HALLUCINOGENIC AMINES AND SCHIZOPHRENIA (WITH A BRIEF ADDENDUM ON N-DIMETHYLTRYPTAMINE)

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SEVERAL simple alkyl derivatives of tryptamine, like α-methyltryptamine, N,N-dimethyltryptamine (DMT), N,N-diethyltryptamine (DET), psilocybin, and psilocin, produce abnormal psychological symptoms similar to LSD-25 or mescaline (Szara, 1957; Murphree *et al.*, 1961; Hofmann *et al.*, 1958).

The symptom complex produced has often been called a schizophrenia-like model psychosis because of the more or less pronounced similarity to symptoms present in schizophrenia. It is significant, however, that the clinical diagnosis of schizophrenia is based not on a single symptom or set of symptoms but, rather, on the entire set of longitudinal and momentarily observable symptom complex. The general consensus of opinion today is that if we take all these factors into consideration the drug-induced states and schizophrenia are two distinctly different entities although some overlap of symptoms exists (Bleuler, 1959; Hollister, 1962; Hoch and Hoff, 1964).

Drug-induced models in animals, however, could be of use as research tools if we first establish what component of the human symptom complex is reproducible in animals and then apply the result to that particular component of the symptom complex in humans (Hoch and Hoff, 1964).

At the outset our interest in the dysleptic drugs was nourished by the apparent similarities between schizophrenia and the drug-induced states and by the eventual possibility that the endogenous psychoses might be explained on the basis of an erroneous metabolism producing a simple toxic derivative of tryptamine. We studied the metabolism of these compounds and found that 6-hydroxylation plays a role in the psychodysleptic action (Szara, 1961). The identity of the actually active metabolite is still unsettled but it is significant that if we prevent the 6-hydroxylation by substituting the 6-position of the indole ring with fluorine, the resulting compound, 6-fluoro N,N-diethyltryptamine (6-FDET), is found to be an active placebo, i.e. produces some autonomic changes without the characteristic psychodysleptic effect in man (Kalir and Szara, 1963).

All attempts so far to find DMT or its metabolites in schizophrenics' urine have failed and there is no evidence that this metabolite is *the* "toxic agent" presumably related to schizophrenia. The reports of Himwich and his group, however, finding large amounts of tryptamine in the urine of patients at the time of increased mental disturbances keep interest alive in the theory that the two phenomena might be causally related and we must therefore continue our search for new, thus far unknown, metabolites of tryptamine as potential toxic agents related to schizophrenia (Himwich *et al.*, 1964; Himwich 1958).

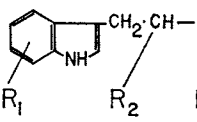
Compound				
	R_1	R_2	R_3	R_4
DMT	-H	-H	$-CH_3$	$-CH_3$
DET	-H	-H	$-C_2H_5$	$-C_2H_5$
SEROTONIN	5-HO-	-H	-H	-H
BUFOTENIN	5-HO-	-H	$-CH_3$	$-CH_3$
dl-αMT	-H	$-CH_3$	-H	-H
PSYLOCYBIN	$4\text{-}OPO_3H_2$	-H	$-CH_3$	$-CH_3$
4-HDMT (Psilocin)	4-HO-	-H	$-CH_3$	$-CH_3$

FIG. 1. Chemical structures of simple derivatives of tryptamine with reported psychotropic activity.

Until we find the elusive "toxin", we felt it was worth while to keep on studying the mechanism of action of these powerful drugs, using the drugs as tools in elucidating the normal and pathological functions of the central nervous system (CNS), in the hope that eventually they might shed some light on the enigma of schizophrenia. Furthermore, these drugs are potentially valuable as aids in psychotherapy but we will have to learn more about their interaction with the functions of the CNS before we can do more than just grope in the dark.

Following is an outline of our research strategy in which we make use of the dysleptic drugs as tools on several levels of approach within a unifying theoretical framework.

I. THE THEORETICAL MODEL

A theoretical model of brain function has been developed from several "precursors" in order to accommodate both the subjective, phenomenological,

and objective behavioral aspects of the CNS functions which might be influenced by drugs.

