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IMMUNE CELL CIRCULATING SUBSETS ARE AFFECTED BY GONADAL FUNCTION

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Summary

Influence on the immune system activity by sex hormones has been widely reported. Fertile women are proner to the onset of autoimmune diseases than men, but this increased susceptibility disappears after menopause. The hormonal changes are very likely to be responsible for this event, but precise correlations between sex hormone levels and immune functions have not been defined. For this reason we have analyzed phenotype and natural cytotoxicity of peripheral blood lymphocytes (PBL) from 35 women in menopause, comparing them with the same parameters of 28 fertile and 8 postmenopausal women and correlating them with the hormonal pattern of each group. We have also considered 8 women with premature menopause. Hormonal levels have been detected by radioimmune assays, while PBL phenotype has been studied by immunofluorescence and FACS analysis. The natural killer (NK) cell activity has been calculated on the basis of a chromium release assay. Postmenopausal women showed a reduction of the number of total lymphocytes (1650±215 cells/mmc) in comparison to fertile women (2081±200 cells/mmc, $P<0.01$). The decrease mainly involved B and CD4+ T lymphocyte subpopulations ($P<0.05$ and $P<0.01$, respectively). Women with premature menopause had lower percentage of CD4 lymphocytes (34% vs 47%, $P<0.01$) and higher percentage of CD8 (30% vs 22%, $P<0.02$) and NK cells (32% vs 14%, $P<0.009$) than fertile women of the same age. The percentage of circulating lymphocytes expressing HLA class II antigens also resulted as being increased (22% vs 9%, $P<0.01$). The number of total, CD2, CD4 T lymphocytes, B and NK cells correlated positively with LH and negatively with FSH serum levels ($P<0.05$ and $P<0.002$, respectively). PRL positively influenced CD2, CD4 and B lymphocyte numbers ($P<0.001$). FSH and 17β-estradiol inversely affected CD8 and B lymphocyte numbers ($P<0.005$ and $P<0.02$, respectively). In conclusion, the increase of FSH and the decrease of PRL levels appear to be involved in the reduction of B and CD4 T lymphocytes thus lowering the risk for the onset of autoimmune diseases during and after menopause. Generalized activation of the immune system (raised expression of HLA class II antigens) with elevated numbers of cytotoxic subpopulations (CD8 and NK lymphocytes) is present in women affected by premature menopause suggesting the involvement of autoimmune dysregulation in the pathogenesis of this syndrome.

Key Words: CD4+ lymphocytes, CD8+ lymphocytes, NK cells, B lymphocytes, gonadotropins, sex hormones

Influence on the immune system activity by sex hormones has been widely reported in both physiological and pathological conditions (1, 2). Higher circulating immunoglobulin levels (3, 4), decreased cellular mediated responses (5, 6), lower natural killer (NK) cell activity (7, 8), and increased susceptibility to autoimmune diseases (1, 2, 9, 10, 11) in women suggest the existence of an immunological sexual dimorphism. The involvement of sex hormones in the regulation of the immune response has been suggested on the basis of the following evidence: a) estradiol shows an inhibitory effect on both the CD8 positive T cell proliferation and the NK activity (12, 13, 14, 15); b) estrogen receptors have been identified on human CD8 positive T lymphocytes (16, 17); c) prolactin-specific binding sites have been characterized on human B and T lymphocytes (18); d) estrogen and androgen receptors have been discovered on the surface of macrophage-like synoviocytes and of CD8+CD29+CD45RO+ T (memory) lymphocytes infiltrating normal and rheumatoid synovial tissues (19). Nevertheless, no clear correlations between specific in vivo endocrine patterns and immune system function have been demonstrated. In the present paper the authors focused on the possibility to reveal these correlations by

studing phenotype and NK activity of peripheral blood lymphocytes from 71 women of different ages with different hormonal and reproductive conditions and from 35 men of corrisponding ages.

