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Chromosome Aberrations and LSD

A Controlled Study in 50 Psychiatric Patients

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While the beneficial effect of lysergic acid diethylamide (LSD) in the treatment of carefully selected patients as an adjunct to psychotherapy has been amply reported (Robinson *et al.*, 1963), concern has been expressed regarding the damage to chromosomes in those taking the drug.

This paper presents the results of chromosome studies in 50 psychiatric patients treated at Roffey Park Hospital, Horsham, with LSD in varying doses and for different periods and in 50 controls matched as far as possible for age, sex and marital status. Controls were all either members of the administration and nursing staff or students attending Roffey Park Hospital. A minor difficulty in matching for sex presented itself: patients were drawn from a wide geographical area and either could not be traced or felt unable to make the journey to Roffey Park Hospital where samples of blood were taken. This produced a difference in sex ratio in that there were more males amongst the patients than amongst the controls.

Patients had been treated with LSD weekly in a quiet semi-darkened room by intramuscular injection under strict medical and nursing supervision. The initial dose was 50 mcgms. of LSD, increasing weekly by 50 mcgms.; the maximum weekly dose given to any individual patients was 400 mcgms.

Each session was terminated after four hours by a combination of chlorpromazine 75 mgms. and Tuinal 100 mgms. For some patients further sedation with these drugs was required in the evening after treatment. The length of weekly treatment varied for each patient, but all treatment had been completed before blood samples were collected.

In all our cases treated with LSD, including those in this project, follow-up studies were carried out at 3, 6 and 12 months to assess patients' clinical condition, both mental and physical after treatment. These follow-up studies were carried out by questionnaires sent to the patients, the patients' close relatives and the patients' family doctors. These last had received full reports of the patients' clinical condition and treatment programme while in hospital. The patients were also seen at out-patient follow-up clinics at the Roffey Park and at the West London Hospital.

In no case was there evidence of any undesirable clinical effects following treatment.

The patients in this study came from London, the Home Counties and the Midlands, and were those who had received LSD in the years 1969 and later; some 80 patients in all were invited to volunteer. Eight patients had gone abroad, of whom five were married women under 30; three other women were engaged to be married and 'wanted to forget' their previous illness and treatment and so did not wish to participate in the study. Another 15, including 6 women, gave samples but unfortunately the cultures died because of the cutting off of electricity to the incubator during a strike, and these patients could not be persuaded to come a second time. Four requests to attend were unanswered. This left the remaining 50, and no patient was excluded for any other reason, so that there was no possible bias in the selection of patients.

The first blood samples were take on 3 November 1970 and the last on 28 July 1972. The mean interval between finishing treatment and the taking of blood for chromosome analysis was three years and one month.

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Method

From each person 10 ml. of blood was drawn into a disposable syringe and transferred into an Evans heparinized tube. The specimens were packed in ice and taken to the Area Cytogenetic Unit at St. Ebba's Hospital, Epsom, where they were cultured within two hours of being drawn. Those examining the specimens had no knowledge of their origin. Furthermore, blood was drawn from patients and controls on a random basis unknown to any of the authors.

The cells were cultured by the method of Moorhead *et al.* (1960) and were processed in batches which were kept as large as practicable to ensure as much uniformity as possible but varied according to the availability of subjects. The cultures were harvested after 48 hours of incubation to ensure that as far as possible cells were in their first division (Buckton and Pike, 1964). The slides were all air-dried and were stained with lactoacetic orcein.

One hundred cells were analysed for each subject, and chromosomes were grouped according to the Denver System (1966). Each aneuploid cell was scored, and the chromosome group to which the extra or missing chromosome belonged was recorded. The number of chromatid and ischromatid gaps and rings was recorded for each cell; a gap being a complete discontinuity of a portion of the chromatid. The chromosome group to which the damaged member belonged was also recorded. Care was taken to avoid scoring secondary constrictions. Unstable chromosome rearrangements, dicentrics and fragments were also noted.

Only when all specimens had been analysed was the code broken and patients and controls divided for comparison.

Care was taken to exclude from this project all persons who had recently suffered from a virus infection or any other condition known to be a possible cause of chromosome damage.

Results

The characteristics of the subjects are given in Table I. It was found that prevalence of all the chromosome abnormalities examined decreased as the chromosome analysis proceeded (Table II). The cause of this change is not known, but there is no evidence to suggest that it is associated with the LSD therapy.

As the early groups contained more patients than controls, this change would bias comparisons made between them. Straightforward analysis of variance techniques were not applicable, as the various effects were not balanced. Instead, the prevalence of each abnormality was fitted to a polynomial where the predictor variable was the subject's serial number, which gives an estimate of when the chromosome analysis was done. Separate polynomials were fitted for subjects and controls (Armitage, P., 1971).

