

Hallucinogenic drugs as precipitants of schizophrenia¹

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SYNOPSIS The authors have examined the drug-taking histories of 46 schizophrenics and 46 matched controls. They have found that the schizophrenics on average used a wider variety of drugs, in greater amounts. Schizophrenics who had used drugs experienced the onset of symptoms on average four years earlier than non-users and were also admitted to hospital four years earlier, on average. Those schizophrenics who had used drugs had had better premorbid personalities than the non drug-users. These results are indicative of some precipitating role of drug abuse in the onset of schizophrenia.

Ingestion of drugs such as amphetamines, marijuana, or the major hallucinogens such as lysergide or mescaline may induce in many subjects both auditory and visual hallucination, persistent feelings of unreality, anxiety, and inability to think clearly or to put their actions into words. This acute reaction may at times resemble the symptomatology of schizophrenia. A schizophrenic-like syndrome is well recognized in amphetamine abuse (Connell, 1958) but this syndrome is a temporary rather than a chronic condition. Controversy continues in the medical literature and in the public press as to whether the use of LSD, mescaline, marijuana, or the more concentrated substance, hashish, can produce schizophrenia.

A number of investigations have attempted to discover a relationship between drug use and psychiatric disorder. In almost all cases, however, they have been unable to demonstrate whether the drug-use precipitated the illness or whether it was a symptom of the illness.

Dube and Handa (1971) in an extensive com-

munity survey in India, reported a higher incidence of 'mental illness' among users of cannabis, but their data did not enable them to say whether onset of drug use preceded the onset of 'mental illness', nor do they define precisely what they mean by 'mental illness'. Tennant and Groesbeck (1972) describe a chronic intoxicated state associated with 'high dose hashish abuse', which, if combined with alcohol or other psychoactive drugs, may result in a psychosis resembling schizophrenia. Three patients after complete discontinuance of hashish abuse exhibited intermittent residual symptoms analogous to those of organic brain disease. Campbell *et al.* (1971) have reported cerebral atrophy in young cannabis users, but these patients had also used other psychoactive drugs. Furthermore, the authors' measure of atrophy presents difficulties in interpretation.

Similarly, Shearn and Fitzgibbons (1972), comparing drug use in young 'psychiatric patients' with that in student controls, found that the 'patients' had a far greater involvement with drugs, but they could not provide evidence to support a causal hypothesis.

Walters *et al.* (1972), who reported that 35.5% of users had visited a psychiatrist, as against 12.2% of all college students, found that half the users at the time they first saw the psychiatrist had not yet started their drug use. Therefore the drug ingestion could clearly not be implicated as

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the causative or precipitating agent in those cases.

In certain Eastern countries, the use of cannabis is widespread and there is thus ample opportunity for studying its effects. In India, Varma (1972) and Thacore and Shukla (1972) report the occurrence of 'cannabis psychosis'. They believe, but have not convincingly demonstrated, that this condition is a syndrome distinct from schizophrenia or affective illness.

Numerous authors have also reported adverse reactions to LSD ingestion. These reactions were well described by Ungerleider *et al.* (1968). Their findings support the view that LSD may cause adverse effects in persons with schizoid personalities and in their study 40% of patients admitted to hospital had been given the diagnosis of 'psychotic'. This term has become so imprecise in current usage, however, that it is almost meaningless, and does not throw any light on the incidence of schizophrenia. Hatrick and Dewhurst (1970) reported two cases of 'delayed psychosis' after ingestion of a single dose of LSD. Both these illnesses had a large affective component and responded well to ECT and chlorpromazine, but their nature is unclear.

Although the amphetamine psychosis has been well recognized and shown to resemble an acute but temporary schizophrenic episode (Connell, 1958), there are little data in the literature concerned specifically with a relationship between amphetamine use and the onset of a persisting schizophrenia.