Materials and Methods

Subjects

71 healthy women with a personal history negative to autoimmune, neoplastic, metabolic, endocrine or infective diseases entered the study. They were subdivided in 6 groups on the basis of their age and of the following endocrine status:

01 Group 1 - 18 women of age ranging between 20 and 39 yrs (mean 29.9) with regular menstrual cycle;
Group 2 - 10 women of age ranging between 45 and 55 yrs (mean 48.8) with regular menstrual cycle;
Che Sun Group 3 - 8 women of age ranging between 39 and 53 yrs (mean 46.3) without menstrual cycles since at least 6 months ago;
Group 4 - 15 women of age ranging between 42 and 56 yrs (mean 48.9) in menopause since 6 months to 2 years ago;
Group 5 - 12 women of age ranging between 41 and 57 yrs (mean 52.9) in menopause since 2 to 5 years ago;
Group 6 - 8 women of age ranging between 61 and 75 yrs (mean 71.6) in menopause since more than 5 years ago;
02 Group 7 - 8 women of age ranging between 25 and 39 yrs (mean 32.5) with premature menopause.

Che Sun 35 men, for controls, were collected and divided as follows:
Group 8 - 20 men of age ranging between 27 and 51 yrs (mean 34.1);
Group 9 - 15 men of age ranging between 65 and 71 yrs (mean 70.9).

Hormone levels detection

Gonadotropins (FSH and LH) and Prolactin (PRL) determinations were performed using commercially available kits (Maiaclone, Ares Serono, Milan, Italy). The sensitivity of the LH assay was 1 mIU/mL and the intra-assay coefficient of variation (CV) was 3.8%. The respective values were 0.8 mIU/mL and 4.5% for the FSH assay, 3ng/mL and 3.8% for PRL.

17-β-estradiol (17βE2)was measured with a no-extraction solid-phase radioimmunoassay (RIA) (Diagnostic Products Corporation, Los Angeles, CA). The sensitivity was 9 pg/mL and the intra-assay CV was 6.7%.

Progesterone (P), total Testosterone (T) and free Testosterone (free T) were measured using RIA kits supplied by Diagnostic Products Corporation (Los Angeles, CA). Sensitivity and intra-assay CV were 0.1ng/mL and 6.8% for P, 0.12 ng/mL and 7.0% for total T and 0.15 pg/mL and 5.0% for free T, respectively.

Dehydroepiandrosterone sulphate (DHEAS) concentration was determined using a RIA kit supplied by RADIM (Rome, Italy). The sensitivity of this assay was 0.02 μg/mL and the intra-assay CV was 6.4%.

Delta-4-Androstenedione (D4-A) was measured using the Amersham RIA kit (Amersham, United Kingdom). The sensitivity of this assay was 0.05 ng/mL and the intra-assay CV was 4.9%.

Estrone (E1) serum concentration was determined by a RIA kit from RADIM (Rome, Italy) after ether extraction (recovery 90% to 91%). The sensitivity was 10 pg/mL and the intra-assay CV was 5.3%.

Total lymphocyte number

The total lymphocyte number was calculated on the count of total leukocytes on the basis of the lymphocyte percentage (evaluated after staining of a film of whole blood on a smear and counting lymphocytes at optical microscopy) as follows:
lymphocyte number = total leukocyte number x percentage of lymphocytes.

Peripheral blood lymphocytes (PBL)

PBL were isolated from heparinized (Liquemin, Roche) peripheral blood through a Ficoll-hypaque gradient centrifugation. Recovered lymphocytes were washed 3 times with Hanks' balanced saline solution and then resuspended in RPMI 1640 supplemented with penicilline 1%, streptomycine 1% and fetal calf serum 10% (complete medium).

Lymphocyte phenotype

Lymphocyte phenotype was determined using fluorescein conjugated monoclonal antibodies (mAbs) directed to the following antigens: CD2, CD4, CD8, CD19, CD56. The mAbs were purchased by Coulter (Milan, Italy). The

HLA class I and class II antigen expression was determined using the W6/32 and Q5/13 mAbs, respectively, supplied by Dr. S. Ferrone (Valhalla, New York).