It was found that a quadratic function fitted all the data adequately, and that, except for the intercept, the coefficients for the patients and controls were not statistically significantly different. So quadratics were fitted to the prevalence of each abnormality, with the same coefficients for patients and controls but different coefficients for the intercepts.

The difference between the intercepts is a measure of the difference in response between the patients and controls which is independent of the change associated with the subject's serial number. It is demonstrated that there is no statistically significant difference between the LSD treated group and the control group in any of the four chromosome abnormalities studied (Table III).

No association was found between the number of chromatid gaps and the following: total dose of LSD, the length of treatment, patient's sex, marital state or age, or the time between the end of the LSD therapy and the time the blood samples were taken.

Discussion

The literature on the damage to human chromosomes by LSD when given therapeutically, taken voluntarily for research purposes, or self-administered by abusers, is extensive and controversial. Earlier reports almost uniformly recorded LSD-induced chromosomal abnormalities (Cohen *et al* 1967a; Cohen *et al.*, 1967b; Egozcue *et al.*, 1968; Irwin and Egozcue, 1967; Nielsen *et al.*, 1968), while later articles questioned whether LSD was capable of producing such abnormalities *in vivo* (Long, 1972; Lucas and Wolfgang, 1970; Rumke, 1964; Stenchever and Jarvis, 1970). A leading article in the *British Medical Journal*, 27 June 1968, gave an objective assessment of previous investigations and emphasized that the amount of LSD taken was sometimes in doubt and derived from users' statements.

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TABLE I

Serial No.	Patient (P) control (C)	Age	Marital status	Sex	Diagnosis	Total LSD in mcgms.	Length of treatment in weeks	Chromatid gaps	Isochromatid gaps	Chromostomes lost/gained	Fragments, Di tri centrics rings
1	P	38	M	M	Anxiety state	3,000	156	3	3	0	0
2	P	38	M	M	Anxiety state	3,825	156	11	1	0	0
3	P	25	S	F	Personality disorder	9,025	260	14	0	0	0
4	C	28	M	M	—	—	—	6	2	0	0
5	C	32	M	M	—	—	—	5	3	0	3
6	P	29	S	F	Personality disorder	1,000	39	9	2	1	2
7	P	31	S	F	Personality disorder	300	4	16	4	0	0
8	C	26	S	M	—	—	—	3	1	0	0
9	C	23	S	M	—	—	—	11	3	0	1
10	C	27	M	M	—	—	—	11	1	0	1
11	P	39	M	M	Obsess/Neurosis	1,000	12	8	0	8	0
12	P	30	M	M	Personality disorder	11,050	208	11	3	0	1
13	P	40	M	F	Personality disorder	975	7	2	0	4	4
14	P	24	S	M	Sexual aberration	1,500	104	15	5	0	0
15	C	48	M	M	—	—	—	14	4	4	1
16	P	24	S	F	Personality disorder	500	5	7	0	0	0
17	P	47	M	M	Alcoholic	1,250	8	10	0	0	0
18	P	34	S	F	Personality disorder	750	6	12	0	0	0
19	C	40	S	F	—	—	—	9	1	0	0
21	C	26	M	M	—	—	—	2	1	0	1
22	P	38	S	M	Personality disorder	1,300	12	2	1	0	0
24	P	32	S	M	Personality disorder	4,400	156	4	0	0	0
25	C	38	M	F	—	—	—	1	0	0	0
26	C	43	M	F	—	—	—	5	0	0	0
27	P	26	S	F	Personality disorder	1,300	12	9	0	0	0
28	P	33	M	M	Anxiety state	825	6	5	0	0	0
29	P	51	M	M	Psoriasis	900	8	5	0	0	0
30	P	35	M	M	Affective disorder	400	6	5	0	0	0
31	C	46	M	M	—	—	—	5	1	0	0
32	C	23	S	F	—	—	—	3	0	0	0
33	C	50	M	M	—	—	—	6	2	1	2
34	P	38	M	M	Anxiety state	3,000	156	4	0	0	0
35	P	20	S	M	Sexual aberration	1,000	12	2	1	0	0
36	C	35	M	F	—	—	—	3	0	0	0
37	C	31	M	F	—	—	—	9	1	3	4
38	C	35	M	F	—	—	—	4	0	2	0
39	P	29	M	F	Obsess/Neurosis	7,475	195	2	1	0	0
40	P	32	S	M	Personality disorder	2,000	26	13	1	1	3
41	P	29	M	F	Sex difficulties	1,900	39	3	0	0	0
42	C	31	M	F	—	—	—	3	1	0	0
43	C	47	M	F	—	—	—	3	0	0	0
44	P	42	S	M	Personality disorder	700	6	5	0	0	0
45	C	25	S	M	—	—	—	3	0	0	0
46	P	38	M	M	Psoriasis	1,250	10	7	0	0	0
47	C	38	M	M	—	—	—	3	1	4	0
48	C	27	S	F	—	—	—	2	4	0	0
49	P	22	M	M	Aggressive psychopath	250	3	4	0	0	0
51	P	38	M	M	Personality disorder	1,150	10	6	0	0	0
52	P	57	M	M	Personality disorder	475	5	4	1	0	0

