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PSYCHOSES PRODUCED BY ADMINISTRATION OF DRUGS*

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The editors are pleased to take this opportunity to thank Dr. Hoch and his colleagues and the A.R.N.M.D. for permission to republish this article. It is essentially what Dr. Hoch presented at the Symposium in Zurich. The editors would like to call attention to one particular sentence in which the authors state that "There is a growing body of evidence that certain drugs do produce acute psychotic states which resemble the functional psychoses more than the acute organic reactions."

Psychotic states following exposure to drugs and toxins may be classified in general into the acute and chronic brain syndromes or organic states. The acute organic syndrome (acute toxic reaction, acute delirium, toxic-infectious psychosis, infective-exhaustive psychosis, etc.) following drug administration is basically similar to that produced by other noxae and consists of the following features: *(a)* Mental clouding with impaired consciousness and fluctuating attention, grasp, retention, and orientation; *(b)* perceptual disturbances, mainly visual and auditory illusions and hallucinations; *(c)* emotional lability, usually with some degree of anxiety, suspicion, brooding unrest, euphoria, or indifference; and finally *(d)* aberrant behavior of various degrees of organized motor activity consistent with the remainder of the reaction. The essential feature for the diagnosis of the syndrome is the presence of the mental clouding and the confused state; the other components may or may not all be present in a given case.

In contradistinction, the chronic organic reaction type is essentially characterized by intellectual deterioration with impairment of orientation and recent and remote memory. The level of consciousness is

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ordinarily not disturbed, perceptual disturbances do not predominate, but various types of disturbed emotional reactions usually occur.

Acute and chronic organic reaction types may be produced in susceptible individuals by a diversity of drugs which have little or no biochemical or pharmacological similarities. Casual inspection of a standard pharmacological text reveals the following partial list of agents which may have this effect: *(a)* Central nervous system depressants (barbiturates, bromides, chloral hydrate); *(b)* central nervous stimulants (benzedrine, caffeine); *(c)* ***analgesics*** (aspirin, acetanilid); *(d)* autonomic activators and blockers (atropine, scopolamine, di-isopropyl fluorophosphonate); *(e)* local anesthetics (cocaine); *(f)* antimalarials (quinine, atabrine); *(g)* oxytocics (ergot alkaloids); *(h)* heavy metals (lead, arsenic, mercury); *(i)* hormones (thyroid); *(j)* gases, including low and high oxygen concentrations in the inspired air; and *(k)* even water in toxic amounts (1).

So far as diagnosis of the drug psychoses is concerned, it is agreed that the psychiatric picture is much less specific than the history of intake, general physical and neurological findings and the analysis of body fluids and tissues for the toxic agent or some derivative thereof.

Several questions have always engaged the interest of workers in this field and most of this presentation will be devoted to consideration of these points of major interest.

Are the reaction types produced by different drugs distinguishable — i.e., is there a specific symptom constellation for each drug? Opinion on this question has been summarized by Wolff and Curran on the basis of a review of the literature and their own data (25). These investigators concluded that the form and content of the delirious reactions were independent of the nature of the causal agent, whether drugs or other noxae. They also stated that the course and manifestations of the delirious reactions did differ in different individuals and appeared to be correlated with the intensity and duration of the functional disturbance, environmental stimuli during the period of the illness and the individual equipment and experience of the subject.

However, there is a growing body of evidence that certain drugs do produce acute psychotic states which resemble the functional psychoses more than the acute organic reactions. In our own experience, mescaline and *d*-lysergic acid diethylamide (LSD-25) regularly produce in normal individuals a hallucinatory-illusional state with emotional changes but without impairment of orientation, comprehension,

and memory (10, 11). These actions occur in the majority of exposed individuals, whereas the acute organic reactions to the many, different drugs previously itemized occur usually in a susceptible minority. Mescaline and LSD-25 occasionally produce an acute confusional state, but this occurs apparently with a very few susceptible individuals under the impact of relatively large dosages. Walton, in summarizing the mental effects of marijuana, concluded that the acute intoxication with this drug was very similar to that with mescaline (23). Descriptions of cocaine poisoning indicate that this drug produces more of a confusional state than the preceding three drugs, although the reaction may be of the functional type in some individuals (16). ACTH also produces symptomatology of the functional psychoses in a minority of exposed subjects (18).