A Coulter Epics Profile II was used for quantitative fluorescence analysis. Approximately 2×10^5 cells were stained with 100 μL of adequately diluted mAbs at 4 °C for 30 min, washed twice and resuspended in 0.5 μL of Hanks' solution for FACS analysis.

Chromium release assay

NK cell activity of PBL was tested in a standard 4 hours ^{51}Cr release assay utilizing as target the K562 human erythroleukemia derived cell line, as target. 1×10^6 target cells were labeled with 150 μCi of $Na^{51}CrO_4$ for 1 hour at 37 °C. After two washes, the target cells were counted, resuspended in complete medium and added at the concentration of 5×10^3 cells/well in quadruplicate to various numbers of effector lymphocytes (50:1, 25:1, 12:1 effector:taarget ratio) in 96 flat-bottom microtiter plates in a final volume of 200 μL. Spontaneous and maximum ^{51}Cr release were determined by incubating target cells in culture medium alone or in 1% Tryton-X, respectively.

The plates were incubated for 4 hours at 37 °C and then centrifuged. 100 μL of supernatant were harvested from each well and the radioactivity was measured by a gamma-counter. The results are expressed in percentage (%) of lysis as follows:

% of lysis= (sample cpm - spontaneous release cpm) / (maximum cpm - spontaneous release cpm) x 100.

Statistical analysis

Mean values of immunological parameters among different groups were compared by Variance Analysis (ANOVA). Regression coefficients between hormone serum concentrations and related immunological parameters were calculated using Multiple Regression Analysis Test.

Results

Total lymphocyte number variations among groups

The total number of lymphocytes progressively decreased from young and fertile to elder and infertile women. The number of lymphocytes in the women conserving the menstrual cycles (group 1: 2065/mmc and group 2: 2081/mmc) resulted higher than in elder women (group 6: 1650/mmc) ($P<0.02$) (table 1).

The lymphocyte number in young men (group 8: 2386/mmc) was higher than in young women of group 1 and the lymphocyte number of old men (group 9: 2045/mmc) was higher than in elder women (group 6: 1650/mmc) ($P<0.04$) (table 1).

Differences in T lymphocyte number and percentage among various groups

The percentage of CD2 positive T lymphocytes was about 75% in all groups with the exception of group 7 in which it appeared reduced (61%) (table 1).

The absolute number of CD2 positive T lymphocytes showed a significant decrease both in the elder age (group 6) and in women with premature menopause (group 7) (1060/mmc and 1280/mmc, respectively) with respect to the young (group 1) (1532/mmc) and menopausal ages (group 4:1379/mmc and group 5: 1733/mmc) (table 1). Moreover, it was higher both in young and elder men (group 8: 1781/mmc and group 9: 1595/mmc) than in women of the same age (groups 1 and 6, 1532/mmc and 1060/mmc, respectively) (table 1).

The percentage of CD4 positive T lymphocytes was significantly lower in elder (group 6: 742/mmc) when compared to young women (group 1: 955/mmc, $P<0.05$) (table 2).

A remarkable reduction of both CD4 T lymphocyte percentage and number was detected in women with premature menopause (group 7) compared to all the other groups (table 2). No significant differences in CD4 T lymphocyte number and percentage were observed between groups of men and women of the same age.

CD8 positive T lymphocyte number and percentage (674/mmc and 34%, respectively) were found elevated in women with premature menopause (group 7) with respect to all the other groups (table 2). Besides, the CD8 T lymphocyte number was more elevated in men than in women of the same age (group 8: 680/mmc and group 1: 440/mmc; group 9: 449/mmc and group 6: 429/mmc) (table 2). These differences did not reach the statistical significance.

B lymphocyte variations among different groups

The percentage of B lymphocyte was higher in women without menstrual cycle (group 3: 10%; group 4: 12%; group 5: 15%) than in still menstrued women (group 1: 9%; group 2: 7%). Significant differences were found between groups 2 and 4 ($P<0.01$) (table 1). However, a remarkable reduction of both B lymphocyte number and percentage was observed in elder women (112/mmc and 6%, respectively) with respect to all the other groups (table 1).

