# Psychotropic Drugs

Edited by

S. Garattini and V. Ghetti

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# PSYCHOTROPIC DRUGS

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# DRUG-INDUCED STATES RESEMBLING NATURALLY OCCURRING PSYCHOSES

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The possibility of experimentally reproducing states of human behavior resembling endogenous psychoses has stimulated studies aimed at understanding the nature of mental illness. Pharmacologic agents capable of such activity have been known for sometime, although work has progressed systematically along clinical, biochemical and neurophysiological lines only in the past five years[1].

I shall pay particular attention in this presentation to various aspects of the studies with mescaline, and touch on other drugs, such as harmine, bufotenine and adrenochrome.

There have been several clinical and electroencephalographic investigations of mescaline in humans[8, 27]. The various phases of the mescaline-induced state have been described elsewhere[12, 13]. It is pertinent to emphasize that mescaline does not produce an intoxication, a psychosis or a neurosis[13]. The mescaline state develops in a clear setting with perfect recall. There is nothing to suggest an organic mental condition, and it is extremely rare that amnesia is claimed for the events. The clinical syndrome differs from one patient to another, and in some it is very difficult to determine any change from the pre-experimental findings. To speak of a "mescaline psychosis" would mean that each patient developed a psychotic state; this does not occur. What happens is variable and totally unpredictable, although symptom manifestations tend to follow the character structure of the patient. For this reason we have proposed describing these events as the "mescaline-induced state"[13]. This covers the range of emotions from sleep to maniacal behavior, passivity to rage, and from mutism to logorrhea.

Drugs capable of producing disorders of mood and thought have been called "hallucinogens"[26]; it being implied therein that they give rise to hallucinations. Therefore, in this light, the *de facto* production of such symptoms would merit consideration of an agent in the biochemical evaluation of psychoses. Visual hallucinations are uncommon in schizophrenia and those pertaining to color are rare. The hallucinations are concerned with places or people, and really are the external symbolization of unconscious conflicts. It would be best if the word hallucinogen was abandoned. Furthermore, it is essential that a drug-induced state resembling schizophrenia actually shows all or the most important features of the psychosis. This must consist in general of a more or less profound disorder of the emotions associated with disintegration of the normal thinking processes taking place in a state of clear consciousness. Alterations of perception may be present but are primary neither in the naturally occurring disorder nor in the drug-induced state.

Attempts to delineate "model psychoses"[24] have led more to confusion than

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clarification. These states are by implication the models of schizophrenia. This is still very much debated. For the time being it would be best to describe what we see without trying to coin specific phrases. In a field still in such a state of movement, specificity should be avoided unless absolutely clear-cut data is available.

Our studies have been clinical and electroencephalographic[12–17, 32, 33]. In this report the literature will be surveyed and our own results incorporated wherever appropriate. Finally, a critique will be made of existing concepts.

## CLINICAL

The intravenous injection of mescaline sulfate (0.5 g per 20 c.c. of saline) usually gives rise to the following sequence: (1) autonomic dysfunction, (2) increasing anxiety, and (3) symptom formation. Nausea, retching, vomiting, generalized discomfort, palpitations, feelings of hot or cold occur within minutes and often during the injection itself, to be followed by restlessness, uneasiness, apprehension and tension. Anxiety, a vague yet often well described feeling, begins to increase with the passing of each minute. Sexual material is most often verbalized spontaneously by many patients. Delusions, hallucinations, ideas of reference, depersonalization and unreality develop subsequently. This picture reaches its maximum at the first hour, begins to recede slowly, and usually has disappeared at 24 hours. Patients recall their feelings and thoughts vividly and speak of a "horror chamber," an "airplane with all four motors going on the flight line," or a "brain wash." Many have found the experience so devastating that they refuse further study. Observations of 192 trials in 113 patients during the past five years have shown clearly that many variations of this basic pattern can be seen. It is useless in this sense to speak of a model. Only continuous study over a long period of time will enable one to gather the full sweep of the drug's action upon the human psyche, or for that matter of the complexity, fluidity, and the enormity of the human psychic apparatus. The psychodynamic[17, 18] findings and therapeutic results[13] incidental and consequential to the use of mescaline have been described elsewhere.

