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CLINICAL REACTIONS OF SCHIZOPHRENICS TO SODIUM AMYTAL, PERVITIN HYDROCHLORIDE, MESCALINE SULFATE, AND D-LYSERGIC ACID DIETHYLAMIDE (LSD-25)

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The effects of administration of a drug on mental symptomatology should depend on the interaction between the specific properties of the drug and individual factors in the subject within the total set of circumstances attending the administration. If drug specificity is significant, (a) a given drug should induce characteristic effects in a series of subjects, and (b) the same subject should display different reactions with dissimilar drugs. If individual factors within the subject significantly influence the reactions, some possibilities are that, (a) the same drug may induce different mental reactions in various subjects; (b) the same subject may show the same mental alterations in response to different drugs. These hypotheses were tested in a series of schizophrenic patients, each of whom received three or four chemically and pharmacologically dissimilar drugs on different occasions. The drugs employed were sodium amytal, pervitin hydrochloride, mescaline sulfate, and d-lysergic acid diethylamide, all of which are capable of producing profound alterations in abnormal mental states (2, 4, 9, 13, 15, 19). The earlier reports of Hoch (4) and Hoch, Cattell, and Pennes (5, 6) will be quantitated in certain aspects and new considerations introduced. Rubin, Malamud, and Hope also used the technique of independent administration of different drugs to study drug-specific and individual-specific psychological changes (16).

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Material and Technique

Fifty-five schizophrenic patients were studied, 28 males and 27 females. These individuals were classified into three groups according to diagnosis and degree of deterioration. Twenty patients classified as Group I presented symptomatology of predominantly severely neurotic type in a basically schizophrenic framework and were diagnosed as pseudoneurotic schizophrenics, in accord with the criteria of Hoch and Polatin (8); no deterioration was present in these patients; mean age was 35.8 years, and mean duration of illness was 12.6 years. Twenty-five patients, Group II, were all overt or classical schizophrenics with no or slight deterioration and were represented by 3 paranoids, 3 catatonics, 1 hebephrenic, and 18 mixed or unclassified schizophrenics; mean age was 32.2 years, and mean duration of illness 9.1 years. Ten patients of Group III were also overt or classical schizophrenics but with moderately severe to severe deterioration, and were represented by 2 catatonics, 1 paranoid, and 7 mixed or unclassified schizophrenics; mean age was 32.4 years, and mean duration of illness 9.9 years. The majority of Group I and II patients were relatively short-term voluntary hospital admissions with average durations of hospitalization of 0.9 and 1.6 years, respectively; all members of Group III were committed state hospital patients, hospitalized on an average for 5.7 years prior to this study. The majority of subjects of Groups I and II had previously received some form of psychotherapy. Electric convulsive and/or insulin coma treatment had been previously administered at least once during the course of the illness to 9 patients of Group I, 22 of Group II, and all 10 of Group III.

The majority of the patients received some type of psychosurgery, principally frontal topectomy, several days to several months after these drug studies. The effects of the surgery on the mental condition will be presented elsewhere (7). All the patients received a preliminary psychiatric study with complete anamnestic data and cross-sectional evaluation of the mental status. Patients had been under close observation by the individual recording the drug data for a period of several weeks to several years prior to the drug experiments. The protocols of the drug experiments were recorded in terms of the usual clinical psychiatric examination. Interview technique during the drug study attempted so far as possible to exclude active manipulation and suggestion by the investigators.

Sodium amytal (Amobarbital sodium, sterile ampoules of 0.5 Gm., provided by Eli Lilly and Company, Indianapolis) was injected intravenously in doses of 0.25-0.50 Gm. in 10 cc. of sterile distilled water at a rate of about 0.05 Gm. per minute. Pervitin hydrochloride (d-

desoxyephedrine hydrochloride, sterile ampoules of 20 mg., Smith, Kline, and French Company, Philadelphia) was injected intravenously in doses of 20 mg., or occasionally 40 mg. over a one to three minute period in volumes of 1.0 or 2.0 cc. of sterile isotonic sodium chloride solution. Mescaline sulfate (Bios Laboratories, New York City. Supplied as the pure salt) was injected intravenously in a dosage of 0.4-0.6 Gm. in 20 cc. of distilled water over a five to 15 minute period; solutions were sterilized by autoclaving. D-lysergic acid diethylamide tartrate (Supplied by Sandoz Pharmaceuticals, New York City, for investigation) was given orally in doses ranging from 0.010 to 0.120 mg. after aqueous dilution of ampoule solutions containing either 0.020 mg. per cc. or 0.100 mg. per cc. For the sake of brevity and conformity with previous usage, this latter drug will be referred to as LSD25 in the body of the report.