Table 1

TOTAL, T AND B LYMPHOCYTE NUMBERS AND PERCENTAGES IN THE DIFFERENT GROUPS

GROUPS	TOTAL LYMPH.	T LYMPHOCYTES+		B LYMPHOCYTES	
	cells/mmc	cells/mmc	percentage	cells/mmc	percentage
1	2065 ± 567	1532 ± 526* vs groups 6,7	74 ± 9	230 ± 60** vs group 6	9 ± 3
2	2081± 200** vs group 6	1566 ± 258	75 ± 15	260 ± 45** vs group 6	7 ± 1** vs group 4
3	1988 ± 778	1405 ± 794	71 ± 10	198 ± 48* vs group 6	10 ± 3
4	1923 ± 444* vs group 6	1379 ± 351* vs group 6	70 ± 10* vs group 9	160 ± 52* vs group 6	12 ± 2** vs group 2
5	1817 ± 507	1733 ± 749* vs groups 6,7	79 ± 7* vs group 7	121 ± 21	15 ± 8
6	1650 ± 215* vs groups 2,4,9	1060 ± 112* vs groups 1,4,5,8,9	76 ± 10	112 ± 31	6 ± 3* vs group 7
7	1991 ± 227	1280 ± 182* vs groups 1,5,8,9	61 ± 17* vs groups 5,9	181 ± 40** vs groups 1,2,3,4,7,9	11 ± 5* vs group 6
8	2387 ± 250	1781 ± 389* vs groups 6,7	76 ± 7	86 ± 47	12 ± 3
9	2045 ± 561* vs group 6	1595 ± 340* vs groups 6,7	78 ± 8* vs groups 4,7	200 ± 36* vs group 6	10 ± 3

THE RESULTS ARE EXPRESSED AS MEAN VALUES ± STANDARD DEVIATION
*= SIGNIFICANT DIFFERENCE VERSUS THE INDICATED GROUP(S) : $P<0.05$
**= SIGNIFICANT DIFFERENCE VERSUS THE INDICATED GROUP(S) : $P<0.01$
+ = CD2+ LYMPHOCYTES WERE CONSIDERED REPRESENTATIVE OF THE TOTAL T LYMPHOCYTE POPULATION

HLA antigens expression in the different groups

No significant variations of the percentage of HLA class I and class II antigen positive lymphocytes were detected among the different groups. The only exception was the high percentage of HLA class II positive lymphocytes observed in the PBL of women with premature menopause (23%) (table 3). Since in this group the percentage of circulating B lymphocytes (which express constitutively the HLA class II antigens) is 11%, one must assume that in the PBL of these women there is another HLA class II positive lymphocyte subpopulation reasonably referred to as activated T lymphocytes.

Table 2

CD4, CD8 AND NK LYMPHOCYTE NUMBERS AND PERCENTAGES IN THE DIFFERENT GROUPS

GROUPS	CD4 T LYMPHOCYTES		CD8 T LYMPHOCYTES		NK LYMPHOCYTES	
	cells/mmc	percentage	cells/mmc	percentage	cells/mmc	percentage
1	955 ±296* vs group 6	47 ± 8* vs groups 1,7	440 ± 154	22 ± 4* vs group 7	286 ± 66	14 ± 6** vs groups 7,9
2	929 ± 114	44 ± 14	483 ± 197	22 ± 9	251 ± 127	12 ± 7* vs groups 7
3	1180 ± 502	54 ± 14* vs group 7	360 ± 112	22 ± 6	570 ± 200	19 ± 5** vs group 9
4	924 ± 301	47 ± 11* vs group 7	388 ± 126	20 ± 5** vs groups 7,8	260 ± 101	14 ± 8** vs group 9
5	1138 ± 610	54 ± 7** vs groups 1,7,8,9	408 ± 103	22 ± 2** vs group 7	254 ± 90	17 ± 3** vs groups 7,9
6	742 ± 91* vs groups 1,9	45 ± 2	429 ± 87	26 ± 2	346 ± 33	21 ± 6** vs group 9
7	674 ± 150	34 ± 7** vs groups 1,3,4,5,8,9	600 ± 132	30 ± 7** vs groups 1,4,5,9	650 ± 180	32 ± 6** vs groups 1,2,5,9
8	1098 ± 201	45 ± 6** vs groups 5,7	680 ± 110	26 ± 6* vs group 4	ND	ND
9	940 ± 280* vs group 6	46 ± 7* vs groups 5,7	449 ± 92	22 ± 5* vs group 7	122 ± 37	6 ± 4** vs groups 1,3,4,5,6,7

