improvement in the results of the glucose tolerance test in 14 out of 15 patients (93%). There was a reversible reduction of tolerance in only one patient.

During long-term treatment with chlorthalidone in therapeutic doses the glucose tolerance was found to be unchanged in 10 out of the 16 patients (55%). In three patients there was only slightly reduced tolerance, while in the remaining three there was severely reduced tolerance, which on follow-up was found to be irreversible in two cases and reversible in the third. The marked reduction in tolerance was found principally in patients in whom the original investigations had shown obviously diabetic glucose and glucose-cortisone tolerance, but it was not found only in the patients who had the longest duration of treatment.

Though the two groups of patients were not identical in all respects, it must be emphasized that 12 of them were treated with the two diuretics alternately. Where glucose tolerance was concerned the two groups were comparable. In order to avoid deterioration in latent diabetes mellitus it would seem practicable to determine the two-hour value in the glucose tolerance test. Increased values in this test indicate a necessity for caution in the use of diuretics, particularly chlorthalidone.

Summary

The administration of ethacrynic acid to 15 patients suffering from essential hypertension resulted in one case of reversible reduction of carbohydrate tolerance. In a similar trial one out of 16 patients who received chlorthalidone developed diabetes mellitus and two others had a considerably reduced carbohydrate tolerance, which in one case was irreversible. Latent diabetes should be taken as an indication for special care in the use of diuretics, especially chlorthalidone.

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Lysergide and Chromosome Abnormalities

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Studies by Cohen *et al.* (1967), Irwin and Egozcue (1967), and Zellweger *et al.* (1967) have shown an increased frequency of chromosome breaks in patients treated with lysergide. Court Brown (1968b) emphasizes the necessity of having controls and of defining the chromosome abnormalities described when studying chromosome abnormalities in patients exposed to drugs or radiation.

Material and Methods

Chromosomes were studied on leucocytes cultured 48 or 72 hours ; 48 hours for the five patients treated with lysergide and for half of the controls. The chromosome analysis was made on film projections in a magnification of approximately 6,000 in combination with analysis in a Zeiss photomicroscope. All aneuploid cells and at least 15 cells with a modal figure were analysed. All cells were, however, analysed for gaps, breaks, and other chromosome abnormalities. Gaps are defined as achromatic lesions with no dislocation, while one of the two chromatid parts are dislocated in breaks. Examples of chromatid as well as of isochromatid gaps and breaks are seen in Fig. 1.

We studied five patients aged 29–48 who had been given from 2,200 to 17,500 μg. of lysergide, with the highest single doses varying from 50 to 300 μg. and with 6 to 38 months between the last lysergide treatment and the chromosome analysis. Table I shows the distribution of the five lysergide-treated patients according to age, sex, lysergide treatment, gaps, breaks, and hyperdiploid cells. Four of the five (Cases 2–5) suffered from neurosis with obsessional traits and had been given lysergide as part of their treatment. None of the five had been exposed to radiation. We also studied 40 controls none of whom had taken lysergide, 30 of them being patients in a psychiatric hospital and 10 being chosen from the personnel in this hospital.

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Results

The results of the study are shown in Table II and Figs. 1, 2, and 3. We found 12 chromatid gaps and 45 isochromatid gaps, giving a total of 57 gaps in 358 cells in the five lysergide-treated patients (15.9%). There were 53 chromatid gaps and

TABLE I.—*Lysergide-treated Patients*

Case No.	Sex	Age	Lysergide					Interval between Last Lysergide-dose and Chromosome Examination (Months)	Gaps (%)	Breaks (%)	Hyperdiploid Cells (%)
			Treatment (Months)	No. of Treatments	Highest Dose (μg.)	Average Dose (μg.)	Total (μg.)				
1	M	48	32	60	300	75	4,500	37	21·9	—	4·1
2	M	38	39	90	50	44	4,500	23	16·1	3·5	—
3	M	35	3	12	200	181	2,200	38	20·6	6·9	1·7
4	F	29	29	90	200	194	17,500	34	12·9	—	3·5
5	M	30	11	36	150	95	3,400	6	10·5	—	—

67 isochromatid gaps, giving a total of 120 gaps in the 1,312 cells from the 40 controls (9.1%) ($\chi^2=13.626$; $P<0.001$).

There were five chomatid breaks and one isochromatid break, making a total of six breaks in the 358 cells from the five lysergide-treated patients (1.7%) compared with two chromatid breaks and three isochromatid breaks, giving a total of five breaks, in the 1,312 cells from the 40 controls (0.4%) ($\chi^2=7.207$; $P<0.01$).