The astute observations of a similarity in chemical structure between mescaline and adrenaline led to a very interesting series of experiments[35]. The psychosomimetic properties of adrenochrome and adrenolutin were tested in these studies. Of the first it was said that "the changes noted were preoccupation with inanimate objects, negativism, loosening of the associative processes, anxiety and distractibility." In auto-experiments, adrenolutin produced the effect of being "very different from his normal self; of being withdrawn, irritable and edgy."

RINKEL has not been able to confirm these findings with adrenochrome[44]. The instability of adrenochrome may be pertinent.

FABING AND HAWKINS[23] studied four patients who received up to 16 mg intravenously of bufotenine. They concluded that intravenous bufotenine was "hallucinogenic." The "effects are reminiscent of LSD-25 and mescaline," and there was a "possible role of anoxemia in the production of the hallucinogenic effects of bufotenine." TURNER *et al.*[50] studied the effects of bufotenine and N,N-dimethyltryptamine in schizophrenic patients and recorded electroencephalograms. "It would seem that any psychic action (of bufotenine) must be of a delirious nature, *i.e.*, of a toxic interference with cerebral mechanisms." N,N-dimethyltryptamine's action was brief, and

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does not merit further consideration. The patient's very severe reaction to bufotenine suggests a strong vascular component. "Several reported a sense of constriction of the chest." One patient's respirations ceased and were restored by artificial respiration. TURNER has personally tried harmine and finds it without psychological effect[51]. PENNES AND HOCH[38] tested harmine in a number of mental patients and found hallucinations via the intravenous route. Another drug, 2-diethylaminoethyl cyclopentyl (2-thienyl) glycolate hydrochloride (Win 2239), and harmine, fundamentally produced an "acute organic reaction type because of the basic mental clouding and confusional effects."

PERETZ *et al.*[40] investigated trimethoxyphenyl-β-aminopropane (TMA), related structurally to mescaline and amphetamine. It produced "euphoria and loosening of emotional restraint" at low doses and visual hallucinations at higher doses. A stroboscope was frequently used to precipitate the visual imagery. The time lag between oral TMA and symptoms was 1–1½ hours, about twice as long as for mescaline.

OSMOND[36] has reported on some personal experiences with "Ololiuqui," *Rivea corynbosa*, describing "apathy and anergia combined with some degree of heightened visual perception and an increase in hypnogogic phenomena." The results differed from mescaline, LSD and adrenochrome. He states, "the paralysis of the will which occurred with the apathy and anergia is not unlike the complaints of some people who are labelled schizophrenics."

## NEUROPHYSIOLOGY

MARRAZZI AND HART[29] studied the effects of various agents on synaptic transmission in cat brain. Using an ingenious system they applied an electric shock to one optic cortex and recorded the nerve impulse arriving at the contralateral cortex immediately after having traversed one group of synapses. This is the "two neuron transcallosal" system. Mescaline injected in the ipsilateral carotid artery regularly produced a marked inhibition of synaptic transmission usually without effect on conduction. Serotonin, adrenaline, noradrenaline, adrenochrome, amphetamine and LSD also produced inhibition. Serotonin was amongst the most powerful inhibitors of synaptic transmission. Mescaline required milligram quantities, while the others, with the exception of adrenochrome, were effective in microgram amounts. As much as 2 mg of adrenochrome was needed to produce comparable effects, thus casting some doubt on its possible endogenous psychosomimetic properties[30]. Serotonin was more active than either adrenaline or noradrenaline. Bufotenine had twice the activity of serotonin. These authors have concluded that "central synaptic inhibition plays a part in the action of the hallucinogens either by direct disruption of normal patterns of synaptic activity responsible for behavior or by altering the normal balance of cholinergic excitation and adrenergic inhibition at susceptible synapses."

Bufotenine caused a marked depression of the post-synaptic response recorded in the lateral geniculate nucleus of cat, and did not decrease the cortical response to optic radiation stimulation[21]. Bufotenine in monkeys may apparently alter transmission of sensory impulses, for there is an impairment in function of certain sensory modalities, while muscular power is retained[22].

Mescaline can facilitate the serotonin-induced contractions of rat's uterus. This increase of serotonin contractions is a reversible phenomena. Curiously enough, when

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large amounts of mescaline are used, the uterine contractions are antagonized by high concentrations of LSD and facilitated by small quantities of LSD. There would appear to be a competition for receptor sites between LSD and mescaline[9].