All 55 patients in this study received amytal, pervitin, and mescaline. Twenty-five patients of this group also received LSD25 in addition, in doses of 0.010 (3), 0.030 (2), 0.040 (1), 0.060 (9), 0.090 (6), and 0.120 mg. (9); 5 patients received the drug twice, the second dose being higher in each case. The sequence of administration of drugs was invariably amytal, pervitin, mescaline, and LSD25. Usually a period of at least two to three days intervened between administration of any two drugs. Amytal and pervitin were given at any time between 9:00 and 4:00 P.M. without restriction of food intake or ordinary ward activities prior to the injection. Mescaline and LSD25 were usually given between 9:00 and 10:00 A.M. after the patient had a very small breakfast without tea or coffee.

Method of Categorization of Drug Responses

Each protocol was analyzed and summarized according to the effects of the drug administration on the clinical symptomatology. Changes in the subjects' pre-existent mental status were categorized phenomenologically in one of three groups: (1) normalization, (2) intensification, and (3) diphasic responses. Both subjective and objective criteria were employed in these ratings. The normalization response consisted of a reduction or elimination of one or more baseline symptoms so that the subjects' mental status was ameliorated to a variable degree. The intensification response consisted of (a) an exacerbation of one or more baseline symptoms, and/or (b) the appearance of psychopathologic manifestations which were previously not grossly overt. The diphasic response consisted of cominations of normalization and intensification responses in the same subject; many subjects displayed both normalization and intensification features to one drug, either at the

same time or in some type of sequence. Considerable variation in degree of response in any direction—normalization, intensification, or diphasic—occurred between subjects which will be referred to later when pertinent.

I. Effects of Each Drug on Clinical Symptomatology

Administration of each drug was followed by relatively specific effects which were to a large degree independent of the individual to whom the drug was administered. The specific effects of each drug were classifiable into two types: (a) basic, primary, or direct actions which occurred fairly independently of the subject's baseline status, and were attributable to the pharmacologic activity of the drug; (b) secondary actions resulting in alterations of the patient's mental status. This classification is offered for convenience in analyzing the complex series of events that usually follows drug administration with the realization that the second type of effect is variably dependent on the basic action of the drug.

The basic actions of the drugs employed are well recognized and may be briefly summarized as follows: Amytal, a barbiturate, consistently produced signs of central depression in the form of sedation and hypnosis (13, 19). Pervitin, a cephalotropic sympathomimetic amine, characteristically yielded signs of central "stimulation" (9, 10, 12). Mescaline and LSD25 basically created transient psychotic phenomena, which included autonomic, sensorimotor, perceptual, emotional, ideational, and behavioral changes in a relatively clear state of consciousness at the dosages employed (3, 5, 18).

The following types of effects occurred with respect to changes in the subject's baseline mental status. Normalization reactions occurred in 65.4 per cent of patients after amytal, 37.0 per cent after pervitin, and in 0.0 per cent after mescaline and LSD25. Intensification reactions were present in 100.0 per cent after mescaline, 64.0 per cent after LSD25, 20.4 per cent with pervitin, and 10.9 per cent with amytal. The remaining responses were diphasic in nature, as follows: pervitin, 42.6 per cent; LSD25, 24.0 per cent (three subjects, or 12.0 per cent, showed no effect on the baseline clinical symptomatology with the dosages of LSD25 employed.—(See Section IB, 2).); amytal, 23.7 per cent, and mescaline, 0.0 per cent. Thus, the majority responses of the group were normalization with amytal, and intensification with mescaline and LSD25. Pervitin was neither a preponderant normalizer or intensifier; the most frequent type of response with this drug was diphasic (42.6 per cent) or mixtures of normalization and intensification.

The sections that follow (IA, B) deal with the specific effects

of each drug in terms of the alterations induced in baseline symptomatology.

A. Amytal and Pervitin. Both of these drugs reduced or increased essentially the same wide range of symptoms in the material as a whole. These normalization and intensification effects occurred with signs of sedation and hypnosis after amytal, and with signs of central "stimulation" after pervitin. A given symptom was either reduced, intensified, or unchanged in different subjects with each drug.