We found seven hyperdiploid cells in the 358 cells from the five lysergide-treated patients and one hyperdiploid cell in the 1,312 cells from the 40 controls (χ^2 (Yates)=17,071 ; $P<0.001$). The reason for examining more cells in the five lysergide-treated patients than in the controls was the smaller number of patients in this group compared with the control group. As shown in Table II the frequency of gaps in the 10 female controls from the personnel was only 5.5%, compared with 9.1% in the whole group ($\chi^2=6.895$; $P<0.01$), and they had no breaks and no hyperdiploid cells.

TABLE II.—*Gaps, Breaks, and Hyperdiploid Cells in Five Lysergide-treated Patients and 40 Controls*

	Cells Examined	Gaps		Breaks		Hyperdiploid Cells	
		Total	%	Total	%	Total	%
5 lysergide-treated patients aged 29–48	358	57	15·9	6	1·7	7	2·0
10 male control-patients aged 18–39	303	31	10·2	1	0·3	—	—
10 male control-patients aged 40–59	322	30	9·3	1	0·3	—	—
10 female control-patients aged 17–39	361	41	11·3	3	0·8	1	0·3
10 female controls (personnel) aged 20–39 ..	326	18	5·5	—	—	—	—
Total, 40 controls ..	1,312	120	9·1	5	0·4	1	0·1

The hyperdiploid cells comprise the following karyotypes: Case 1, two cells with endoreduplication, 46,XY ; one with 47,XY,G+. Case 3, one cell with 47,XY,r. Case 4, one cell with 47,XX, small acrocentric chromosome ; one with 47,XX,G+ ; and one with 48,XX,C+, large acrocentric chromosome.

The only hyperdiploid cells found in the control population was a cell with 47,XX,C+ in a female patient.

Discussion

Our findings showed a statistically significant increase in the frequency of gaps, breaks, and hyperdiploid cells in the five patients treated with lysergide, compared with the control group, none of whom had taken lysergide, but some of whom had been treated with large amounts of psychotropic drugs. We found no significant difference in the frequency of gaps, breaks, and hyperdiploid cells between the controls with a culture time of 72 hours and those with a culture time of 48 hours.

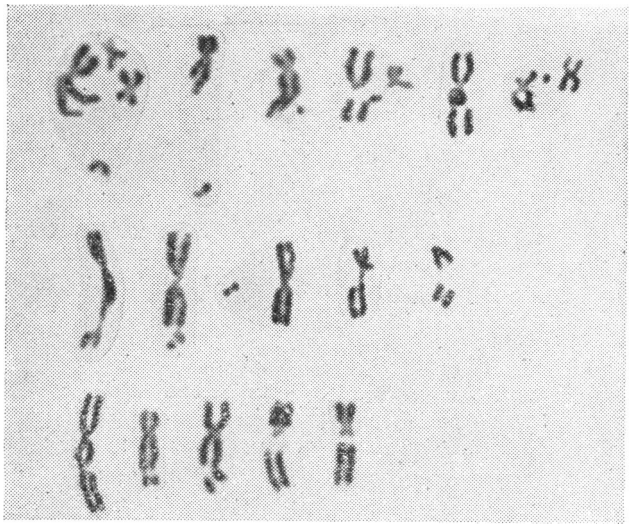

FIG. 1.—Breaks and gaps in cells from patients treated with lysergide and from controls.

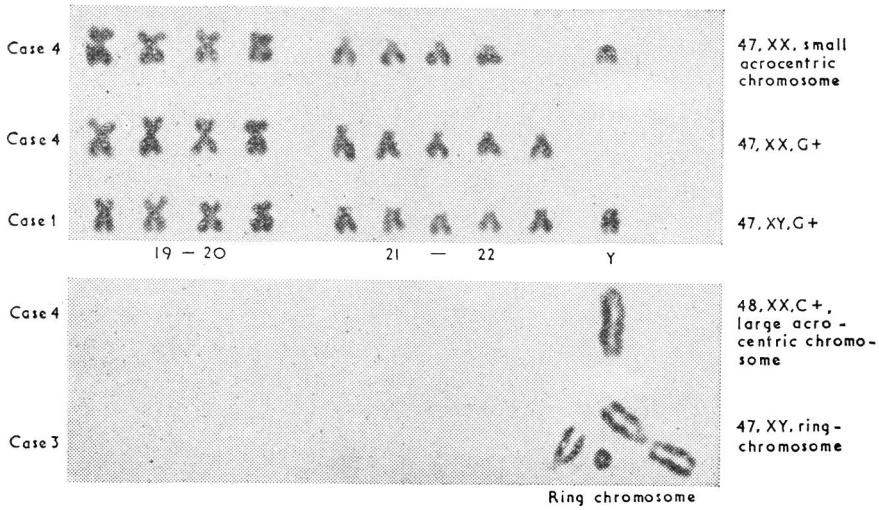

FIG. 2.—Hyperdiploid cells in five patients treated with lysergide.