The existing literature fails, therefore, to clarify the issue of whether the use of hallucinogenic drugs may act as a causal or precipitating factor in the onset of a schizophrenic illness. No author has attempted to separate out schizophrenics from loosely-defined 'psychotics' or 'psychiatric patients' and no study has made a satisfactory attempt to separate cause and effect.

It is the purpose of this investigation to study a group of patients diagnosed as schizophrenic according to defined criteria and to ascertain the relationship between the onset of the illness and the use of cannabis, lysergide, mescaline, or amphetamines. Not having an opportunity to make a prospective study of the effects of drug ingestion, which would clearly be a preferable research design, the authors have made use of available data from hospitalized, acutely ill patients.

There are many theories concerning the aetiology of schizophrenia, but few known facts. There is general agreement, however, that a hereditary factor is of importance, and that pre-morbid personality gives an index of constitutional predisposition. If it could be shown that drug-taking schizophrenics had healthier pre-morbid personalities than non drug-taking schizophrenics, this would support the hypothesis that the drug-taking played some role in precipitating the illness in people who might otherwise have remained well.

This study was of a group of hospitalized young schizophrenics and concerned itself with several questions: Did drug-taking precede or follow upon the onset of schizophrenia? Did drug-taking appear to accelerate the onset of symptoms? In those patients who took drugs before the onset of their illness, was there a lower incidence of other evidence of predisposition—namely, family history of schizophrenia and/or abnormal personality?

METHODS

Four hundred and sixty-three patients between the ages of 15 and 30 years were admitted to The New York Hospital, Westchester Division, during the period of March 1970 to October 1971. Their case records were scrutinized and those patients whose records indicated that they were likely to be schizophrenic were interviewed during their hospitalization. Of these, 46 were accepted as being definite cases of schizophrenia, according to criteria defined in a previous publication (Breakey and Goodell, 1972).

In personal interviews with each patient, and in most cases family members also, it was ascertained which drugs the patient had used including, specifically, marijuana, hashish, LSD, mescaline, and amphetamines. The age of onset of schizophrenia was estimated by asking the patient and family members at what date a noticeable change in behaviour occurred which they considered at the time or in retrospect to be the first sign of onset of the illness, at what date the first symptoms appeared, and at what date he first consulted a psychiatrist.

The amount of drug use was estimated in terms of duration, frequency, dose, and the names of drugs taken, and it was noted whether drug use preceded the onset of schizophrenic symptoms, whether the onset of symptoms preceded the onset of drug use, or whether drug use and schizophrenic symptoms appeared to begin at the same time.

A premorbid personality score was computed from

data obtained from the hospital chart, the interview with the patient, and from family informants relating to the period of the patient's life before the onset of schizophrenic symptoms. A slightly modified form of the Phillip's Scale of Premorbid Adjustment in Schizophrenia was used for this purpose. This scale was adapted from that given by Farina and Webb (1956), the adaptation being necessary in view of the younger ages of our patients.

In outline, aspects of subjects' personality, before the onset of the illness in the case of schizophrenics, were rated on five sub-scales:

- A. A seven-point scale of *Recent Sexual Adjustment*, ranging from 'Stable heterosexual relation and marriage' (Score 0) to 'No sexual interest in either men or women' (Score 6)
- B. A seven-point scale of *Social Aspects of Sexual Life During Adolescence and Immediately Beyond*, ranging from 'Always showed a healthy interest in the opposite sex—with a "steady" during adolescence' (Score 0) to 'No desire to be with boys and girls; never went out with opposite sex' (Score 6)
- C. A seven-point scale of *Social Aspects of Recent Sexual Life* ranging from 'Married, living as a family unit, with or without children' (Score 0) to 'Single, never interested in or never associated with either men or women; asocial' (Score 6)
- D. A six-point scale of *Personal Relations: History* ranging from 'Always has been a leader and always has had plenty of close friends' (Score 0) to 'Never worried about boys or girls; no desire to be with boys and girls' (Score 6)
- E. A six-point scale of *Recent Adjustment in Personal Relations*, ranging from 'Habitually mixed with others, was always a leader' (Score 0) to 'Antisocial, actively avoided contact, acted out against others' (Score 6)

Demographic data of age and sex, and the socioeconomic status (SES) were tabulated, the latter according to the system of Hollingshead and Redlich (1958).