1. NORMALIZATION RESPONSES. Characterictic symptom-complexes were reduced or eliminated by amytal and pervitin. In Group I (pseudoneurotics) and some of Group II (overt schizophrenics, no or slight deterioration), these symptoms included anxiety, tension, irritability, hostility, depression, guilt, and inferiority feelings, and self-concern; in some of Groups II and III, (overt schizophrenics, severely deteriorated), unreality feelings, affective and contact impairment, gross catatonic manifestations, mannerisms, and stereotypies, and occasionally thinking disorders were lessened. The normalization effects were quite transient, lasting usually one to three hours with amytal and six to eight hours or longer with pervitin. In general, the frequency of occurrence and intensity of normalization response with both drugs were highest in the pseudoneurotic and least in the severely deteriorated schizophrenic group. In a small minority of subjects, rather complete normalization occurred after a small dosage of amytal (0.05—0.10 Gm.) with little, if any, apparent sedative action.

The higher frequency of amytal over pervitin as a normalizer was most apparent in Group II subjects (overt schizophrenics with no or little deterioration) in whom 64.0 per cent of patients normalized with the former drug and 28.0 per cent with the latter. The smallest difference between amytal and pervitin as normalizers occurred in the pseudoneurotics of Group I of whom 75.0 per cent normalized with amytal and 55.0 per cent with pervitin.

2. INTENSIFICATION RESPONSES. Most of the symptoms that were reduced in some subjects (I.A.1) were intensified in other subjects. The range of symptoms intensified by each drug included emotional lability or instability, with depression, self-depreciation, shame, hostility, suspicion, and tension; anxiety, phobic or hysterical manifestations; catatonic withdrawals, excitement, rigidity or cerea flexibilitas; paranoid reactions; inappropriateness, grimacing, mannerisms and stereotypies; thinking disorders; auditory hallucinations; and compulsive urges.

The intensification reactions occurring under pervitin were usually more intense and of longer duration than those under amytal. In particular, emotional outbursts of diverse types and catatonic exacerbations

(withdrawal or excitements) were often quite severe under pervitin and in some cases much more intense than the reaction of the same subject even to mescaline of LSD25.

Neither the nature or the intensity of the reactions to either drug could be predicted in a given subject on the basis of his previous clinical status.

3. Diphasic Responses. The changes enumerated above under normalization and intensification were all represented in the diphasic responses. Subjects reacting in this fashion were characteristically rendered quite unstable and fluctuant; symptomatic reduction in one sphere was attended either simultaneously or in sequence with intensification effects in other spheres.

4. Comparisons of Reactions of Same Individual to Amytal and Pervitin. Pseudoneurotic schizophrenics (Group I) normalized with both drugs in 45.0 per cent of cases, whereas the overt schizophrenics normalized with both in 28.0 per cent of Group II and in 10.0 per cent of Group III. Symptom intensification with both drugs (either as part of a pure intensification or a diphasic response) on the other hand occurred more frequently in the overt than in the pseudoneurotic schizophrenics: the frequencies were 20.0 per cent in Group I, 36.0 per cent in Group II, and 40.0 per cent in Group III. In those subjects who showed intensification phenomena with both drugs, the particular symptoms which were exaggerated were the same under both drugs in 9 (Table I, Group A, and subjects 3, 5, and 7 in Group B) and different in 8 patients (Table I, Group B, all subjects except 3, 5, and 7).

B. Mescaline and LSD25. The characteristic effect of both these drugs (exclusive of the basic action) consisted of an exacerbation of pre-existent symptoms. The description that follows refers only to changes in these baseline manifestations.

1. Responses to Mescaline. Administration of mescaline resulted in some degree of increase of some aspects of pre-existent symptomatology in all 55 patients in this series, (100.0 per cent intensification effects). Most of the symptoms intensified by amytal and pervitin (I.A.2) were the same as those exacerbated by mescaline. These symptoms were: anxiety and tension, hostility; paranoid manifiestations; depression, usually agitated but occasionally retarded; hypochondriasis, phobias, somatic delusions; inappropriateness, silliness, mannerisms, and stereotypies; hysterical manifestations; inferiority feelings; catatonic withdrawals, occasionally excitement; unreality feelings; and thinking disorder. Patients in Groups I and some of II tended to react to mescaline with a predominantly anxiety-tension-hostility-paranoid syndrome; some patients of Groups II and all of III reacted with exaggerated overt

schizophrenic symptomatology. Four patients out of 20 in Group I were also considered to display overt schizophrenic reactions under the drug, whereas the remainder in this group showed some type of intensification of the pseudoneurotic baseline.