Kety presented a simple model for information processing brain functions some time ago in which he described how the sensory information is encoded and stored in memory tapes and how a built-in "computer" makes a decision on which behavioral program to use in a particular situation (Kety, 1961). He admitted, however, that he was unable to introduce into his model a physical-chemical mechanism for feeling and consciousness. I would like to propose now a model of brain function which might offer physico-chemical substrate for consciousness using the information processing language as Kety did, retaining the idea of the "behavioral programmers", but omitting the power supply since, as he pointed out, "it takes just as much oxygen to think an irrational thought as it does to think a rational one".

Before presenting the information-flow chart for the central processes in the nervous system we should get acquainted with the notion of the Turing machine (Turing, 1936).

Briefly, a Turing machine is a finite automaton A, together with a potentially infinite tape (which at any moment contains only a finite number of non-blank symbols) divided lengthwise into squares (each square being a blank or bearing one symbol) and a device connected to the finite automaton and capable of functioning as:

1. Tape scanner (reading one square of tape at one moment of time).
2. A printer and eraser mechanism capable of erasing the symbol and/or printing a new symbol on the square actually scanned.
3. Tape mover.

We will regard the finite automaton A as a "black box", meaning that irrespective of its internal structure it has the following functional characteristics:

1. It can accept any of a finite number of inputs.
2. It has a finite number of internal states.
3. It can emit any of a finite number of outputs.

We assume, furthermore, that the input and state at time t determine the output and state at time $t+1$.

Any Turing machine is completely described by a *machine table* which consists of detailed instructions for operating the scanning device.

The notion of a Turing machine is also subject to generalization of various sorts as shown by Davis (1958) and we will take full advantage of this.

It should be mentioned that Turing machines are capable of doing anything that any computing machine (of whatever kind) can do. This follows from Turing's original hypothesis based on Church's thesis, i.e. an effective procedure for calculating the sequences of symbols exists if the function to be computed is recursively enumerable (Arbib, 1964).

Although the idea of the single-tape Turing machine as a generalized model of finite automaton adequately describes the logical functions of digital computers, it is an adequate model for brain functions. This inadequacy is most prominent if we try to apply it to solve the puzzle of privacy, the phenomena of subjective experience, or, in general, the problem of consciousness. Putnam has examined this problem and came to the conclusion that the mental states and "impressions" of human beings do not form a causally closed system to the extent to which the "configurations", i.e. logical states, of a Turing machine do (Putnam, 1960).

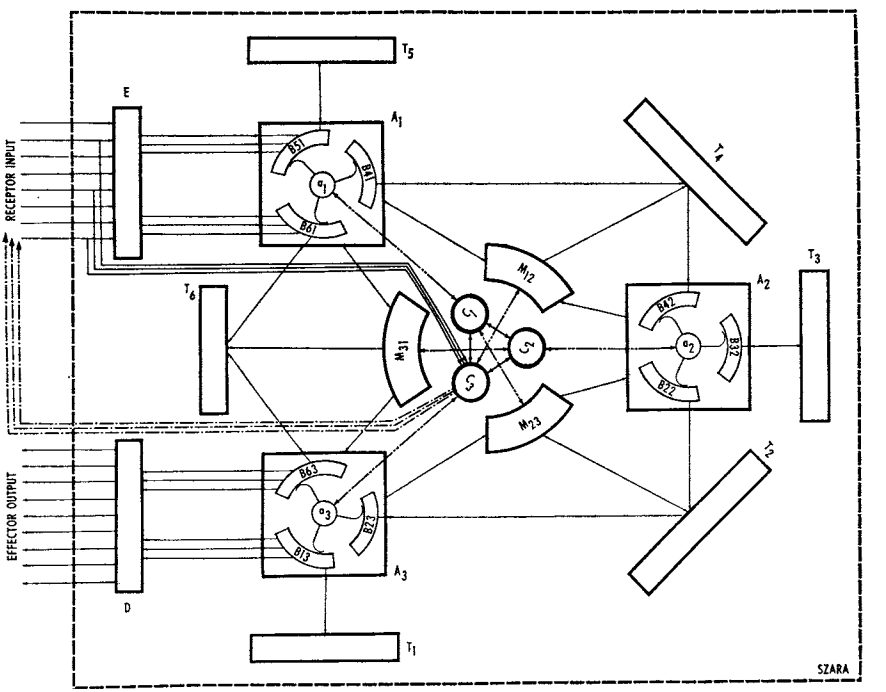


FIG. 2

The logical limit for the finite deterministic automaton are set by the basic incompleteness theorem of Gödel (for formal discussion see Arbib, 1964). If we have two or more tapes in the automaton they have to be read alternately one at a time in order to operate effectively. If both tapes are read simultaneously the correspondence problem is not effectively solvable and as a matter of fact all hope of any constructive decision processes is lost (Rabin and Scott, 1959). In other words, Turing machines with two or more tapes are inherently non-deterministic, i.e. it is impossible to predict their state at any time of $t+1$ even if all the relevant information is available at time t.

