CHROMOSOMES AND AN ORAL CONTRACEPTIVE (LYNDIOL 2·5)

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(Received 24th March 1969)

Summary. The discovery of non-specific chromosome abnormalities in repeated peripheral blood cultures from a patient taking an oral contraceptive, Lyndiol 2·5, led to the investigation of the effect of this preparation on human chromosomes. From the results it is concluded that Lyndiol 2·5 has not been shown to have a direct effect on human chromosomes.

The chromosomes of a patient, then aged 25 years, were examined 3 months after she had given birth to a female infant with spina bifida and hydrocephalus. The first pregnancy, 2 years before, had ended in a spontaneous abortion at 2 months. The patient's chromosomes showed non-specific abnormalities which were found in two repeat cultures. The chromosome counts of the three cultures are given in Table 1 and the results of 14 karyotypes in Table 2. The

TABLE 1

CHROMOSOME COUNTS OF LYMPHOCYTES CULTURED FROM THREE PERIPHERAL BLOOD SAMPLES TAKEN FROM A PATIENT WITH PERSISTENT NON-SPECIFIC CHROMOSOMAL ABNORMALITIES

<i>Blood culture date</i>	<i>Counts</i>							<i>Cells counted</i>
	< 44	44	45	46	47	48	> 48	
1. 15/3/1967	2	0	1	7	2	0	0	12
2. 19/4/1967	1	2	1	6	2	0	0	12
3. 21/6/1967	0	1	1	8	2	0	0	12
Total	3	3	3	21	6	0	0	36
Percentage	8·3	8·3	8·3	58·3	16·7	0	0	

husband's chromosomes were normal. The non-specific nature of the abnormalities found suggested the possibility of radiation, virus or drug damage. The persistence of the abnormalities reduced the likelihood of a virus infection as the possible cause. The patient knew of no exposure to radiation and had not been X-rayed during pregnancy, nor had she taken any drugs during her pregnancy but at the time of the chromosomal examination she was taking an oral contraceptive, Lyndiol 2·5, which suggested a possible causal connection

TABLE 2

NON-SPECIFIC CHROMOSOMAL ABNORMALITIES IN KARYOTYPES OF FOURTEEN CELLS IN PERIPHERAL BLOOD CULTURES FROM A PATIENT TAKING LYNDIOL 2.5

<i>No. of cells</i>	<i>Karyotype</i>
2	46, XX
3	46, XX, 3?—
1	46, X, ?16+, 3?—
2	46, XX, 2q—
1	47, XX, ?12+, 2q—
1	47, XX, ?19+, 2q+
1	46, XX, 4p—
1	47, XX, G+, 4p—
1	47, XX, ?14+
1	46, XX, 1?—

+ or — indicates that the chromosome of the autosome number or group letter immediately preceding the sign is extra or missing, or when placed after the arm at structural designation indicates that the particular arm or structure is larger or smaller than normal.

? questionable identification of chromosome or chromosomal abnormality.

p short arm of chromosome.

q long arm of chromosome.

TABLE 3

EFFECT OF LYNSTRENOL ON THE MITOSIS OF PHYTOHAEMAGGLUTININ-STIMULATED LYMPHOCYTES IN VITRO

<i>Lynestrenol (mg/10 ml)</i>	<i>Mitoses/1000 cells</i>	<i>Percentage of control</i>
0.083	30.5	101.7
0.0083	25.0	83.3
0.00083	25.0	83.3
0.0 (Control)	30.0	100.0

TABLE 4

EFFECT OF MESTRANOL ON THE MITOSIS OF PHYTOHAEMAGGLUTININ-STIMULATED LYMPHOCYTES IN VITRO

<i>Mestranol (mg/10 ml)</i>	<i>Mitoses/1000 cells</i>	<i>Percentage of control</i>
0.0025	20.5	68.3
0.00025	23.0	76.7
0.000025	20.5	68.3
0.0 (Control)	30.0	100.0

with the chromosome abnormalities seen. This possibility was investigated by (a) *in vitro* studies of the effects of the steroids in Lyndiol 2.5 on human chromosomes, and (b) by examination of the chromosomes of other patients taking this oral contraceptive.

(a) Samples of the steroids in Lyndiol 2.5, lynestrenol and mestranol, were kindly supplied by Organon Laboratories Ltd. Each tablet of Lyndiol 2.5 contains 2.5 mg lynestrenol and 0.075 mg mestranol. In a woman weighing 60 kg (about 9½ stone) the plasma volume is about 3 litres (Wright, 1952). Therefore, for lynestrenol, the maximum daily plasma concentration is 0.83 mg/litre (= 0.0083 mg/10 ml culture). For mestranol, the daily dose equals 0.025 mg/litre (= 0.00025 mg/10 ml culture).

All the chromosome cultures were grown from peripheral blood lymphocytes stimulated with phytohaemagglutinin P (Difco). The growth period was 72 hr at 37° C. The experimental cultures had the steroid added at the start of the culture period. Blood for these experiments, which were all performed in duplicate, was obtained from healthy volunteers with no history of steroid treatment. The results given in Tables 3 and 4 show that there was some depression of the mitotic index, here defined as the number of mitoses per 1000 cells, particularly with mestranol. No structural or numerical abnormalities of the kind found in the chromosomes of the original patient were observed.

(b) The chromosomes of nineteen women who had been taking Lyndiol 2.5 for a number of years were examined using the same culture method. Their average age was 34.2 years (range 25 to 43); the average number of pregnancies before taking Lyndiol 2.5 was 3.5 (range 1 to 7). They had been taking Lyndiol 2.5 for an average of 3.6 years (range 3 to 5). Only one patient was regularly taking another drug, a diuretic. The chromosomes of all these patients were quite normal and no abnormalities were detected.

The *in vitro* experiments suggest that the steroids in Lyndiol 2.5 may have a slight anti-mitotic effect but do not provide any evidence that the steroids caused structural chromosomal abnormalities. These results, together with the normal karyotypes found in the nineteen patients who had been exposed to Lyndiol 2.5 for much longer than the original patient, make it reasonable to conclude that this preparation has not been shown to have an adverse effect on chromosomes, although the possibility that the original patient was for some reason particularly sensitive to Lyndiol 2.5 cannot be excluded.

My thanks are due to Professor A. E. H. Emery for his advice and encouragement, to Dr M. Lee for permission to examine the chromosomes of her patients, to Dr W. J. Tindall of Organon Laboratories Ltd, for the samples of steroids and to the Smith, Kline and French Foundation for financial support.

REFERENCE

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