The reactions produced by mescaline and LSD-25 are basically similar and we feel that it is impossible to distinguish the two drugs on the basis of the mental-symptom picture of the acute intoxication. LSD-25 produces a full-blown reaction in pharmacologically minute doses, i.e., less than 100 micrograms in many individuals, whereas mescaline must be given in dosages of over 0.10 grams (often 0.50 to 0.75 grams) to produce an equivalent reaction (11).

What is the role of factors within the individual in influencing the psychotic reaction to drugs? Individual factors of all types enter into the determination of both the form and content of the reaction to drugs. This has been well known for a long time and we wish only to mention the following points in this context: *(a)* Not all presumably normal individuals display an acute or chronic organic reaction type on exposure to the same concentrations of a given agent. Explanations have been offered in such terms as susceptibility, sensitivity, idiosyncrasy and decreased tolerance, but the precise underlying mechanisms have not been clearly defined. *(b)* Not all organic reactions to a given agent are the same in different individuals. Thus, in the case of the alcoholic psychoses, one of us (P.H.H.) found that the prepsychotic personality was correlated with the type of psychosis that developed. The extrovert type was in the preponderance in cases of alcoholic confusion, delirium tremens and Korsakoff's psychosis; the introverts were in the majority among the cases of acute and chronic hallucinosis and paranoid trends. Furthermore, introverted individuals tended to maintain paranoid delusions and auditory hallucinations for a longer time after the withdrawal of alcohol than did the extroverts (9). *(c)* The

same mental patient may react similarly to independent administration of chemically and pharmacologically dissimilar agents. The similarity has been described in terms of the underlying personality equipment and experiences and the content of the psychosis (20). This finding with drugs in mental patients parallels the observation of Wolff and Curran that personality factors help determine the form and content of delirious reactions to various noxae in normal individuals (25). (*d*) From a somewhat different point of view, one of us (H.H.P.) analyzed the reactions of a series of schizophrenics to independent administration of four drugs (amytal, pervitin, mescaline, and LSD-25); it was found that 28.8 percent of the group reacted with intensification of symptoms with each drug. Thus, from a group of apparently similar mental patients, a subgroup could be distinguished of so-called "intensification reactors" who responded adversely to each new agent (17).

What is the reaction of psychotic subjects to drugs which have strong psychological effects or induce psychotic states in normal individuals? This complex subject has received much investigation from the present authors in a series of contributions (3, 10, 11, 17). A brief summary of the major findings is as follows: *(a)* The majority of schizophrenics displayed intensification of their pre-existing symptomatology on administration of mescaline or LSD-25; pervitin (desoxyephedrine, methyl benzedrine) was somewhat less effective as an intensifier of abnormal mental phenomena, while sodium amytal was the least effective intensifier of the four drugs employed. *(b)* The reactions of schizophrenic patients to mescaline and LSD-25 are usually marked with severe anxiety and other emotional patterns, while disorganization of thought and behavior patterns may be profound. *(c)* Mescaline psychosis in normal individuals bears only a partial resemblance to natural schizophrenia (11). The point has been made that chronic administration of mescaline might elicit a reaction more closely approximating the chronic schizophrenic state, but the necessary experiments have not been reported. Of the earlier workers, Stockings (21) and Bensheim (1) felt that schizothymic and cyclothymic individuals reacted differently to mescaline. However, Beringer in his exhaustive 1927 monograph was forced to the conclusion that there was no correlation between the previous personality and the reaction to the drug in normals (2). It would seem, however, that schizophrenic patients do react differently to the drug from normals.

In general terms, schizophrenics display severe anxiety and intensification of their original thought and behavior disorganization, whereas normals usually do not pass into a frank schizophrenic episode. In terms of reality control, schizophrenics respond to the intoxication with a further disruption of their faulty reality-handling mechanisms, whereas normals tend to cope with the intoxication in a basically adequate fashion.