Age did not appear to play any part in the differences found. There is no statistically significant increase in the frequency of gaps, breaks, and hyperdiploid cells up to the age of 54 (Court Brown, 1967a), nor did we find any difference in the frequency of gaps, breaks, and hyperdiploid cells between the 10 control patients aged 18–39, with a mean age of 27.8 ± 6.11 years, and the 10 control patients aged 40–59, with a mean age of 46.3 ± 5.20 years. The mean age of the five lysergide-treated patients was 36.4 ± 6.47 years, and the mean age of the total number of controls was 33.3 ± 16.18 years.

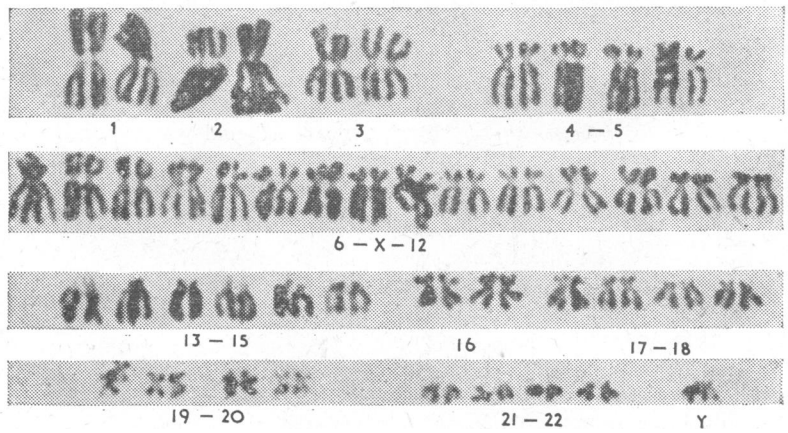

FIG. 3.—Case 1. One of two karyotypes with endoreduplication, 46,XY.

The comparatively high frequency of gaps and breaks may give an increased risk of malignant disorders, but no evidence has yet been presented to prove that this is so.

We found two cells with endoreduplication among the 358 cells from the five lysergide-treated patients. Reissman *et al.* (1963), Friedman *et al.* (1964), and Houston *et al.* (1964) found endoreduplicated cells in two patients with leukaemia and in 11 patients with disseminated cancer. Endoreduplicated cells may, however, also be found in healthy persons, and it may be induced by in-vitro factors such as cooling of the blood samples for a longer period of time, as mentioned by Bishun and Morton (1965) and Boczkowski and Teter (1965).

We found one ring chromosome among the 358 cells from the five lysergide-treated patients, the only one seen in the 475 patients studied in the laboratory. Court Brown *et al.* (1966) found no ring chromosomes in a random population sample of 438 persons, and Bloom *et al.* (1967) found three ring chromosomes among 6,778 cells from 77 heavily exposed survivors from Hiroshima and Nagasaki, but no ring chromosomes among 7,188 cells from 80 control persons.

The finding of trisomy 21–22 and trisomy 6-X-12 as well as the finding of a ring chromosome indicates that there might be an increased risk of parents treated with lysergide having children with trisomy if such hyperdiploid cells are produced by meiotic as well as mitotic non-disjunction. The inheritance risk of cells with chromosome breaks are indicated by the finding of an increased frequency of chromosome breaks in children of parents treated with lysergide as reported by Zellweger *et al.* (1967) and the *Journal of the American Medical Association* (1967).

That lysergide is quite a dangerous drug is strongly indicated by the findings of an increased frequency of chromosome abnormalities in persons taking lysergide, the finding by Alexander *et al.* (1967), and Auerbach and Rugowski (1967) of teratogenic effects of lysergide on rats and mice ; the findings by Zellweger *et al.* (1967) of a possible teratogenic effect of lysergide on human beings and the inheritance of chromosomes with breaks ; the findings by, among others, Frosch *et al.* (1965), Ungerleider *et al.* (1966), Bewley (1967), Blumenfield and Glickman (1967), and Milman (1967) of serious psychiatric side-effects of lysergide ; and the preliminary findings reported in the *Journal of the American Medical Association* (1967) of an increased blood flow, an increased capillary permeability, and petechial bleedings in the brain of rats given lysergide intravenously. Further studies of the toxic effect of drugs on chromosomes are needed, and new drugs of any kind should be tested for toxic effect on chromosomes in animals and in vitro before they are released for general use.

Summary

An increased frequency of gaps ($P<0.001$), breaks ($P<0.01$), and hyperdiploid cells ($P<0.01$) has been found in five patients treated with lysergide compared with 40 controls.

The results show that lysergide has a toxic effect on chromosomes, and this finding, together with other serious side-effects, indicates that lysergide is quite a dangerous drug.

Further studies of the toxic effect of drugs on chromosomes are needed, and new drugs of any kind should be tested for such effect on chromosomes in animals and in vitro before they are released for general use.

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