Rough clinical quantitation of the mescaline intensification response (exclusive of physiologic and perceptual effects) showed that 39.0 per cent of subjects reacted severely, 32.2 per cent moderately, and 28.8 per cent slightly to administration of the drug. About half of the 28.8 per cent who were slight reactors showed only threshold changes from the baselines. It is apparent therefore that the intensification reaction to mescaline varied widely in intensity in different subjects. Individual prediction of the intensity of the response could not be made accurately in a given subject on the basis of the clinical status.

2. Responses to LSD25. Responses to LSD25 in 25 subjects were classified as intensifications in 16 (64.0 per cent), diphasic (mixtures of intensification and normalization) in 6 (24.0 per cent), and absent in 3 (12.0 per cent), LSD25 intensified essentially the same symptoms in the total material as have been itemized for amytal, pervitin, and mescaline. Normalization features with LSD25 in the 6 subjects rated as diphasic reactors were: (a) definite relaxation, descreased anxiety and tension, descreased concern over phobias and compulsive urges, 4 patients; (b) subjective euphoric state with lifting of depression, 1 patient; (c) improved affective display and general contact, 1 patient (catatonic). In addition to these major reactions, minor degrees of relaxation occurred in at least 4 other patients. Objective signs of sedation, such as drowsiness and slurred speech, were present and patients some times commented on the "sedative" action of the drug with several comparisons to the effects of alcohol by mouth. Despite a relaxant action of the drug, some subjects simultaneously felt anxious under LSD25, because they feared a repetition of the mescaline experience (mescaline was always administered before LSD25 in this series).

The threshold dosage of LDS25 varied over the following range. The 0.010 mg. dosage produced some physiologic responses in 3 patients without definite psychic change; these 3 subjects have been classified above as nonreactors. At 0.060 mg., 5 out of 9 subjects reacted with physiologic, perceptual, and emotional changes; the same occurred with 4 out of 6 subjects given 0.090 mg., and in all 9 subjects who received 0.120 mg. Previous observers have also noted this variation in threshold response to the drug (3, 18).

3. Comparisons of Emotional and Behavioral Intensification Reactions of Same Individual to Mescaline and LSD25. Three relation-

ships could be discerned between the reactions of the same patient to both drugs. The first group of 9 subjects showed similar emotional and behavioral intensification responses to both drugs: (a) 6 were predominantly anxious, agitated with depressive features, and also displayed varying degrees of hostile-paranoid-reactions; (b) 1 was only irritable, hostile, and tense; (c) 1 was predominantely ecstatic (sexual content) with concomitant hostile and paranoid features, and (d) 1 ambulatory catatonic showed increased withdrawal. A second group of 9 patients had qualitatively dissimilar emotional and behavioral reactions to the two drugs: (a) 5 intensified in various fashion with mescaline but were normalized to some degree with LSD25 (the diphasic reactors of I.B. 2); (b) 1 had different intensification reactions under both drugs; and (c) 3 who intensified under mescaline showed little or no reaction to LSD25 (at the 0.010 mg. dose). In the third group of 7 patients, the emotional and behavioral responses were partially similar and partially dissimilar under the two drugs.

II. Comparison of Reactions of Same Individual to Amytal, Pervitin, Mescaline, and LSD25 (Table 1)

In this section the term "intensification reactor" designates a subject who displayed some type of intensification of symptomatology with each drug. Seventeen such patients out of the series of 55 (31.0 per cent) responded in this manner to amytal, pervitin, and mescaline; in the 25 cases receiving LSD25 in addition, 7 (28.0 per cent) reacted likewise. There was no group of "normalization reactors" in the material each of whom could be characterized by normalization features with all drugs, because all the responses to mescaline were rated as intensification. The relatively high frequency of normalization with amytal and pervitin, particularly the former, of course lowered the incidence of subjects reacting with symptom intensification to all drugs.

A. Analysis of the Group of Intensification Reactors (Table 1.).

1. Only 2 subjects (Table I) had pure or uncomplicated intensification responses to all drugs. The remaining 15 showed a diphasic response to either amytal or pervitin, or both, and in one case to LSD25 (B 9, Table I). Consequently, most of this group of intensification reactors had partial normalization responses to amytal or pervitin, or both, and in one case to LSD25, but each individual in the group did show some type of symptom exacerbation with each drug as tabulated.