Now we are ready for the model which is shown in Fig. 2.

FIG. 2. INFORMATION-FLOW CHART FOR THE CENTRAL PROCESSES IN THE NERVOUS SYSTEM

Symbol	Function	Tentative functional identification
E	Encoder for sensory input	Geniculate bodies Sensory nuclei of cranial nerves in the brain stem
D	Decoder for effector output	Pontobulbar and spinal motor mechanism
A_1	Sensory recognizer system (automaton)	Thalamic system
a_1	Scanning center for A_1 (tape mover)	Non-specific thalamic nuclei
B_{51}	Banks for the scanning center	Specific thalamic nuclei
B_{41}	connecting to adjacent structures	Limbic nuclei of thalamus
B_{61}	(Read-write heads for tapes T_5, T_4, and T_6, resp.)	Sensory nuclei of medulla Certain cerebellar nuclei
A_2	Comparator organizer system	Hippocampal limbic system
a_2	Scanning center for A_2	Septal nuclei
B_{42} B_{32} B_{22}	Banks for the scanning center a_2	Hippocampus and dentate gyrus
A_3	Motor effector system	Pyramidal and extrapyramidal motor system
a_3	Scanning center for A_3	Motor reticular nuclei of brain stem
B_{23}		Basal ganglia
B_{13}	Banks for the scanning center a_3	Certain thalamic nuclei (A.M., A.V.)
B_{63}		Nucleus ruber Certain cerebellar nuclei (dentate n)
M_{12}	Feedback center regulating the functional relationship between A_1 and A_2; biased by C_3	Mammillary body
M_{23}	Feedback center between A_2 and A_3; biased by C_1	Amygdala
M_{31}	Feedback center between A_1 and A_3; biased by C_2. Also provides shortcut (reflex) pathway between sensory input and motor output	Certain pontine and mesencephalic nuclei. (Sup. and inf. colliculi; dorsal tegmental nuclei; subst. nigra.)
C_1	"Anxiety" center; ergotropic system (Hess; Brodie)	Adrenergic nuclei of hypothalamus
C_2	"Pleasure" center; trophotropic system (Hess; Brodie)	Serotoninergic areas of hypothalamus
C_3	"Arousal" center	Amine modulated areas of midbrain reticular formation
T_5	Storage of primary sensory data	Granulous type cortex (Konio cortex, Economo). Areas 17, 41, 42, 26, 27 (Brodmann)
T_4	Storage of complex sensory data (sensory association)	Polar type cortex (Ec.) Areas 18, 19, 11, 12 (Br.)
T_3	Storage of complex symbols	Parietal type cortex (Ec.) Areas 39, 40, 22, 36, 37, 10 (Br.)
T_2	Storage of goals, goal-directed behavior patterns (motor association)	Frontal type cortex (Ec.) Areas 7, 89, 44, 45, 46, 47, 40, 31, 23, 20, 21, 38 (Br.)
T_1	Storage of subgoals, methods	Agranular pyramidal motor cortex (Ec.) Areas 3–1–2 (Br.)
T_6	Sensory-motor association (coordination)	Cerebellar cortex

Solid arrows: specific pathways.
Broken arrows: non-specific pathways.
Association pathways (interconnecting links between tapes T_1 through T_6) were omitted for the sake of clearness of figure.

We visualize the information flow in the CNS as being processed by three Turing machines (A_1, A_2, and A_3) each having its own "private" tape (T_5, T_3, and T_1) and interconnected in a specific way by common tapes (T_4, T_2, and T_6), feedback units (M_{12}, M_{23}, and M_{31}) and central regulating units (C_1, C_2, and C_3).

Each automaton has read-write heads interconnected with the tapes (B units), the banks of which are activated periodically by a scanning mechanism (a_1, a_2, and a_3).