Intravenous or intracarotid mescaline in the cat regularly depressed or eliminated the primary evoked responses of the optic cortex elicited by electric or photic stimulation. The inhibitory action seemed to occur primarily at a cortical rather than a subcortical locus. Mescaline applied topically to cat cortex caused a spontaneous cortical discharge but no change in the primary evoked response[39]. However, ROVETTA[45] found an increased amplitude and prolonged latency of the evoked cortical potentials with mescaline applied topically to the optic cortex in cat. Mescaline produced an increase in all components of the response to light flash at the lateral geniculate. Intravenous mescaline decreased the amplitude and increased the duration of cortical and geniculate potentials evoked by light flash. "Responses which were very small or not present before topical mescaline were so accentuated as to be clearly visible after topical mescaline."

Mescaline produced an alerting response in the rabbit corrected by azocyclonal[43]. The electroencephalographic changes induced in man by mescaline have been reviewed elsewhere[14]. The intravenous injection of 0.5 g of mescaline sulfate in 25 schizophrenic patients caused a disappearance of alpha activity in 20 patients, an increase in four, and relatively little change in one. We found no relationship between brain waves and clinical phenomena, although others have observed such changes[8, 27]. Intravenous mescaline sulfate abolished the high voltage slow wave activity produced by electroconvulsive treatment[32]. Mescaline causes a sharp decrease or disappearance of delta activity in the epileptic. Spike wave patterns disappear for variable periods of time[15].

Intravenous bufotenine in schizophrenic patients produced only a slight slowing and decrease of alpha amplitude[52].

Twenty-five schizophrenic patients received 50 mg of chlorpromazine intramuscularly to block the mescaline-induced state. Within two minutes, alpha waves began to revert to their pre-mescaline pattern. All signs and symptoms of the mescaline-induced state had disappeared one hour after the injection of chlorpromazine. COURVOISIER[11] repeated our mescaline-chlorpromazine studies in the rat, observed similar results and confirmed our findings. Large doses of mescaline produced exophthalmia, salivation, sweating, and increased reactivity to all external stimuli. Chlorpromazine blocked this state, leading to "absolute calm."

Intramuscular prochlorperazine was much less effective in blocking the mescaline-induced state, and at times temporarily aggravated its effects. Muscle tension measured by the electroencephalogram was still present 15 minutes after the injection. Several hours later while the restlessness had lessened, the patients continued to be tense and apprehensive and were not drowsy nor sleepy as with chlorpromazine. However, the psychotic content had disappeared.

Intramuscular promazine (100 mg) showed no blocking effect in preliminary trials. While promazine can induce drowsiness within a short time after injection, the psychotic manifestations due to mescaline were still present four hours after beginning the experiment. This would be in conformance with the generally inferior clinical results as compared with chlorpromazine.

Mescaline is blocked by chlorpromazine in the transcallosal preparation[31].

Adrenochrome failed to cause any specific changes in the normal electroenceph-

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alogram[49]. It aggravated the abnormality in epileptic patients, causing an increase in the paroxysmal activity with higher amplitudes. Nicotinic acid "seemed to reverse the effect due to adrenochrome." Curiously enough, adrenochrome and mescaline have different effects upon the epileptic electroencephalogram. The first aggravates the abnormality, and the second abolishes the slow waves. This certainly suggests that the action of each *in vivo* is subserved by different pathways.

Pre-medication with chlorpromazine, diethazine or promethazine can considerably decrease the clinical symptomatology due to mescaline[17]. The same was not true when saline was used as a control. Pre-treatment with diethazine in some cases followed by mescaline induced an acute state featured by panic, muscular weakness, staggering gait and dysarthria. The patients showed extreme difficulty in verbalizing their thoughts, although they were apparently trying to speak. In a parallel field this data is at variance with FISCHER[24], who states that diethazine appears to be the most effective compound in blocking out LSD symptoms. Our comparative studies to date show chlorpromazine to be the most effective blocking agent for mescaline, and I would assume that this also holds true for LSD.

WITT[54] has found that mescaline produced a disordered web pattern in the spider, whereas LSD had the opposite effect. He suggested that "the similar effect which the two drugs have on man is brought about by attack from different points."

