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Schizophrenic Birth Order: the Last but One Position

RESULTS of birth order studies on schizophrenics from the United States, Canada and Britain suggest an increased incidence of patients born late in the family[1-7].

A recent study, however, concludes that there is "an accumulation of evidence that the birth order distribution of schizophrenics varies with family size"—schizophrenics are born late in large families and early in small families[8]. Part of the evidence referred to is the sample of Solomon and Nuttall[9] which included a large number of small families of high social class and which showed an increased incidence of early born patients. This bimodal result was explained by separate class-dependent factors operating in the different sizes of family. It is the purpose of this communication to test a single-factor explanation.

It is possible that the schizophrenic patient tends to occupy a certain position in relation to the end of the family rather than in relation to the beginning (a reverse ordinal position), so that the penultimate sib, for example, is born late in large families, while in two-sib families it is the first born. The hypothesis is that there is over-representation of the penultimate reverse ordinal position in schizophrenic samples.

By collecting data from the literature, a very large sample can be amassed. Five studies in the literature report samples of schizophrenics (total $N = 3,482$) in such a way that distribution of the reverse ordinal positions can be calculated. The expected distribution is calculated by the Greenwood–Yule method[10]. Over-representation is calculated as the difference between the observed and expected distribution as a percentage of the expected distribution. Table 1 shows that there is no continuous increase in over-representation towards the end of the family. There is a peak of over-representation at the last but one position—this is true consistently for all five samples individually.

There are two samples of non-schizophrenic psychiatric patients reported in the literature which allow a similar analysis—498 manic-depressives[1] and 2,500 neurotics[11].

In this non-schizophrenic sample there is no over-representation of the last but one position. Table 3 shows the fit between the schizophrenic sample and the non-schizophrenic sample (family size distribution corrected to that of the schizophrenic sample). The disparity between the samples is clearly greatest at the last but one position.

Table 1. DISTRIBUTION OF REVERSE ORDINAL POSITIONS

Reverse ordinal position	Observed distribution	Expected distribution	Percentage over-representation $\left(\frac{\text{Observed}-\text{Expected}}{\text{Expected}} \times 100\right)$
Last	1,162·5	1,145	+1·5
Last but one	943	860	+9·7
Last but two	534·5	563	−5·1
Last but three	347	339	+2·4
Rest	495	575	
N	3,482		

$\chi^2 = 121{\cdot}05$ $d.f. = 4$ $P < 0{\cdot}001$

Table 1a. SAMPLES CONTRIBUTING TO TABLE 1

Study	N	Country	Reference
Malzberg, 1940	549	USA	1
Solomon and Nuttall, 1967	291	USA	9
Barry and Barry, 1967	1,019	USA	8
Gregory, 1959	431	Canada	6
Granville-Grossman, 1966	1,192	England	7

Table 2. DISTRIBUTION OF REVERSE ORDINAL POSITIONS OF NON-SCHIZOPHRENIC PATIENTS

Reverse ordinal position	Observed distribution	Expected distribution	Percentage over-representation
Last	1,004	927	+8·3
Last but one	663	685	−3·2
Last but two	480	474	+1·2
Last but three	319	328	−2·7
Rest	532	584	
N	2,998		

$\chi^2 = 12{\cdot}78$ $d.f. = 4$ $P < 0{\cdot}02$

Table 3. FIT BETWEEN THE SCHIZOPHRENIC AND NON-SCHIZOPHRENIC SAMPLES

Reverse ordinal position	Schizophrenic distribution	Non-schizophrenic distribution (corrected)	Percentage over-representation $\left(\frac{\text{Schiz.}-\text{Non-schiz.}}{\text{Non-schiz.}} \times 100\right)$
Last	1,162·5	1,229	−5·4
Last but one	944	833	+13·4
Last but two	534·5	573	−6·8
Last but three	347	332	+4·5
Rest	494	515	
N	3,482		

$\chi^2 = 22{\cdot}9$ $d.f. = 4$ $P < 0{\cdot}001$

This new analysis of already published data clearly indicates that the presence of one younger sib is associated with schizophrenia and can explain the anomalous results of Solomon and Nuttall without the introduction of social class factors.

One ordinal position is now identified with schizophrenia, so selection of these patients for further study will allow better understanding of what, if any, is the unique psychological position of the schizophrenic in the family.

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Evaluation of Teratogenicity of Lysergic Acid Diethylamide

THE concern about the psychological and physiological effects of lysergic acid diethylamide (LSD) has naturally led to the desire for experimental models to study the spectra of effects suspected to be caused by LSD. Among the recent reports of its biological effects when pregnant animal models are used, one involving rats is negative[1], another[2] is ambiguous because although stunted and still-births were reported with LSD at 10 days post partum the offspring were unusually large, weighing 44–46 g. Results with hamsters[3] are equivocal because of the small incidence of malformations reported, and those for mice are positive[4].

This report describes an attempt to demonstrate a teratogenic response to LSD using pregnant mice and hamsters. In addition, secondary Syrian hamster cultures were examined for growth alteration and for chromosomal aberrations in the presence of LSD. 'Delysid' (LSD-25) was obtained from the US National Institutes of Health as a solution containing 0·1 mg/ml. of LSD tartrate (Sandoz, lot No. 65002). Immediately before use, further dilutions were made with Dulbecco's salt solution which was also used for the control groups.