We assume that each Turing machine is capable of reading one tape at a time (i.e. it functions deterministically) only after certain regulators are set. These regulators would be primarily C_1, C_2, and C_3, which are responsible for the scanning speeds of the individual automaton and are also interconnected (i.e. they are not independent). The functions of these units are enumerated in the legend for Fig. 2 and their potential anatomical identifications on a functional basis are noted—but it should be strongly emphasized that the identifications are highly tentative, open for change, correction, and further specifications on the basis of further experimental data.

It would be impossible to justify the anatomical identifications listed within this given space and I am sure somebody could come up with better guesses than I. My sole purpose was to show that the information processing functions presented in the chart are more or less consistent with present-day anatomical physiological pictures, but the elements of the model are not necessarily anatomical structures. For example, the cortex, with its various types of short and long-axoned cells, specific and association afferent and efferent connections, seemed to be a likely candidate for the function of a tape (Lorente de Nó, 1949). Information processing and storing ability of self-organizing nets with structures similar to that of cortex is being studied widely and discussed by engineers (Rosenblatt, 1962; Greene, 1962, 1964) and neurophysiologists alike (Jung, 1961; Penfield and Perot, 1961). At the other end, the reticular system with its short-axoned network, non-specific connections, and spontaneously firing units seemed to be a logical candidate for scanning, i.e. firing off periodically connecting specific units. Such function has already been suggested by neurophysiologists (Moruzzi and Magoun, 1949; Magoun, 1958; Hernández-Peón, 1961).

Without further elaboration of anatomical, physiological, or biochemical correlates let us follow the main pathway of sensory information as processed by the three automata (Fig. 2):

1. A_1 compares the specially coded (through E encoder) sensory input with primary sensory symbols (stored in T_5) and with sensory motor association symbols (stored in T_6) and sends the information to T_4 for further association with complex symbols on command from the feedback unit M_{12}.

2. A_2 "reads" the information on T_4 and compares it with stored complex memories (T_3) and makes a decision if action has to be taken. Based on the information about the need of the system and on available methods (M_{23}) a command is transmitted to T_2 where the goal directed motor patterns (behavioral programs) are stored.

3. A_3 "reads" the behavioral pattern to be followed (from T_2), selects the appropriate methods from T_1, assesses the data on current situation (from T_6) and on command from M_{31} sends out the proper codes through the decoder (D) to the effector system.

You may be able to recognize in this model several more "precursors" like the information-flow model of MacKay (1956), the idea of a concentric nervous system built around biased homeostats (Pribram, 1960), the organization of receptor and effector processes in human skill (Crossman, 1964), the essentially statistical character of notation employed by the mixed digital–analog functioning nervous system (von Neumann, 1958), and the idea of plastic correlation between perceptual and motor processes (Holst, 1954; Held, 1960).

II. THE EFFECT OF HALLUCINOGENIC DRUGS

Radioactive DMT and some of its basic metabolites penetrate the blood brain barrier in mice and reach high levels in the first 10 min, the neocortex showing larger quantities than others. After this, there is at first a sharp, then a gradual, decline in all areas except the hippocampus which seems to retain this drug in greater quantities than other areas. This distinct difference in distribution at the early and later periods might be related to the behavioral changes observed in the animals.

The normal exploratory behavior of the mice (broken line in Fig. 4) is significantly affected by supressing the hyperactivity in the first 30 min, and after this period in causing a hyperactivity when compared to the behavior of control (non-treated) animals in the same situation.

Adey and his collaborators have found that hippocampal tissue exhibited a greater susceptibility to LSD and psilocybin than subcortical and cortical areas examined (Adey, 1963). These investigators have found also that these drugs produced abnormal seizure-like discharges in the hippocampus of cats which were closely related to the deteriorated performance of a learned discriminative task (Adey *et al.*, 1962). These seizure-like episodes seemed critically dependent on reduction of visual and auditory sensory influences. Similar close relationship between the effect of these drugs on electrical activity of the brain and sensory inputs was noted by Bradley and Elkes in cats although these authors claim the main effect was at the site of afferent sensory collaterals impinging upon the brain stem reticular formation (Bradley and

Elkes, 1957). De Baran *et al.* (1963) working on rabbits have placed the site of action of LSD-25 into the hippocampus again.