## BIOCHEMICAL

Mescaline is 3,4,5-trimethoxyphenylethylamine. It contains an aromatic nucleus with an aliphatic two carbon-amine side chain and is closely related to various sympathomimetic amines. Different analogs of mescaline have been synthesized and extensively studied. It would be of extreme interest to know if ring substitution or side chain rearrangement would affect the drug's activity. The biochemical and physiological results of such experiments have not yet been reported. While mescaline has a slight stimulating action on cytochrome oxidase activity and inhibits succinic dehydrogenase, 2,4,6-trimethoxy-$\beta$-phenylethylamine and its corresponding triethoxy compounds markedly inhibit cytochrome oxidase activity of brain homogenates[3–5].

QUASTEL AND WHEATLEY[42] noted that mescaline, tyramine, $\beta$-phenylethylamine and others inhibited the oxidation of glucose, lactate, pyruvate and glutamate by minces of guinea pig brain. Ethylamine and histamine had relatively little such effect. A disturbance in detoxification of amines by the liver was suggested as the possible basis of certain mental abnormalities. SCHEULER made similar observations[48].

Mescaline failed to influence the uptake of oxygen by slices of guinea pig brain. However, with electrical stimulation in the Warburg apparatus, $10^{-3}M$ of mescaline could produce inhibition of the extra uptake of oxygen. Mescaline at $10^{-3}M$ had no effect on either the uptake of oxygen or on the associated phosphorylation in preparations of mitochondria of rat brain respiring *in vitro* on a pyruvate substrate[2]. The brains of animals treated with mescaline showed no change in their acetyl choline content[41].

The absorption, distribution and urinary excretion of mescaline have been studied in dog. An initial rise in the plasma was followed by a fall, probably owing to the drug's redistribution to the tissues. Mescaline disappeared from the blood in six to eight

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hours. The highest peak was achieved with the intravenous route, although the plasma decay curve was similar for all routes of administration. It appeared in the urine in detectable amounts as early as 30 minutes after administration, with the maximum rate of excretion at 2–4 hours. The liver and kidneys showed the highest concentration of mescaline at one and four hours, with lowest levels in the brain and blood[10]. Oxidative deamination to 3,4,5-trimethoxyphenyl acetic acid exists as the possible major pathway of mescaline metabolism in dog, although this still lacks confirmation.

The greatest accumulation of radioactive mescaline administered intraperitoneally to rat was found in the liver and kidneys; the smallest amounts in brain and spinal cord. It is interesting to speculate on this relation to the large concentration of amine oxidase in liver and kidneys. Mescaline completely disappeared from brain and cord in 30 minutes[37]. Radioautographic analysis of hydrolysates of liver indicated that mescaline as well as β-phenylethylamine may react with protein *in vitro* and are probably incorporated enzymically[7]. FISCHER[24] has studied the effects of various agents with regard to their affinity for wool proteins. Mescaline, methadrine, LAE and LSD, showed increasing absorption for wool proteins going parallel with decreasing amounts of the same drugs necessary to produce a "model psychosis." High affinity of basic compounds for wool seemed also to be associated with very potent biological activity. Adrenergic blockade and stress appeared to be necessary for the precipitation of a psychotic state.

Oral TMA was excreted slowly after the first two hours, reached a peak at four hours, and declined steadily thereafter. The drug was not detectable after 22 hours. There was correlation of the feeling of "drunkenness" with the rapid climb in the plateau of excretion. "The possibility that the phenomena of hallucinogenesis is involved with inhibition of amine oxidase," was suggested[40].

Whether or not the various oxidation products of adrenaline, such as adrenochrome, adrenolutin or adrenoxin, are a factor in the endogenous psychosis is still very much debatable and remains to be confirmed. Tryptamine has been reported as being able to produce "negativism and catalepsy in cats"[34]. Serotonin can be transformed into bufotenine in man[47].

QUASTEL AND WHEATLEY already suggested "a disturbance in hepatic detoxification mechanisms" as a possible cause for the psychological disturbances. GEORGI *et al.*[25] have discussed the liver's role in such problems, and RUPLI[46] questioned the possibility of some functional disturbance in deamination by the liver.