A series of 46 control subjects were matched for sex and for age within two years of each case. The control subjects were volunteer hospital workers, nurses, aides, high school and college students, medical students, and office workers. Each control subject was interviewed so that each could be scored

for 'personality' according to the Phillips' scoring system. Their drug usage, family history of psychiatric disorder, and SES were recorded.

RESULTS

COMPARISON OF GROUPS

There were no significant differences between the schizophrenic and control groups with regard to age, sex, or socioeconomic status (Table 1).

TABLE 1
COMPARISON OF GROUPS

	Sex			Age		Socioeconomic status			
	N	M	F	Mean	SD	I	II	III	IV
Schizophrenics	46	28	18	22.5	4.0	10	13	17	6
Controls	46	28	18	22.8	3.5	10	16	19	1

DRUG USE The forty-six schizophrenics comprised 14 subjects who had not taken drugs, hereafter referred to as 'non-users', 26 who had used drugs before the onset of their schizophrenic symptoms, hereafter referred to as 'users', three patients who had started drug-taking after the onset of schizophrenia and three in whom it could not be determined whether drug taking had or had not preceded the onset of the illness, or in whom the onset of drug-taking and of schizophrenia appeared to be contemporaneous. These last six patients were excluded from further study (Table 2a).

The forty-six control subjects consisted of 28 who had taken drugs ('users') and 18 who had not taken drugs ('non-users').

The groups differed in their drug usage, the schizophrenic users having taken a greater variety of drugs than controls (Table 2b); and for the most part they were heavier users of individual drugs (Table 2c).

None of the schizophrenic users had used only one drug; the median number of drugs they used was four. Eight of the control users had used only one drug, and the median number of drugs used by the controls was three.

AGE OF ONSET (Table 3) Onset of schizophrenia occurred, on average, at 19 years in users and 23 in non-users. This earlier age of onset was significantly different ($P < 0.002$).

TABLE 2
2a USERS AND NON-USERS

	Users	Non-users	Total
Schizophrenics	26 (+6)*	14	46
Controls	28	18	46

2b NUMBERS OF DIFFERENT DRUGS USED BY SCHIZOPHRENICS AND CONTROLS

	No. of different drugs used		
	1	2	3, 4, or 5
Schizophrenics	0	4	22
Controls	8	9	11

2c NUMBERS OF USERS AND PERCENTAGE OF HEAVY USERS OF EACH DRUG IN SCHIZOPHRENIC AND CONTROL GROUPS

	Total users		Percent heavy users in each group of users	
	Schizophrenics	Controls	Schizophrenics	Controls
Marijuana	25	24	72	29
Hashish	12	18	58	28
LSD	23	14	35	26
Mescaline	13	12	8	42
Amphetamines	19	12	31	25

*Six schizophrenics were excluded because drug-use did not clearly precede the onset of symptoms

Similarly, users were admitted to The New York Hospital at an average of 21 years and non-users at 25 on average. The earlier age of admission to hospital was also significantly different ($P < 0.002$).

The ages of the drug users and non-users in the control population were compared. The means and standard deviations were 22.4 ± 3.1 for users vs 23.6 ± 3.2 for non-users. Although the users were slightly younger than the non-users, the difference is not significant by *t* test.