In our attempt to find regional differences in the metabolic effects of hallucinogenic tryptamine derivatives which might be relevant to the specific dysleptic effect, we studied the effects of the hallucinogenic DET and the non-hallucinogenic 6-fluoro analog (6-FDET) on the metabolism of C^{14}-labeled precursor of serotonin in small areas of mice brain. The method is reported at the meeting of the Federation of American Societies for Experimental Biology (Szara, 1965).

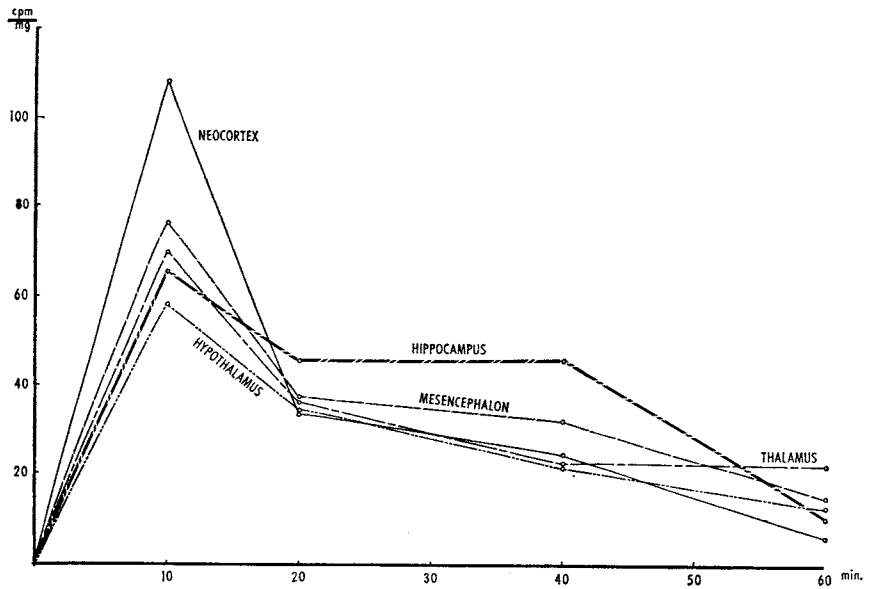


FIG. 3. Levels of combined basic metabolites of DMT-H^3 in various regions of the mouse brain. Injected amount: 250 μg of DMT-H^3 (specific activity 109 mC/mM) intraperitoneally corresponding to 10 mg/kg dose. Found values expressed in counts per min per mg of wet brain tissue. Counting efficiency of technique used: 3·7%.

The highlights of this report are shown on Fig. 5. The results show that the levels of C^{14}-serotonin (5-HT-C^{14}) in the different regions of the brain are not affected equally by the drugs tested. The maximal relative changes were found in the thalamus of the animals after both DET and 6-FDET. But this change, since it occurred after both the hallucinogenic and non-hallucinogenic drugs, cannot be related to the hallucinogenic action of DET. In other areas, however, there were significant differences in the shift of C^{14}-serotonin level due to these two drugs. In the anterior hypothalamus there was a highly significant increase after DET, but the increase after 6-FDET was much smaller and not significant statistically. On the other hand, in the

posterior hypothalamus and, to a smaller extent, in the hippocampus, we found a statistically significant increase after 6-FDET only, but not after DET. In other areas of the brain, both drugs changed the serotonin levels to approximately equal degree. The 6-hydroxy metabolite of DET (6-HDET) did not change the C^{14}-serotonin levels significantly when compared to the control levels.

We cannot go into a detailed analysis of the remainder of the data here, but it suffices to say that the uptake of 5-hydroxytryptophane (5-HTP-C^{14}) into the brain was not influenced by either DET or 6-FDET, and we found a