2. Each intensification reactor showed either the same (Table I, A, 6 patients) or different (Table I, B, 11 patients) symptom exacerbations with all the drugs. A uniform reactor had the same manifestations

TABLE I.—Qualitative Comparison of Intensification Responses of Same Patient to Amytal, Pervitin, Mescaline, and LSD25

A. *Similar Intensification Responses to All Drugs*

PATIENT	ANYTAL	PEVITIN	MESCALINE	LSD25
1. B.L.(I)	D Anger, tension, depression, frustration	D	I	—
2. I.D.(SH,II)	I Irritability, suspicion, hostility, evasiveness, blocking and fragmentation	I	I	—
3. B.W.(SM,II)	I Depression, self-depreciation, anger, perplexity, and obsessive-rumination	D	I	I
4. R.L.(SU,II)	D Anxiety and depression	I	I	I
5. A.S.(SM,III)	I Hebephrenic accentuation with agitation, stereotypies, mannerisms, grimacing, and helplessness	I	I	—
6. M.M.(SC,III)	I Increased catatonic status	D	I	—

B. *Dissimilar Intensification Responses to All Drugs*

1. K.T.(I)	D Transient auditory and visual hallucinations	I Tension and depression	I Hebephrenic-type disintegration	—
2. K.C. (I)	D Anxiety, hysterical pain, and hyperventilation	D Guilt, shame, and depressive discharge	I Pseudo-ecstatic sexualized response, with overt hostile-paranoid features	I As for mescaline
3. S.B.(I)	D Depressive discharge	D As with amytal	I Terror, agitation; fragmentation more marked	I As for mescaline
4. E.E.(SM,II)	I Anxiety, hostility, suspicion, evasiveness	D Agitated, depressive discharge	I Schizophrenic disintegration	—
5. G.G.(SU,II)	D Grandiose, flighty, confused, circumstantial	D As with amytal	I Hostile, suspicious, depressed, silly; at times grandiose	—

B. *Dissimilar Intensification Responses to All Drugs (continued).*

PATIENT	AMYTAL	PERVITIN	MESCALINE	LSD25
6. D.R.(SP,II)	I Verbal and motor withdrawal with paranoid "drugged" feeling	D Impairment of contact	I Primitive terror reaction with reactivation former acute paranoid phase of psychosis	I Agitation, followed by catatonic withdrawal, followed by reactivation former acute paranoid phase
7. M.G.(SM,II)	D Increased anxiety, dependency, lability with crying	D As with amytal	I Terror, agitation with hysterical-catatonic reactions	I Agitation, hysterical-catatonic, suspicious, irritable, hostile
8. D.R.(SC,II)	D Emotional instability, with agitated depression	I Severe excitement, hostility, crying	I Slight increase catatonic withdrawal	—
9. N.E.(SC,II)	D Increased shame, guilt, depression	I Catatonic withdrawal: dazed, preoccupied, withdrawn, rigid affect	I Catatonic withdrawal: flat, evasive, autistic	D Alternating periods improved and decreased affect and contact
10. P.F.(SM,III)	D Increased grandiosity, inappropriateness	D Increased incoherence, decreased contact	I Agitation followed by massive catatonic withdrawal	—
11. L.M.(SM,III)	D Increased inappropriateness, more actively paranoid delusional	I Catatonic disintegration, withdrawal, depression, inappropriateness, increased auditory hallucinations	I Massive catatonic withdrawal with occasional rage outbursts	—

The above table lists those subjects who displayed symptom intensification of any type under each drug that was administered (intensification reactors). Each intensification reactor either had similar (Group A.) or dissimilar (Group B.) manifestations with all the drugs. The over-all reaction to each drug is classified either as diphasic (D) or pure intensification (I). Diphasic reactors also showed some normalization features with the drugs which are not included in the tabulation. For analysis of table, see text II, A.

The parentheses after the patients' initials contain the diagnosis and deterioration rating as follows:

I = pseudoneurotic schizophrenia, undeteriorated
II = overt schizophrenia, absent or slight deterioration
III = overt schizophrenia, moderately severe or severe deterioration
S = schizophrenia
H = hebephrenic
C = catatonic
P = paranoid
M = mixed
U = unclassified

and a nonuniform reactor had different manifestations under the drugs. The terms "uniform" and "nonuniform" reactors refer in this connection only to the symptom intensification aspects of the drug reactions. It is not implied that uniform reactors necessarily duplicated the same ideational and behavioral output in the complex series of events that followed administration of each drug. In particular, the ideational content sometimes varied considerably under different drugs, even in a uniform intensification reactor.