DENIKER[20] showed that following intravenous mescaline in man the blood sugar increased. There was a persistent fall in blood potassium, a marked leucocytosis with equally abrupt fall in the eosinophiles. The increase in 17 keto-steroids was inconstant. In our own work we have observed a marked leucocytosis as well as an accelerated sedimentation rate.

## DISCUSSION

### *Clinical*

In analyzing the clinical data relevant to mescaline and similar drugs, one is struck by the confusion created by the equation of hallucinogens with endogenous psychosis. The large sweep and diversity of human behavior is affected by many variables. I do not believe it possible to assign specific importance, or prime importance, to any one single symptom. Neither generalizations nor conclusions can be drawn from studying

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the action of a drug in three or four patients. Since some patients become somnolent with mescaline, can one rightfully speak of a blocking action unless at least 10 or, perhaps, 20 patients have been studied? The comprehension of schizophrenia comes through a long study of the clinical disease. Only then can the four "A's" of BLEULER be understood — disintegration of the associations, autism, splitting of the affect and ambivalence[6]. Since schizophrenia is a total disease, one must take into account the heredity, the person and the environment. Research studies must further account for the setting of the investigation and the personality of the investigator. Neither biochemical facts alone nor psychoanalytic deductions in themselves will elucidate this complex mystery. The extraordinary interplay between internal and external milieu factors must be thoroughly evaluated. Experimental data obtained from drug studies with volunteers, esoteric, gifted individuals or others, while giving valuable information about the psychodynamics of such persons cannot be transferred to the problem of schizophrenia.

Only mescaline and LSD at present produce what is incontestably the closest analog to clinical dementia praecox. I base this statement on a five year study of 113 patients receiving mescaline during 192 trials and a careful review of the literature on LSD. The data concerning adrenochrome, adrenolutin, harmine and bufotenine have not been confirmed. We have no knowledge either regarding adrenoxin. Nevertheless, on the basis of his experimental, data, MARRAZZI[31] has concluded that, "serotonin or its dimethyl derivative bufotenine comes close, even closer than does LSD-25, to representing the type of endogenous psychotogen that might be a natural cause of some forms of mental disturbance." There is a strong possibility that the acute state with bufotenine is primarily vascular in nature. One could ask whether the hallucinations result from anoxemia of the optic lobes? The situation with harmine is "extremely complicated"[53], and there are indications that this drug produces a toxic psychosis[38].

*Neurophysiological*

MARRAZZI has postulated that psychoses "can be produced by direct perversion of normal patterns of neuronal activity by undue influence of synaptic inhibitors or, indirectly, by such inhibitors impeding the flow of impulses from higher controlling centers and releasing the more primitive, simpler and less well adapted patterns of activity that we call abnormal[31]." We have unpublished anatomical evidence of a synaptic disturbance in psychotic patients. Biopsies of cerebral cortex collected at lobotomy from eight schizophrenic patients were silver-stained according to WEBER's modification of BIELSCHOWSKY's classical method. WEBER has postulated a continuous cycle of degeneration and regeneration of the synapse taking place under physiological conditions. My observations in humans confirm these views. I found, in addition, a profusion of nerve endings by actual counts of the sections either at the beginning or end of the cycle, with a relative paucity of forms in the middle. The possibility existed of a block in this cycle giving rise to a preponderance of nerve endings in various phases. This led me to suggest that we were dealing with a physiological disturbance at the synaptic level which could have consequences to an orderly flow of information across the synaptic junction. These anatomical observations would confirm MARRAZZI's fascinating work on the neurophysiological level.

Our mescaline electroencephalographic studies indicate that the drug or its metab-

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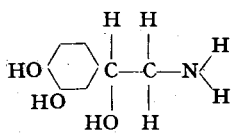
olite act upon centers in the walls of the third ventricle—the diencephalon. Certainly there is no direct cortical action. If anything, the picture suggests subcortical release with loss of cortical control.

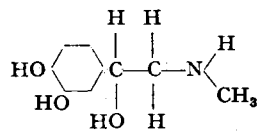
*Biochemical*

The sequence of clinical events following the use of mescaline would be in conformance with BLOCK's idea that the actual agent producing the symptoms is a secondary metabolite, resulting, perhaps, from transformation in the liver. To date we have no information or knowledge of what this might be. Two groups of compounds have been considered in the experimental production of disordered human behavioral states: (1) Those containing an aromatic nucleus with an aliphatic side chain and amine group, (2) the indoles. Hydroxylation seems to decrease, while addition of methoxy groups appears to increase psychosomimetic properties.