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TABLE I—*continued*

Serial No.	Patient (P) control (C)	Age	Marital status	Sex	Diagnosis	Total LSD in mcgms.	Length of treatment in weeks	Chromatid gaps	Isochromatid gaps	Chromosomes lost/gained	Fragments, Di tri centrics rings
53	P	53	M	M	Alcoholism	14,169	312	2	0	1	3
54	P	38	M	M	Sexual aberrations	17,000	338	4	0	0	0
55	P	48	M	M	Sexual aberrations	250	4	2	0	0	0
56	C	30	M	F	—	—	—	1	1	0	0
57	C	26	M	F	—	—	—	3	0	0	0
58	C	30	S	M	—	—	—	3	0	0	0
59	P	44	M	F	Phobic anxiety	425	4	2	1	0	0
60	P	32	M	F	Phobic anxiety	1,225	14	2	0	0	0
61	P	46	M	F	Obsess/Neurosis	175	4	4	1	0	0
62	C	26	S	F	—	—	—	8	1	0	0
63	C	19	S	F	—	—	—	0	0	0	0
64	C	49	M	F	—	—	—	1	0	0	0
65	P	23	S	M	Anxiety state	300	4	1	0	0	0
66	C	28	S	F	—	—	—	1	1	0	0
67	P	24	S	M	Psoriasis	750	6	0	0	0	0
68	C	30	M	F	—	—	—	0	2	0	0
69	P	47	S	M	Sexual aberrations	1,125	9	2	0	0	2
70	P	40	S	F	Personality disorder	800	6	2	3	0	0
71	P	25	S	F	Personality disorder	300	5	3	1	0	0
72	C	56	M	F	—	—	—	2	0	0	0
73	C	32	S	F	—	—	—	4	3	0	0
74	C	45	S	F	—	—	—	4	1	3	4
75	P	37	M	M	Personality disorder	1,300	8	4	0	0	0
76	P	23	S	F	Obsess/Neurosis	650	6	0	0	2	0
77	P	44	M	M	Sexual aberrations	350	3	2	0	0	0
78	P	23	S	M	Obsess/Neurosis	500	6	5	0	0	0
79	P	29	M	F	Obsess/Neurosis	1,755	78	1	0	0	0
80	P	24	M	F	Sexual aberrations	1,125	13	4	0	0	0
81	P	55	M	M	Sexual aberrations	300	4	4	1	0	0
82	P	22	M	F	Personality disorder	395	5	4	0	0	0
83	C	18	S	M	—	—	—	3	1	0	0
84	C	37	M	F	—	—	—	5	1	0	0
85	C	18	S	M	—	—	—	4	0	0	0
86	C	26	M	F	—	—	—	5	0	0	0
87	C	27	M	F	—	—	—	1	0	0	0
88	C	40	M	M	—	—	—	1	1	0	0
89	C	25	S	M	—	—	—	2	0	0	0
90	C	25	S	F	—	—	—	1	0	0	0
91	C	29	M	M	—	—	—	1	0	0	0
92	C	26	M	M	—	—	—	2	1	0	0
93	C	25	M	M	—	—	—	3	0	0	0
94	P	38	S	M	Obsess/Neurosis	125	2	3	2	0	0
95	C	42	M	F	—	—	—	1	1	0	0
96	C	57	M	F	—	—	—	2	1	0	0
97	C	60	M	F	—	—	—	6	3	1	0
98	C	61	M	F	—	—	—	5	1	0	0
99	C	62	M	F	—	—	—	7	0	0	0
100	C	58	M	M	—	—	—	0	3	0	0
101	C	56	S	F	—	—	—	1	0	0	0
102	P	44	M	M	Personality disorder	4,400	156	4	1	0	0
103	P	38	M	M	Anxiety state	3,000	156	4	0	0	0

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TABLE II

Mean number of chromosome abnormalities per subject (100 cells) in patients treated with LSD and controls according to batch