THE RESULTS ARE EXPRESSED AS MEAN VALUES ± STANDARD DEVIATION
*= SIGNIFICANT DIFFERENCE VERSUS THE INDICATED GROUP(S): $P<0.05$
**= SIGNIFICANT DIFFERENCE VERSUS THE INDICATED GROUP(S): $P<0.01$

NK cell activity and NK cell number in the different groups

The NK cell activity didn't show significant changes among the female groups. However, significant differences were detected between women and men of corrisponding age. In fact, the percentage of natural cytolysis was 40% for group 1 (young women) and 62% for the group 8 (young men) ($P<0.001$). It was 34% for group 6 (elder women) and 52% for group 9 (elder men) ($P<0.01$) (figure 1).

The NK cell absolute number and percentage were quite constant among all groups with the exception of group 7 (women with premature menopause) in which elevated values were observed (650/mmc and 32%, respectively) (table 2). The number (90/mmc) and percentage (6%) of NK cells was lower in the elder men with respect to all of the women groups (table 2).

Comparison between hormonal and immunological parameters

The absolute numbers of the different lymphocyte subpopulations statistically correlated with different hormonal patterns. In particular, the absolute numbers of total lymphocytes, CD2 and CD4 positive T lymphocytes, and of B and NK cells positively correlated with the LH serum levels and negatively with the FSH serum concentrations (tables 1, 2, 4 and 5). PRL showed a positive correlation with the number of CD2, CD4 and B lymphocytes (tables 1, 2, 4 and 5). The CD8 T lymphocyte and B cell numbers were inversely related to the serum levels of FSH and 17βE2 (tables 1, 2, 4 and 5).

Table 3

EXPRESSION OF HLA CLASS I AND II MOLECULES ON PBL FROM THE DIFFERENT GROUPS

GROUPS	HLA CLASS I	HLA CLASS II
1	85 ± 10	9 ± 7** vs group 7
2	92 ± 4	8 ± 5* vs group 7
3	80 ± 15	13 ± 4
4	91 ± 9	15 ± 6
5	86 ± 15	18 ± 6
6	78 ± 19	9 ± 2
7	95 ± 4	22 ± 8** vs groups 1,2,8,9
8	95 ± 7	7 ± 5** vs group 7
9	92 ± 10	10 ± 8* vs group 7

THE RESULTS ARE EXPRESSED AS MEAN VALUES ± STANDARD DEVIATION AND
ARE REFERRED TO THE PERCENTAGE OF HLA MOLECULE EXPRESSION ON PBL.
*= SIGNIFICANT DIFFERENCE VERSUS THE INDICATED GROUP(S) : P<0.05
**= SIGNIFICANT DIFFERENCE VERSUS THE INDICATED GROUP(S) : P<0.01