In addition to the preceding drugs, the present authors have had more recent experience with three others which in some subjects may greatly intensify underlying symptomatology in mental patients (12). These drugs are the stimulant morphine derivative, N-allylnormorphine; the synthetic scopolamine-like drug, WIN-2299, and the potent anticholinesterase agent, *d*-isopropylfluorophosphonate (DFP). These drugs are irregular in their psychosis-intensification properties as compared with mescaline and LSD-25 and tend to produce in addition a slight to moderate confusional state. Wikler found that N-allylnormorphine produced vivid daydreaming and dysphoria in a series of post-addicts (24); we have confirmed these findings in mental patients and have also observed in contrast that the drug sometimes acts as a potent relaxant of emotional tension (12). English investigators have reported the capacity of DFP to reactivate acute psychotic phenomena in chronic schizophrenies (19). Other drugs recently reported to exacerbate symptoms in some schizophrenics are atropine (5), posterior pituitary hormone (4), and ACTH (6).

What is the relationship between the perceptual and emotional changes occurring in acute mescaline and LSD-25 psychoses? Acute mescaline and LSD-25 psychoses form an ideal situation in which the relationships between perceptual and emotional disturbances in response to a known noxa may be examined in a setting of relatively clear consciousness. In the ordinary acute delirious states, these relationships are obscured by the clouding of consciousness which may facilitate misinterpretation of external and internal events and lead to the appearance of anxiety, suspicion, excitement, and withdrawals; all these symptoms probably express disruption of the integrative function of the ego. The following results were obtained by the present authors with mescaline and LSD-25 (10, 11, 12): *(a)* In the majority of subjects the apearance of anxiety was concomitant with the onset of the perceptual abnormalities. Both the form and content of these perceptual abnormalities apparently served to generate a reactive or

secondary anxiety. Apart from this general relationship, little appeared that could be correlated in a more specific way. For example, *(b)* different subjects had different emotional reactions (anxiety, depression, hostility, suspicious-paranoid) despite perceptual experiences of the same form. *(c)* There was often no evident correlation between the apparent intensities of the perceptual and concomitant emotional experiences in different subjects. *(d)* Finally, the same individual on repeat administration of the drug could in some cases experience approximately the same type and degree of perceptual change with a decreasing or qualitatively different emotional reaction.

It is apparent therefore that perceptual changes may be correlated with the affective responses in acute mescaline or LSD-25 psychosis, but the relationship is neither qualitatively nor quantitatively direct or specific and often appears to involve higher-level symbolic reactions. The autonomic and sensorimotor reactions to these drugs are also extremely difficult to correlate with the remainder of the response, either qualitatively or quantitatively.

How can the various manifestations which may follow drug administration in a single individual be classified? Single administration of a drug to a subject may be followed by a complex of simultaneous or sequential events that occur at all levels from the molecular to the most integrated behavioral and symbolic levels. These drug effects may be viewed conveniently from any of the frames of reference usually employed to describe or analyze drug-free human behavior — biochemical, physiological, personality, psychodynamic, environmental-interactional and others. Many of the analyses of the reactions of individuals to drugs have been cast in terms of only one of these frames of reference. The following schema is proposed to classify the clinical events induced by drug administration.

EFFECTS OF DRUG ADMINISTRATION:

1. Primary *(direct).*

a) Positive: increase of pre-existent function. Example: central nervous system stimulation, as with the cephalotrophic sympathomimetic amines.

b) Negative: decrease of pre-existent function. Example: central nervous system depression as with the barbiturates and other sedatives.

