.
5	Few	D	Many	„	+ „ „	„	„	C.G.H.
6	„	B	„	„	+ „ 3 atretic	„	„	Prolif.
7	Many	D/B	Few	„	± „ cystic	„	„	„
Group 2								
8	„	B	„	„	+ in cystic	„	Yes	—
9	„	D	Many	„	+ „ „	„	„	C.G.H.
10	Few	D	Few	„	± „ „	„	„	C.G.H.
11	Many	D	„	Scanty	± „ „	„	„	Secretory
12	„	D	„	Present	+ „ „	„	„	C.G.H.
13	Few	D	„	„	+ „ „	„	„	—
14	Many	D	Many	„	+ „ „	„	„	—
Group 3								
15	„	B	Few	„	± in cystic	„	No	—
16	„	B	„	„	± „ „	„	No	—
17	„	D	„	„	± „ „	„	Yes	—
18	„	D	Many	„	{ + „ „ }	?	No	—
19	Few	D	Few	„	± „ „	No	Yes	—
20	Many	D/B	„	„	± „ „	„	No	—
21	„	D	Many	„	± „ „	„	„	—

+ Signifies "within normal limits." ± Signifies "present." B=Bulging surface. D=Deep. C.G.H.=Cystic glandular hyperplasia.

TABLE II.—*Clinical Findings*

Case No.	Age	Menstrual Hist.	Fertility	Hirsuties	Obesity	Other Inf.	Follow-up
<i>Group 1</i>							
1	21	Am. 9 mths.	0	Slight	Yes		Pregnancy
2	26	Men. 13, 7/28 to 17, then 2-14/6 to 12 mths.	0	Considerable	No		None
3	24	Men. 13, 6 to 12 mths.; Am. 14 mths.	0	Slight	"		Pregnancy
4	26	Men. 13, 5/2 to 5 mths.	0	"	"		Reg. periods—relapse after 5 mths.
5	21	Men. 15, regular 1 yr., then Am. up to 1 yr.	0	"	"		Reg. periods till relapse after 6 mths.
6	25	Men. 13, Am. up to 1 yr. Wedge resection 2 yrs. ago = Am. up to 9 mths.	0	Considerable	Yes		No period, ? hirsuties less
7	19	Men. 12, 5/28 to age 15, then always irregular	0	"	No		Reg. periods 3 mths.
<i>Group 2</i>							
8	27	Men. 13, 5/28	1 child	Considerable	No		Periods 5/26
9	26	Men. 13, 7/28 for 8 yrs., then Am. up to 12 mths.	0	"	Yes		" regular
10	36	Men. 16, 6/2 to 3 mths.; Am. 8 mths.	0	Slight	No		None
11	25	Men. 11, 5/35, then Am. 16 mths.	0	Considerable	"		Periods regular
12	32	Men. 12, 5/28 to age 27; then Am. 3 to 4 mths.	0	Face, trunk	"		" "
13	19	Men. 15, Am. up to 6 mths.	0	Slight	"		"
14	34	Men. 16, Am. up to 6 mths.	1 child	Considerable	"	Depression	Periods 5/21 for 6 mths., then amenorrhoea
<i>Group 3</i>							
15	26	Men. 13, 5/1 to 6 mths.	0	No	No	Infertility.	None
16	31	Men. 11, 6/28	1 child	"	Yes	Hydrosalpinges	
17	24	Men. 11, 7/1 to 2 mths.	0	"	No	Dyspareunia	Normal
18	17	Men. 12, 2/1 to 2 mths.	0	Considerable	"	Ruptured luteal cyst	
19	20	Periods 6/28	0	No	"	Enlarged ovary	Monthly periods
20	34	Periods 4/1 to 3 mths.	1 child	"	"	Opn. for abdo. pain	Normal
21	26	Men. 15, 5/35	2 children	"	"	Oophorectomy at opn. for backache	"
						Enlarged ovary	"

Men.=menarche. Am.=amenorrhoea.

cases, but noted the occurrence of endometrial carcinoma in cases with long histories. Kaufman *et al.* (1959) found a higher incidence of endometrial hyperplasia, as we have done. It may be suggested that the diagnosis in some of these cases should therefore be metropathia haemorrhagica. However, typical cases of metropathia haemorrhagica do not have periods of amenorrhoea lasting longer than three months. At this hospital cystic glandular hyperplasia is found more often than was formerly suspected, and it may occur in patients who are menstruating regularly. It is sometimes found in association with corpora lutea, and pregnancy has been seen to occur in a uterus which showed cystic glandular hyperplasia.