COMPARISON OF HEAVY VS LIGHT DRUG USERS IN INDEX GROUP (Table 3) We searched for significant features that might demonstrate a greater effect from larger drug dosage. It was difficult to estimate reliably the total amount of drug taken, so we decided to compare in the index group, those who admitted to experience with

TABLE 3
SCHIZOPHRENIC USERS AND NON-USERS: AGE OF ONSET OF ILLNESS AND ADMISSION TO HOSPITAL

	Onset of illness			Age at time of admission		
	Mean	SD	P <	Mean	SD	P <
Users	19	2.5	0.002	21	3.2	0.002
Non-users	23	4.6		25	4.5	
Users of 3 or more drugs	18.5	1.8	0.05	20.8	2.8	0.10
Users of 2 drugs	21.3	4.6		23.3	4.6	

two drugs with those who admitted to experience with more than two drugs (we had no index patients who had taken only one drug), for age of onset and Phillips' score.

The mean age of onset (with SD) of schizophrenic symptoms was 21.3 ± 4.6 years for the two-drug users and 18.5 ± 1.8 for the 3, 4 and 5-drug users—this difference is significant at the $P < 0.05$ level (one tail). Age of admission (mean $\pm$ SD) was 23.3 ± 4.6 years for two-drug users, and 20.8 ± 2.8 for three, four, and five-drug users. This difference approaches significance with $0.05 < P < 0.1$. There is no significant difference in Phillips' scores between these two groups.

PREMORBID PERSONALITY (Table 4) The Phillips' premorbid personality scores of the control subjects were significantly healthier (lower) than those of the schizophrenic group. Average score for the control group was 5.57 ($SD \pm 2.89$) and for the schizophrenic group 15.72 ($SD \pm 6.61$) ($P < 0.001$). This difference persists through the different subgroups studied—that is, subjects with and without family histories of psychiatric disorder, users of different types of drugs, etc. Within the schizophrenic group, the users had premorbid personality scores with a mean of 14.7 and a SD of 5.94 and thus could be adjudged to have a healthier personality than non-users whose scores were slightly higher, with a mean of 19.4 and SD 6.19 ($P < 0.02$). In the control group, a significant difference was not found between the scores of users and non-users.

FAMILY HISTORY (Table 5) The incidence of positive family history of schizophrenia was very

TABLE 4
PREMORBID PERSONALITY SCORES

	Phillips' score		
	Mean	SD	P <
Schizophrenics			
Non-users	19.4	6.19	0.02
All users	14.7	5.94	
Heavy users	14.56	5.25	NS
Whole group	15.72*	6.61	
Controls			
Non-users	5.83	3.03	NS
All users	5.39	2.83	
Heavy users	4.29	2.06	NS
Whole group	5.57*	2.89	

*P=0.001

TABLE 5
NUMBERS OF SUBJECTS WITH FAMILY HISTORY OF SCHIZOPHRENIA OR OTHER PSYCHIATRIC DISORDER, IN SCHIZOPHRENICS AND CONTROLS, USERS AND NON-USERS

	Family history of:					
	No family history		Schizophrenia			
	S	C	S	C	S	C
Users	11	19	4	0	11	9
Non-users	8	13	1	1	5	4

low. Only in two families of schizophrenics did schizophrenia occur in a first-degree relative. One was the relative of a drug user and one of a non-user. Three users gave histories of schizophrenia in a more distant relative. There is a higher incidence of other psychiatric disorders in both schizophrenic groups, 42% in users and 35.7% in non-users. The slightly higher incidence in users was not significantly different.

In the control group families there was a lower incidence of psychiatric disorder, 2% for schizophrenia in non-users and 32% and 22% for other conditions in users and non-users respectively.

AMPHETAMINE ABUSERS Of the 26 index patients who took drugs, six were heavy users of am-

phetamines along with other drugs. Their mean age of onset of schizophrenia was 20.2 years, their mean age of admission was 22.3 years, and their mean Phillips' score was 14. If these patients were removed from the study because of the possible contamination with amphetamine psychosis, the significant differences in the age of onset, age of admission, and Phillips' scores between our index drug users and non-users would remain.

DISCUSSION

Of a total of 46 schizophrenic patients included in this study, 32 had taken drugs in one form or other. This proportion is slightly higher than that in the control group, which is in agreement with the findings of research referred to above, although our findings did not reveal a statistically significant difference.