2. Secondary *(indirect).*

a) Alteration: any change in the overt predrug state which is probably a direct consequence of the primary drug action. The relief of anxiety by the central depressant action of sodium amytal on the production of an excited, agitated state by the central stimulant action of benzedrine would be a typical example.

b) Release: the appearance of an effect which has been observationally subthreshold in the predrug state. Clinical evidence for release in the strict neurological sense after drugs is very scanty, obviously from the disparate nature of clinical and neurophysiological data. Thorner attempted to explain some of the action of sodium amytal as a neurophysiological release mechanism on the basis of the appearance of a Babinski reflex in certain patients under the drug (22). It is tempting to some to consider the schizophrenic reactions which may occur after alcohol (9) or bromides (15) as caused by the process of neurological release.

c) Disorganization: In contrast with release, this effect may be considered as a disordered mechanism or disintegration of function. In psychiatric terminology, such descriptive phrases as "disruption of integrative function of the ego" or "impairment of reality control" could be considered as pertaining to reactions which fall under this heading. The phenomenon of regression, viewed either in the libidinal or adaptational contexts, could also be included.

d) Reaction or compensation: These effects are taken to represent the handling by the individual of all the previous effects, and express the activity of that portion of his equipment which has been relatively unaltered by the drug. As an example of reaction, the anxiety occurring in some people after LSD-25 administration may be proposed as an induced effect resulting from the recognition by the subject of other effects produced by the drug which are construed as dangerous or threatening.

This classification of events following drug administration is closely analogous to Gordon Holme's classification of the manifestations of nervous system lesions (13). However, it also includes the personality and psychodynamic factors which enter into drug reactions. In particular, this is true for the clinical data which are incorporated under the headings of release, disorganization, reaction and compensation. These factors often reflect for a given individual, in their particular form and content, his personality structure in terms of equipment and experiences and his basic psychodynamic structure as exemplified in

the drug experience. The details of the psychodynamic manifestations in drug states form a chapter in themselves and have been elaborated by Kubie and Margolin (14), and Cattell (3), among others.

Actually the delimitation of drug effects into primary and secondary is often difficult because of the relative lack of knowledge of the actual physicochemical and physiological aspects of drug action. Distinguishing clinical criteria of primary actions could be considered as follows: (*a*) All individuals show the particular manifestation under the drug; (*b*) the effect occurs only with the particular or related drugs of the same pharmacological class; (*c*) the reaction is limited to the average known duration of the drug action. The secondary effects which are set into motion as a consequence of the direct drug action might be expected to (*a*) vary with the individual and the environmental setting, and (*b*) possibly outlast the primary drug action.

Acute mescaline or LSD-25 psychosis probably consists of a complicated admixture of primary and secondary symptomatology in most all individuals. Under primary or direct effects, there could be included the autonomic, sensorimotor, perceptual and also the thinking disturbance. The emotional and behavioral reactions may represent secondary effects of various types. Under alteration, the relief of unreality symptoms in certain patients under mescaline as described by Guttman and MacClay would be an appropriate example (8). Under release, there would be included the appearance of hebephrenic and paranoid components in ostensibly normal individuals (21), or the appearance of overt schizophrenic symptomatology in certain patients who previously displayed only neurotic type symptoms. Under disorganization, the repressive behavioral phenomena can be cited. In the realm of reaction or compensation, the anxiety or suspicious-hostile reactions which occur so frequently are probably activated by the more basic components of the reaction (10, 11).

The further utilization of psychosis-producing drugs as investigational tools will certainly continue fruitful as attention is directed more to the actual mechanisms of these drug actions.

CONCLUSIONS:

1. Drug-produced psychoses are of two types: *(a)* The classical acute and chronic organic reaction types, produced by a large number of drugs; (*b*) reaction types approximating the functional psy-

choses as caused by mescaline and LSD-25, probably marijuana and irregularly by other drugs.

2. Individual factors of many types enter into the determination of both the form and content of the reaction to drugs. The previous personality in terms of equipment and experience often exerts a large influence.

3. Psychotic subjects (schizophrenics) usually display symptom intensification on administration of mescaline and LSD-25. The same phenomenon has been more recently observed with an increasing number of agents, although in an irregular manner.

4. The basic perceptual disturbances produced by mescaline and LSD-25 are sometimes correlated with the emotional and behavioral responses, but the relationship is neither quantitatively nor qualitatively direct or specific and often appears to involve higher-level symbolic reactions.

5. A working classification of the events which follow drug administration has been offered which is basically along classical neurological lines but which can include individual personality factors.

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