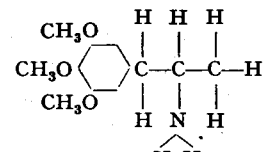
Adrenaline, amphetamine, methedrine, mescaline, tyramine and trimethoxyphenyl-β-aminopropane (TMA), contain an aromatic nucleus, either hydroxylated or with methoxy groups (Figs. 1–2). The side chain features a two carbon-amine linkage.



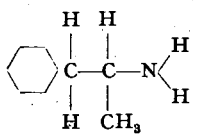
Nor-adrenaline



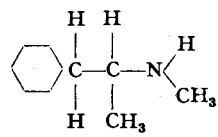
Adrenaline



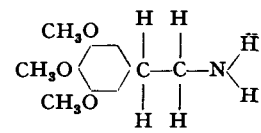
TMA



Amphetamine



Methedrine



Mescaline

Fig. 1

Fig. 2

Amongst the indoles that have received consideration are adrenochrome, bufotenine, harmine and LSD (Figs. 3–4). Serotonin, of which bufotenine is the dimethyl analog, is included, in view of its possible role in the endogenous psychoses. Serotonin, bufotenine, and LSD, are distinguished from the others by its side chain with a two carbon-amine linkage or tertiary amine (LSD). Neither harmine nor adrenochrome show this characteristics. According to this concept, the indole nucleus would be without psychosomimetic action; the latter being a function of the side chain. The evidence I have reviewed shows that agents with an aliphatic two carbon-amine linkage attached to an aromatic ring play some role in the production of experimental disorders of behavior. It would be appropriate to indicate that a defect in oxidative deamination of naturally occurring amines (*i.e.*, tyramine) could lead to the formation of toxic aldehydes[28] and disordered behavior. Such aldehydes it is known are capable of depressing cerebral oxidative mechanisms. Amine oxidase catalyzes these reactions, and one could ask whether this system is defective. One could ask further if gene-deficient individuals are particularly susceptible to these amines as well as their

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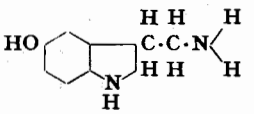
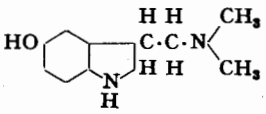
intermediary breakdown products. Since deamination takes place in the liver for the most part, one could wonder whether some metabolic defect in this organ is contributory. It is possible that mescaline actively competes for available amine oxidase and thus prevents the normally occurring deamination from proceeding.

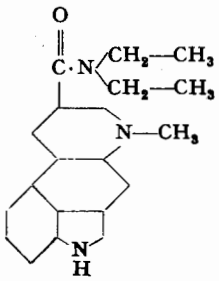


Serotonin

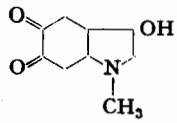


Bufotenine

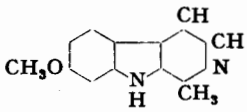
Fig. 3



LSD



Adrenochrome



Harmine

Fig. 4

I have elsewhere indicated a parallel line of reasoning for this hypothesis with the work on Iproniazid and BW-203, both agents containing an amine in their side chains, and both having psychosomimetic properties. BW-203 (*n*-butyl-*o*-anisyl urea), which does not inhibit amine oxidase, is capable of reactivating a quiescent psychosis[19].

I should like to emphasize in concluding that man is an integrated being. He exists in a dynamic equilibrium and it is impossible to consider any one part to the exclusion of the others. Genetic, anatomical, neurophysiological, biochemical, and psychodynamic factors, are all operative. Our problem will be solved through an effective synthesis of these various components.

## SUMMARY AND CONCLUSIONS

1. The clinical, neurophysiological and biochemical evidence have been reviewed concerning the induction of disordered states of human behavior by various pharmacologic agents.

2. Mescaline and LSD are most potent in this regard.

3. Synaptic inhibition and subcortical effects of mescaline have been studied. Various methods of blocking this drug have been described.

4. The available evidence does not support the indole theory.

5. Suggestions concerning the relation of an aliphatic two carbon-amine linkage to the general problem have been made.

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