Serial number group		1	2	3	4	5	Totals
Patient serial number		1 to 19	21 to 40	41 to 60	61 to 80	81 to 104	
Chromatid gaps	Total*	9·3	4·7	3·3	2·4	3·0	4·45
	Patient	9·8	5·1	3·7	2·3	3·8	
	Control	8·4	4·2	2·63	2·5	2·8	
Isochromatid gaps	Total*	1·7	0·47	0·47	0·65	0·74	0·81
	Patient	1·5	0·4	0·18	0·42	0·8	
	Control	2·1	0·56	0·88	1	0·72	
Chromosomes lost/gained	Total*	0·9	0·37	0·26	0·25	0·043	0·35
	Patient	1·1	0·1	0·091	0·17	0	
	Control	0·57	0·67	0·5	0·38	0·056	
Fragments rings bi/tricentrics	Total*	0·68	0·53	0·16	0·3	0	0·32
	Patient	0·58	0·3	0·27	0·17	0	
	Control	0·86	0·78	0	0·5	0	
Subjects	Total	19	19	19	20	23	100
	Patient	12	10	11	12	5	50
	Control	7	9	8	8	18	50

* The differences between the serial number groups are statistically significant at the 0·001 level.

TABLE III

Type of abnormality	Mean number per subject	Difference between patient and control groups	95% confidence limits	Probability
Chromatid gaps*	0·53*	0·09*	+0·2* −0·02	0·2 > p > 0·1
Isochromatid gaps	0·81	−0·35	+0·08 −0·78	0·2 > p > 0·1
Chromosomes lost/gained	0·35	−0·11	+0·35 −0·58	0·7 > p > 0·6
Fragments Di/tricentrics rings	0·32	−0·13	+0·23 −0·5	0·5 > p > 0·4

* Calculations on chromatid gaps were done on a $\log_{10}$ transformation of the original data. The transformed results are shown in this Table.

Nielsen *et al.* (1968) reported an increased frequency of gaps and breaks in the chromosomes of 17 psychiatric patients treated with different psychotropic drugs compared with those of 13 not so treated. Nielsen *et al.* (1969), reported a further study of cultures from 13 patients treated with chlorpromazine, 15 treated with perphenazine, and 9 treated with LSD. They concluded that chlorpromazine had some effects on chromosomes, but not to the extent found with perphenazine and LSD. Perphenazine had effects on chromosomes similar to those of LSD. They furthermore noted a significantly higher frequency of breaks, gaps and hypodiploid cells in patients treated with perphenazine and LSD compared with 41 controls. Their results indicate that the higher the dosage and the longer the treatment the more frequently

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are abnormalities to be found in the chromosomes of patients treated with perphenazine. The accumulated daily dosage over a period of 5–12 months amounted to a total of 6–15 g.

Our controlled study of the largest number of patients yet reported concludes that there is no evidence that LSD in the doses used caused any change in the number of chromosome abnormalities. It further supports the conclusions of a recent review (Long, 1972) that LSD does not cause chromosome damage, quoting the report by Tjio *et al.* (1969) after our study began. These workers studied the chromosomes of 32 patients before and after they took LSD as part of a double-blind controlled research. Statistical analysis revealed no significant difference between the 'before' and 'after' LSD chromosomal aberration rates. In addition post-LSD studies of 8 normal subjects who had received LSD in previous experiments, using the same methods, showed no chromosome aberrations.

Our project has involved analysing 10,000 cells. Chromosome damage falls into two categories: (a) minor damage, such as chromatid gaps and isochromatid gaps which are stable and some of which are repairable; (b) major damage which results in unstable chromosomes such as rings and dicentrics, related to irradiation dosage (Lloyd, D. C. *et al.*, 1973).

In our investigation there is no significant difference in either major or minor damage between patients and controls. Overall there was slightly (but not significantly) more damage in the controls.

Pregnancy

Research into the teratogenic effects of LSD in animals has shown conflicting results (Alexander *et al.*, 1967; Auerbach and Rugowski, 1967; Geber, 1967; Zellweger *et al.*, 1967), and created concern lest LSD might have teratogenic effects on the human foetus. Evidence shows that the action of a drug in a given strain of species cannot be reliably inferred from another of the same species, and findings from animal experiments cannot be used for a reliable prediction of the effects of such a drug in humans (Rumke, 1964).

There are a number of reports, based on single cases, of mothers who had taken LSD during pregnancy and gave birth to an abnormal foetus (*Birth Defects*, 1966; Irwin and Egozcue, 1967; Sturelid and Kihlman, 1969; Zellweger *et al.*, 1967). However, since these mothers were also taking other drugs no specific causal relationship can be proved against LSD. The literature does not indicate the number of mothers taking LSD who gave birth to normal infants.

In our study 5 patients gave birth to a total of 7 healthy infants (4 boys and 3 girls) and there were no abnormal births.

Further studies

Large-scale scanning programmes using all the criteria we have adopted would be extremely time-consuming and involve a large number of highly-trained staff. It is probable that such programmes will not be practicable until the advent of computer analysis of cells.

Summary

This controlled study of chromosome aberrations of 100 lymphoid cells in each of 50 patients and 50 controls shows no significant difference between the control and patient groups, and supports the latest review of the literature that LSD does not cause chromosome breakage.

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