Of these 32 patients, in only six cases had the drug taking not clearly preceded the onset of schizophrenia. This is in contrast with the findings of Walters *et al.* (1972), although they concerned themselves only with subjects who had consulted a psychiatrist, for whatever reason, rather than with confirmed schizophrenics. Our finding permits us to proceed to the question of whether the drug-taking might be understood to have played a role in precipitating schizophrenia, at least in the 26 cases where it preceded the onset of illness.

Were the 26 users different from the 14 non-users? If not, it could be assumed that the drug-taking was incidental, and not related in any important way to the onset of the illness.

Our data first indicate that the users of drugs experience the onset of schizophrenic symptoms on the average, four years earlier than do non-drug users. They also are admitted to The New York Hospital four years earlier, on the average. These results could be explained if drug taking were a behaviour of younger people. But whereas the users are significantly younger than non-users in our index group this is not true in the control group.

Another possible explanation for the earlier onset of schizophrenia among our drug users would be that they were more predisposed to schizophrenia and thus might manifest symptoms earlier in life. However, we find that the

drug users have significantly better premorbid personalities than non-users, by the Phillips' Scale, a result contradicting the opinion that they are more predisposed. Bowers (1972) also makes the point of better premorbid personality characteristics in patients with acute drug-induced psychotic reactions, as compared with patients with acute psychotic reactions unrelated to drug abuse.

On the basis of these results it seemed plausible to conclude that the taking of drugs—amphetamines, marijuana, hashish, lysergide, or mescaline might play some precipitating role in the onset of schizophrenia, bringing this disorder on more quickly, and to patients who seemed somewhat less constitutionally vulnerable.

We searched our data for a 'dose response' with early onset associated with heavy usage. We were constrained to use numbers of drugs rather than amounts as an expression of dosage, but in this way did find the expected relationship.

It was also found that when drug users were compared, by each criterion employed, schizophrenics had a pattern of greater drug use than controls. The schizophrenic users used greater variety of drugs than the control users; and the schizophrenic users used a greater amount of drugs. This could be considered to give added weight to the idea of a causal effect, but could also be interpreted to indicate that increased drug use is a symptom of schizophrenia.

We considered the possibility that the observed precipitating effect in users rested upon the inclusion of amphetamine takers in the group. If the data relating to subjects who indulged heavily in amphetamines are removed, however, the results are essentially unchanged, so that the amphetamines cannot be implicated in this case. It is difficult, moreover, to implicate any individual drug, since there was not a single schizophrenic who used only one drug.

It might be thought that because of social stigma, subjects would be reluctant to discuss their usage frankly, but our impression was that in the current youth culture in the Eastern United States, wherein drug use, though illegal, is widely accepted, our subjects felt little inhibition. It must be acknowledged, though, that the reliability of the data given by the subjects is open to question, as is the exact nature of the substances used and their degree of purity.

We had also hoped to cast some light on the question of predisposition to schizophrenia by comparing family history data in users, non-users, patients, and controls. Because of the small numbers, however, any meaningful statistical analysis was impossible. Five of the 46 schizophrenics (10.8%) gave a history of schizophrenia in the family. The true incidence may possibly have been higher as we did not rigorously investigate the families to find all cases; on the contrary, if in doubt as to whether a family member were truly schizophrenic, he was excluded from the reckoning.

A notable feature of this study is that, whereas most earlier research has concerned itself with 'psychosis', this study has been concerned specifically with schizophrenia, which has been defined as precisely as possible so that the study can be replicated with similar patients. Some subjects who were, in fact, schizophrenic may have been excluded because the criteria were too rigorous, but there is no doubt that the 46 subjects included were definitely schizophrenic by the criteria used.

This was a retrospective study with a small sample and the results therefore need to be interpreted with caution. This is particularly so because, if the effects we have observed are, in fact, true effects, they are of great significance in the debate on the harmful effects of hallucinogenic drugs. Further research is of urgent importance to clarify the issues raised.

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