The earlier and larger series of cases quoted do not appear to have had routine endometrial biopsies taken, and it is possible that many more would have shown this histological picture.

The results of wedge resection in group 1 show that regular menstruation has not persisted for longer than six months, with the exception of two women who became pregnant two and three years respectively after operation. In group 2, where ovulation was occurring, of the six patients followed up, two had menstruated normally for more than a year. Regular menstrual periods had occurred in one patient for six months, but after this time she relapsed into amenorrhoea. The other three patients were still menstruating regularly at the end of four months, but a longer follow-up is not available. Stein (1958) has reported re-establishment of normal menstruation in 95% of patients, and 88% of his cases became pregnant.

Discussion

The aetiology of the Stein-Leventhal syndrome has received a great deal of attention and several theories have been advanced to explain it. However, the occurrence of the ovarian histological picture without symptoms, the absence of hyperthecosis, and the presence of corpora lutea in such a large proportion of the cases studied here make it difficult to accept any theory so far advanced. It has already been shown that it is not possible to pick out a case of this syndrome from the series presented. Since the appearance of the ovarian cells gives no true indication of the conditions which have produced this appearance we cannot go beyond reporting the features encountered in the cases seen at this hospital. The answer to the problem of aetiology is not likely to be found by ordinary histological examination.

It may be said that all our cases are in the early stages of a progressive disorder, but the age incidence is the same as that in published series. Symptomatology and histology do not necessarily go together, and it is difficult to believe that there is such a definite entity as a Stein-Leventhal syndrome.

The histological findings in the ovaries are shown to be present in the absence of symptoms, and it is strange that the only definite and constant part of the syndrome should occur also in the controls. It would be more apt to refer to the condition as multiple small follicular cysts of the ovary, rather than cling to the eponymous nomenclature suggesting symptoms and signs which may not be present.

If a patient is infertile and has palpably enlarged ovaries and no evidence of ovulation, there is adequate

justification for the performance of wedge resection, which gives her a chance of ovulating and becoming pregnant.

Summary

Histological studies were made of the follicle linings in ovarian tissue from 21 patients.

The cases were divided into three groups, and the third of these groups was used as a control.

The histological and clinical features of the cases are discussed, and the conclusion is reached that the Stein-Leventhal syndrome does not appear to be a well-defined entity.

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THALASSAEMIA IN A GURKHA FAMILY

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The thalassaemia syndrome is occasionally encountered by clinicians in Gurkha (Nepalese) subjects, but there are few reports of cases in the literature. Brain and Vella (1958) reported haemoglobin-H disease (haemoglobin-H thalassaemia) in a Gurkha woman, and a second such case has recently been found, again in a pregnant Gurkha woman, in Malaya.

The present report deals with a case of thalassaemia-like disease in a young Gurkha girl. This diagnosis is supported by a family study.

Case Report

A female Gurkha child aged 3 months was seen at the British Military Hospital, Kinrara, in July, 1954, when she was referred for investigation for a hypochromic anaemia. Examination then revealed a relatively well-nourished infant with pallor of the mucous membranes and marked hepatosplenomegaly.

Laboratory investigations showed: haemoglobin, 5.5 g./100 ml.; W.B.C., 9,300/c.mm. (neutrophils 50% lymphocytes 40%, eosinophils 5%, basophils 3%, monocytes 2%); reticulocytes, 2%. Erythrocyte osmotic fragility was decreased. Peripheral blood films showed hypochromia, anisopoikilocytosis, microcytosis, target cells, and many normoblasts. No malarial parasites were noted on repeated