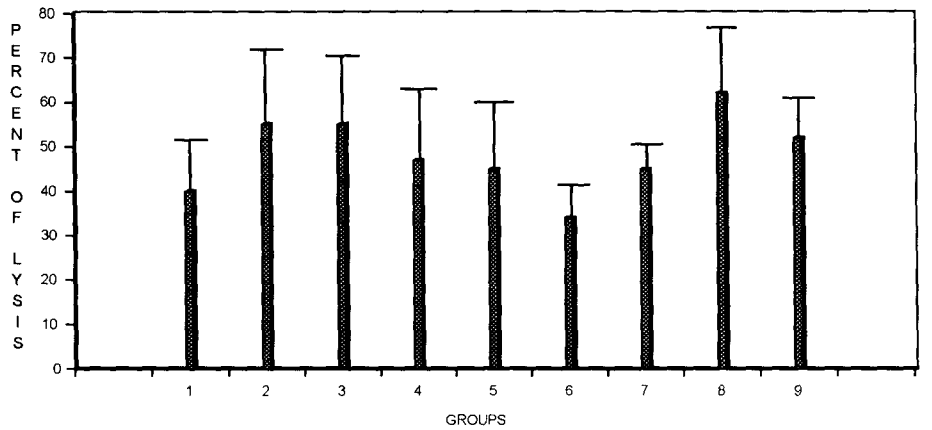

Fig. 1

NK cell activity in the different groups

Discussion

The concept of immunological sexual dimorphism has been generated on the basis of the discrepancy existing between male and female immune function in both physiological and pathological conditions (1, 2). Our data are in agreement with this hypothesis since both the number of each lymphocyte subpopulation and the natural cytotoxic activity were found to be increased in men with respect to women of the same age. In order to analyze the mechanism through which the female gender affects the immune balance, the relationship between immune and endocrine parameters was analyzed in women at various ages. Peripheral blood lymphocyte subpopulations showed different patterns at each age which correlated with the hormonal status. 17βE2 levels were inversely related with CD8 lymphocyte number and B lymphocyte number and percentage while gonadotropins showed a wider spectrum of correlations. In particular, LH serum concentrations directly correlated and the serum levels of

Table 4

CONCENTRATIONS OF HYPOPHYSIAL AND OVARIAN HORMONES IN THE DIFFERENT GROUPS OF WOMEN

HORMONES	GROUPS						
	1	2	3	4	5	6	7
FSH*	4.9 ± 2	15.8 ± 12.3	27.40± 23.1	76.79± 30.7	77.82± 29.9	100.4± 46.5	89.48± 29.0
LH*	4.1 ± 1.4	8.21 ± 6.24	18.74± 9.57	23.4 ± 7.04	19.93± 5.37	37.75± 26.3	38.9 ± 7.3
PRL**	9.9 ± 4.6	6.95 ± 3.04	11.7 ± 9.58	8.87 ± 4.38	7.66 ± 3.95	3.05 ± 2.0	10.43± 4.1
17ßE2***	118 ± 80.8	93.2 ± 65.9	85.33± 36.9	16.8 ± 10.2	21.70± 27.8	8.4 ± 4.9	17 ± 4.0
E1***	39.4 ± 35.0	20.3 ± 12.9	36.1 ± 23.9	20.1 ± 9.5	16.75± 13.6	4.0 ± 2.1	29.6 ± 8.1
P**	8.8 ± 6.2	5.35 ± 4.69	3.5 ± 3.7	0.29 ± 0.2	0.37 ± 0.32	0.10 ± 0.1	0.37 ± 0.05
T**	0.36 ± 0.21	0.27 ± 0.17	0.33 ± 0.18	0.2 ± 0.1	0.5 ± 0.09	2.7 ± 1.3	2.18 ± 1.77
FREE T***	2.7 ± 1.3	2.18 ± 1.77	2.13 ± 0.77	2.15 ± 1.1	2.02 ± 0.92	1.75 ± 0.25	2.97 ± 1.62
D4-A**	1.63 ± 0.69	1.29 ± 0.6	1.53 ± 0.47	1.26 ± 0.4	1.08 ± 0.6	1.25 ± 0.25	1.45 ± 0.35
DHEAS****	1508 ± 822	1374± 1112	884 ± 304	1368 ± 681	1158 ± 630	1100 ± 400	2690 ± 995