Syrian hamsters from the NIH breeding facilities, 9–11 weeks old and weighing approximately 100 g, were used. This species has responded to a wide variety of teratogens[5-7]. They were injected intraperitoneally during the time of greatest differentiation with a single dose of 10 μg (two animals), 100 μg (four animals), 200 μg (three animals) or 300 μg (four animals) on days 6, 7 or 8; in one case,

Table 1. ABNORMALITIES INDUCED BY LSD-25 INJECTED INTO PREGNANT MICE

Strain	LSD dose (μg)	No. of females	No. of progeny	No. of malformations	No. of litters with malformations	No. of malformed animals with any malformations/litter
G.P.	0	6	58	0	0	0
	0·5	4	27	0	0	0
	1·0	2	19	0	0	0
	20·0	13	96	0	0	0
	30·0	3	25	0	0	0
A/Cum	0	10	66	2	1	2/4
	0·5	1	7	0	0	0
	1·0	2	13	3	1	3/7
	10·0	4	18	3	1	3/8
	20·0	2	14	0	0	0
	30·0	5	27	9	4	4/5; 3/4; 1/6; 1/7

repeated doses of 100 μg were given on days 7, 8 and 9. All pregnancies were terminated on day 14.

Within the fourteen treated hamsters, 171 implantation sites were noted: 168 were live foetuses of which one had microphthalmia; three cases of resorptions were found. Animals treated with LSD did not vary statistically from control animals in weight changes of pregnant mothers, or in average litter weight or size; furthermore, no more resorbed foetuses occurred in animals which had been treated with LSD than in control animals. On rare occasions control animals do exhibit spontaneous exencephaly.

Neither 1·0 nor 20 μg of LSD/ml. of Eagle's minimal essential medium plus 10 per cent foetal calf serum altered the logarithmic growth of secondary Syrian hamster embryo cultures originally made from trypsinized minced whole embryos 12–14 days old. After 24 or 48 h of exposure the cell counts were similar to those obtained in control cultures. Nor was any evidence of chromosome breaks found in 274 colcemide arrested metaphases after 24, 48 or 72 h exposure to 0·9 μg. 18 μg or 45 μg of LSD/ml. of culture medium, respectively.

NIH General Purpose and A/Cum mice (Table 1) weighing approximately 31 and 25 g, respectively, were injected intraperitoneally according to the schedule of Auerbach and Rugowski[4]. Further animals were given multiple injections to ensure that the critical period (day 7) referred to by Auerbach had been properly covered. The total amount received by each pregnant animal ranged from 0·5 μg to 30 μg. Mice were killed on the eleventh or fourteenth day. Of 167 General Purpose mouse foetuses examined from twenty-two treated mothers, no external malformations were found and no statistical differences in size or weight were noted between 167 foetuses obtained from mothers treated with LSD and fifty-eight foetuses obtained from six mothers injected with salt solution. From fourteen pregnant A/Cum female mice treated with LSD, seventy-nine foetuses were obtained; six litters had fifteen foetuses with abnormalities consisting of hare lip, cleft palate or micrognathia. Examination of sixty-six foetuses from ten females of the control group revealed two foetuses (from one litter) with abnormalities similar to the mice treated with LSD. No other difference between the two groups was observed.

The present investigation failed to demonstrate that LSD is teratogenic for NIH Syrian hamsters and for general purpose mice. Although the negative results we obtained with the hamsters are statistically different from the positive results reported by Geber[3] we interpret them as being not essentially different. In the case of positive results one would expect a dose response relationship and an increase in abnormalities much higher than the variation from 5 to 8 per cent[3] (average of less than one in each litter). It would be expected that with controlled conditions including known amounts of chemical, a genetically defined animal population, and defined periods of maximum organogenesis, a positive teratological response would be demonstrated by a greater shift.

The results of Auerbach and Rugowski[4] with mice show an appreciable incidence of malformations (57 per cent). Abnormalities of a similar type normally occur in 10 per cent of the same colony. The overall frequency of malformed foetuses in our A/Cum mice was 19 per cent. The malformations in A mice were similar to those which occur spontaneously in this strain. The doses of LSD that gave teratogenic effects are of the order of 25–1,000 times the average single human dose. The relatively low number of malformations obtained with large amounts of LSD may reflect potentiation of individual threshold differences for these malformations. Differences in threshold responses for cleft palate have been reported for C57Bl/6J mice[8]. There is evidence for strain specificity in the incidence of malformations produced by trypan blue in rats that varies from strain to strain[9] and by thalidomide which produces malformations in A strain mice[10] but not in C57Bl/6J mice[11]. Our results suggest no firm conclusions concerning the possible teratogenicity of LSD in rodents other than the possible potentiation of threshold difference in some A mice.

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Electroencephalographic Alerting Sites of *d*-Amphetamine and 2,5-Dimethoxy-4-methyl-amphetamine

The amphetamine derivative, 2,5-dimethoxy-4-methyl-amphetamine (STP), is a new psychotomimetic drug, considered to be about one hundred times more powerful than mescaline in producing psychedelic symptoms in human beings[1]. We have made an electroencephalographic (EEG) analysis to determine the sites of action in rabbit brain of *d*-amphetamine and STP. It has been shown that non-psychotomimetic congeners provoke EEG alerting from the midbrain level, while their psychotomimetic congeners such as LSD, psilocin and mescaline cause alerting by their action at a lower level in the brainstem[2–4].

Forty-one albino rabbits ranging from 2·2 to 3·0 kg were tracheotomized under ether and local anaesthesia, curarized and artificially respired. To record the electrical