(a) Six uniform intensification reactors (Table I, A) showed the following responses under each drug. Subject 1: Increased anger, tension, depression, and frustration. Subject 2: Increased irritability, suspicion, hostility, evasiveness, blocking, and fragmentation. Subject 3: Increased depression, self-depreciation, anger, perplexity, and obsessive-ruminative activity. Subject 4: Increased anxiety and depression. Subject 5: Increased hebephrenic reaction. Subject 6: Increased catatonic reaction. It is apparent that the quality of a uniform intensification reaction differed considerably in the various subjects.

(b) Eleven nonuniform intensification reactors varied both as to types of intensification reaction displayed by a given subject with the different drugs and between different subjects (Table I, B). In a slight majority of cases, 3 different types of intensification reactions occurred under amytal, pervitin, and mescaline for a given subject, while the response to LSD25 tended to parallel the mescaline response.

3. In practically all reactions, both uniform and nonuniform, the intensification phenomena listed in Table I. were exaggerations of pre-existent manifestations which were previously present either subjectively or objectively. The principle exceptions were: (1) 1 subject (K.T.) who had auditory and visual hallucinations under amytal without a previous history of such; (2) 1 subject (K.C.) who was paranoid under mescaline and LSD25, but who showed little or no evidence for this trend otherwise, and; (3) 1 subject (D.R.) who showed a cataonic reaction under LSD25 although diagnosed as an uncomplicated paranoid.

B. Analysis of Possible Differences Between Intensification Reactor Group and Remainder of Material. The delimitation of an intensification reactor group within the total material was a product of the methodological approach operating on certain possible differences between the subjects composing the series.

1. Methodological Considerations. (a) The sequence of drug administration to each subject was invariably amytal, pervitin, mescaline, and LSD25. It was possible that as a subject was progressively exposed to a series of drugs, some power of resistance on the part of the

patient to these successive changes of internal environment weakened and intensification reactions occurred more readily. Since all patients received the drugs in the same order, this explanation would not be sufficient to account for the differences in response between the intensification reactors and the rest of the material. Moreover, an intensification reactor had to display some type of symptom exacerbation with amytal, the first drug to be administered, to be classified as such a reactor. Some subjects showed less intensification effect with mescaline than with pervitin which had been given previously. Finally, some subjects receiving LSD25, the last drug in the series, had considerable normalization with this drug (Section I, B, 2) after preliminary intensification with the earlier drugs.

(b) The three or four drugs were usually administered over a minimum six to eight day period. Subjects with intense and frequent fluctuations of the baseline clinical status during this period might be supposed to be inherently more unstable and consequently more predisposed to disintegration under drugs. However, there were roughly equal spontaneous fluctuations within the intensification reaction group and the remainder of the series. Spontaneous fluctuations actually were rather infrequent and minor in the total material which had been seriously ill for relatively long periods and had adjusted to the hospital environment in which the drugs were administered.

2. Differences in the Material. (a) Major differences could not be found between the group of intensification reactors and the remainder of the subjects as to age, sex, duration of illness or hospitalization, diagnosis, intensity of major symptoms, or degree of deterioration.

(b) It is possible that certain psychologic differences occurred between intensification reactors and the rest of the material. Drug administration to a subject invariably entails a psychologic constellation which involves the subjects' emotional, attitudinal, and motivational reactions to the investigator and the total setting of the procedure. These factors begin to operate before the drug is given, may potentially modify the response during the drug action and imbue the entire experience with individual meaning and significance, as analyzed for patients under mescaline by Cattell (1). Patients approached the investigator and drug administration with various mixtures of anxiety and tension, resentment and suspicion, depression, guilt, optimism (hope of therapeutic effect), apathy, indifference, submissiveness or resistance, or inappropriateness. The individual's approach to the procedure was heavily influenced by and merged with his current psychopathologic status, and, as already stated, the intensification phenomena under the drugs were nearly always exacerbations of that status.

It may be supposed that in the intensification reactors, the psycho-

logic constellation was qualitatively and/or quantitatively such that disintegration under the drugs was facilitated. In a considerable proportion of intensification reactors, the predominant drug response often appeared to be a direct continuation of the pre-existent emotional status, attitudes, and motivations. This factor weighed heavily in the reactions of those 6 subjects who displayed the same intensification phenomena under all drugs (Table I, A). In these subjects there was a more or less overt interplay between the patient's approach to the experiment, his previous affective, attitudinal, and motivational reactions, and his responses to the drugs. Anxiety, hostility, depression were verbalized in terms of the immediate situation with emphasis on such factors as fear of the direct effects of the drug, resentment at being subjected to an unusual procedure, and depression in terms of increased feelings of frustration and futility.