*= mIU/mL; **= ng/mL; ***= pg/mL; ****= µg/mL

Table 5

STATISTICALLY SIGNIFICANT CORRELATIONS BETWEEN HORMONE LEVELS AND LYMPHOCYTE NUMBERS AND PERCENTAGES

	FSH	LH	PRL	E2
LYMPHOCYTE NUMBER	P<0.02	P<0.05		
T LYMPHOCYTE NUMBER	P<0.03		P<0.005	
CD4 LYMPHOCYTE NUMBER	P<0.04		P<0.02	
CD8 LYMPHOCYTE NUMBER	P<0.005			P<0.02
B LYMPHOCYTE NUMBER			P<0.001	P<0.04
NK LYMPHOCYTE NUMBER	P<0.01	P<0.002		
B LYMPHOCYTE PERCENTAGE			P<0.01	P<0.02
NK LYMPHOCYTE PERCENTAGE		P<0.005		

FSH inversely correlated with the absolute number of T cells, CD4 and NK cells. These findings suggest that gonadotropins may modulate, in some cases, by themselves (with opposite effects) rather than through the ovarian hormones, the phenotype and the distribution of the circulating lymphocytes. Since steroid and gonadotropin levels are subjected to cyclical modifications during the life span of sexual active women, it is possible that also the lymphocyte distribution through the body compartments can be influenced leading to cyclical variations of the immune competence. An alternative explanation to our findings is the possibility that gonadotropins and ovarian hormones might modulate the expression of relevant membrane antigens like CD4, resembling the action of corticosteroids on the HLA class II antigens (20). If this is the case, the lymphocyte functions triggered by these determinants may fluctuate according to the actual status of gonadal hormones and gonadotropins secretion.

The inverse correlation between FSH serum levels and the number of cytotoxic circulating CD8 and NK cells suggests that the increase of this hormone may affect the function of cellular effector mechanisms involved in the cytotoxic activities. Such an effect may lead to a defective control of viral infections and neoplastic diseases as well as an impairment of suppressor mechanisms as the one involved in the pathophysiology of autoimmune diseases (21). Since the number of circulating CD4 T lymphocytes is also inversely related with FSH levels, it may be suggested that the cyclic increase of FSH corresponds to a phase of relative immuneimbalance which, in women with appropriate genetic background, may yeld to immune-mediated diseases.

Both LH and PRL serum levels show a direct relationship with the number of circulating CD2, CD4 and NK cells. This observation might indicate that the cyclic variations of these hormones positively affect both the antigen recognition phenomena and the natural cytotoxic activity. Nevertheless, since an overactivation of CD4 T cell subset is known to be a hallmark of autoimmune disease (22), responsible for the policlonal B lymphocyte activation and autoantibodies production (22), these two hormones may contribute to the triggering mechanism of immunologic disorders in fertile subjects with an appropriate genetic substrate. Recently, two different subsets of CD4 T lymphocytes (Th1 and Th2) have been identified whose dysregulation appears to be involved in the pathogenesis of different autoimmune diseases (23). Further studies directed to highlight the effects of gonadotropins and sex hormones on these two lymphocyte subpopulations could be useful to understanding better their role in the onset of autoimmune processes.

Interestingly, elevated numbers of circulating CD8, NK and T cells expressing the HLA class II antigens (activated T cells) have been observed in the peripheral blood of women affected by premature menopause in comparison to healthy women of the same age. Although it is not possible to assess with certainty if these changes are the cause or simply the consequence of the endocrine imbalance peculiar of this syndrome, it is conceivable that the immune pattern observed, in which the cytotoxic subpopulations prevails, can be charged with a pathogenetic role.

In conclusion, it appears that hormone changes may reduce the risk for the onset of autoimmune diseases in menopausal women by lowering B and CD4 T lymphocyte numbers. Gonadal hormones definitevely play a role (12-17, 19) and our data suggest that gonadotropins are also involved in these phenomena. Moreover, the generalized activation of the immune system characterized by increased numbers of cytotoxic subpopulations strongly supports the hypothesis of the involvement of autoimmune dysregulation in the pathogenesis of premature menopause.

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Immune cell circulating subsets are affected by gonadal function

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