However, the individual psychologic constellation could not be considered of crucial importance in creating the intensification reactor group because other subjects with apparently similar approaches both qualitatively and quantitatively in terms of emotional, attitudinal, and motivational factors were not in this group.

(c) It is possible that all mental patients have an inherent tendency to disintegration or symptom intensification, independently of psychologic factors, which is rendered overt by the application of drugs independently of the particular nature of the drugs. If this explanation of nonspecific reaction to any stress were sufficient, it would be expected that the responses of a given subject to each drug, regardless of direction, would show certain intensity relationships. For example, (1) subjects normalizing poorly with amytal or pervitin (the most potent normalizers of the four drugs) should have the most severe intensification under mescaline. Such results did not occur consistently because, for example, 3 out of 4 cases with the most complete degrees of normalization under amytal and pervitin (pseudoneurotics, Group I) also had the most severe disintegration effects under mescaline; (2) subjects with the most severe intensification under amytal and pervitin (the most potent normalizers) should likewise have the most severe intensification with mescaline. This result did not eventuate consistently because the most severe pervitin intensifiers (usually Group II) often had relatively mild effects with mescaline; (3) as already mentioned (II, A, 1), most of the intensification reactors showed a diphasic response to either amytal or pervitin, or both, and in one case to LSD25. In many of these diphasic responders, the normalization features of the response were at least as strong or stronger than the intensification features, under amytal or pervitin, or both.

The lack of crucial evidence for the above hypothesis (c) is partially

caused by the fact that amytal and pervitin (and to some extent LSD25) possess considerable normalization to potential and consequently these drugs cannot be regarded as pure or unalloyed stresses. For the rigorous qualitative and quantitative testing of the hypothesis that latent disintegration tendencies were rendered overt, pure stresses would naturally have to be applied. It is consequently concluded that the intensification reactors may still differ qualitatively or quantitatively from the rest of the material as to a latent disintegration tendency, but that this difference could not be inferred with the special methodology employed, particularly on account of specific drug properties.

Discussion

The mental reactions to drug administration were significantly influenced both by the specific nature of the drug and individual properties of the subject, and an interaction between these two factors within the total set of circumstances attending the administration. The specificity of all the drugs used in this study was manifested in two ways. The first was a basic, primary, or direct drug action which eventuated independently of the subject's baseline status and which represented the pharmacologic fraction of the drug's effects. These effects were qualitatively dissimilar for the different drugs, the closest resemblance being between mescaline and LSD25, and tended to occur in a stereotyped form in the majority or all subjects with a given drug. The portion of this report dealing with drug specificity has been mainly concerned with the second type of drug-specific action, characterized by change-normalization, intensification, or diphasic—in the subject's mental status. In general each drug had a relatively specific action viewed within this framework.

Individual factors also significantly affected the mental reactions to drug administration in the sense that (a) the same drug induced a wide variety of different mental reactions in various subjects, (b) the same subject, in 28.0-31.0 per cent of the material, showed intensification reactions, either uniform or nonuniform, despite chemical and pharmacologic differences between the drugs. Rubin, Malamud, and Hope also concluded that their schizophrenic subjects showed changes partly specific for the drug and partly for the individual (16). Their individual factors were analyzed in terms of the particular personality of the subject and specific content of the psychosis, whereas the individual factors in the present study were analyzed in terms of normalization and intensification of the psychopathologic clinical status.

Intensification reactors showed symptom exacerbation under amytal and pervitin (instead of pure normalization) as well as under mescaline

and LSD25. The mechanism is not established whereby some subjects intensified under amytal and pervitin whereas others of the same clinical description normalized with these drugs. The literature on the effects of sodium amytal in mental patients has in general stressed the therapeutic, or normalization action of the drug. However, Wolf and Ripley, among others, have also noted that symptoms such as anxiety and tension may be increased under the drug, particularly by appropriate manipulation of the interview by the examiner (21). In the present series no psychologic manipulation or suggestion was intentionally employed and all the effects ensuing with amytal, as well as the other drugs, occurred independently of this factor. The literature on pervitin has also consistently revealed that this drug may either relieve or exacerbate the same abnormal mental state (2, 9, 12).

As far as mescaline and LSD25 are concerned, both of these drugs produced intensification effects regularly as part of an artificial, transient psychosis (5). However, LSD25 possessed definite normalization effects as described which were not shared by mescaline; part of this dissimilarity may be caused by the difference in routes of administration in this study, mescaline being injected intravenously and LSD given orally. It is known that the ergot alkaloids, of which LSD25 is a partially synthetic representative, both stimulate and depress the central nervous system in a highly complex manner in experimental pharmacology (14). Recent clinical reports have furthermore appeared to the effect that the dihydrogenated ergotamine and ergotoxine alkaloids are capable of allaying states of psychomotor agitation in schizophrenics (17). Previous observers have described the euphorizing and relaxant action of LSD25 (3, 15, 18).

The physiologic and perceptual-distortion effects of mescaline and LSD25 were most probably a consequence of the direct or basic pharmacologic activity of these drugs. Accentuation of a variety of psychopathopathologic constellations by these drugs would appear to be less validly explained by this mechanism. A more probable explanation at the present time would be that these intensification reactions were secondary effects characteristic of the reaction patterns of the particular subject who had been exposed to the nonspecific stress of the direct actions of these drugs. The validity of the secondary, nonspecific origin of intensification effects is supported by the fact that a certain group of subjects also reacted with symptom exacerbation to amytal and pervitin (intensification reactor group).

Since intensification reactors to all drugs in this study could not be distinguished by any criteria or hypothesis (II, B, 2) from the rest of the material, it is apparent that there must be undefined differ-

ences between mental patients who are apparently similar according to clinical descriptive criteria. This conclusion is in accord with the varied responses of apparently similar mental patients to other procedures employed in psychiatry such as the shock treatments and the psychotherapeutic and psychosurgical techniques.

Much of the data in this study suggest that the mental and behavioral effects of the drugs employed would be difficult to explain exclusively in terms of their "direct" or pharmacologic activity. These data include the following: (a) the same drug produced a wide diversity of effects in different subjects; (b) different drugs sometimes produced the same type of effects in a given subject (c) the same drug often had the opposite effect on the same symptom in different subjects; (d) intensification effects under the drugs were nearly always exaggerations of pre-existent subjective or objective manifestations; (e) the subjects' "psychologic" reactions in many cases seemed to form an important part of the reaction, sometimes continuing after the "direct" drug action should have disappeared. A comprehensive theory of action of any drug used in this study would have to explain at least all these facts to attain general validity.

Specific or "direct" drug action contributed some fraction of the total effect of each drug. Above a certain level of response, it would seem that the mental and behavioral responses became secondary or indirect and resulted from interaction between the pre-existent status of the individual, the drug, and the particular environment (including its methodological approach). Much of the effects with any drug would then be secondary to the primary, or more direct events produced by the agent. These considerations have been expressed in a more general form as "organism," and "stimulus" interaction and properties by Wikler in his recent report on drugs as related to personality function (20). Klüver has enunciated the concept of "equivalence of heterogeneous stimuli" at the Hixon Symposium on Cerebral Mechanisms in Behavior (11), emphasizing that diverse chemical substances may produce the same effects and also that the same stimulus may be dealt with by diverse actions and reactions at the most complex levels of personality. Analysis of the data in this report on the clinical level fully supports Klüver's concept and his conclusion that the properties responsible for particular forms of equivalence are thus far not capable of positive definition. Ultimately much of the data explained above as secondary, indirect or interaction drug effects may be brought into closer relationship with the direct or specific drug action. This would seem to depend on the more exact physicochemical delineation of the

mechanism and structure of the psychopathologic symptomatology and drug action.

Summary

1. Sodium amytal, pervitin hydrochloride, and mescaline sulfate were administered independently to each of 55 schizophrenic patients, of whom 25 received LSD25 in addition. The resultant effects were described and analyzed in terms of normalization (reduction) and intensification (increase) of the pre-existent clinical symptomatology.

2. Each of these drugs produced specific effects in two categories (a) direct or basic or primary pharmacologic activity, (b) characteristic effects on mental symptomatology which were a more or less direct consequence of the pharmacologic action. In the latter category, amytal may be classified as preponderantly a normalizer of clinical symptomatology; mescaline and LSD25 as intensifiers; while pervitin tended to produce an unstable state with grossly equal representation or normalization and intensification responses.

3. A subgroup of subjects existed, each of whom showed intensification reactions with each drug that was administered. This and other findings which have been presented indicate that the total effects of drug administration seem to require explanation in terms of secondary, indirect or interaction factors in addition to drug specificity.

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