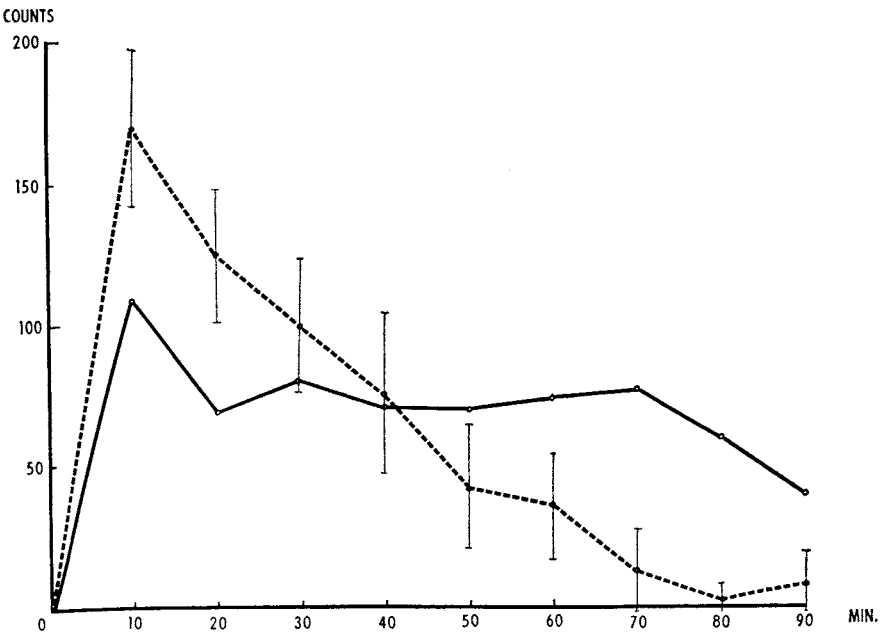


FIG. 4. Effect of DMT (20 mg/kg) on mice in activity cage. Number of crossing of light path in a round activity cage by four animals in a cage. Average of three experiments. Broken line: controls. Solid line: drug treated animals (Szara *et al.*, 1962).

decrease in the concentration of 5-hydroxyindoleacetic acid (5-HIAA-C^{14}), closely corresponding to the increases of 5-HT-C^{14}) concentration. This would point to a decreased function of monoamine oxidase (MAO) resulting from either a direct inhibitory action of the drug on the enzyme or from an indirect mechanism which increases the storage of 5-HT, thus preventing the action of MAO on serotonin.

But in a separate experiment we could see no difference in the activity of MAO prepared separately from the anterior and posterior part of the hypothalamus. Both enzymes were equally sensitive to the competitive

inhibition by DET, even when the enzymes were prepared from DET pretreated animals.

It seems unlikely then that the differential effect in the two parts of the hypothalamus (as seen in Fig. 5) would be a direct metabolic effect of DET. Unless we find a specific metabolite acting selectively in the anterior hypothalamus as an additional MAO inhibitor, or in the posterior hypothalamus as a "releaser" of 5-HT, we have to assume that this metabolic effect is an indirect

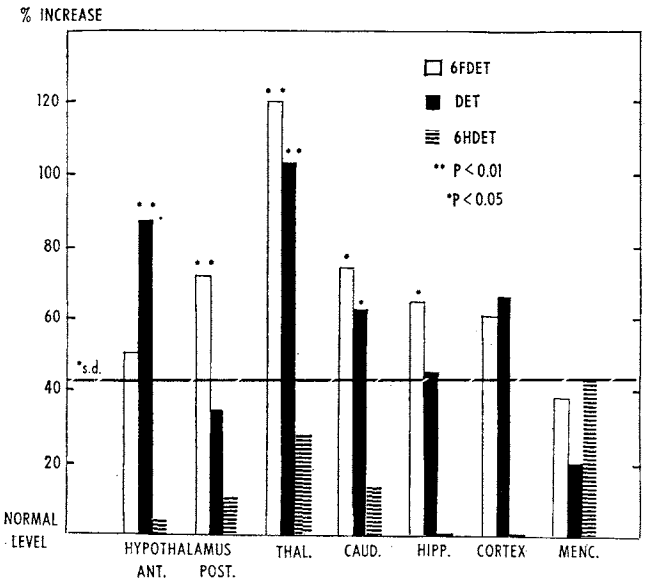


FIG. 5. Increase of 5-HT-C^{14} levels in various regions of mouse brain in the presence of tryptamine derivatives. For abbreviation of drugs see text. Normal levels of 5-HT-C^{14} obtained 30 min after the injection of 5-HTP-C^{14} (spec. act.: 2·64 mC/mM; 25 mg/kg intraperitoneally, equivalent to 8 μc/30 g animal) in the various areas (calculated as μg/g of wet tissue) were: hypothalamus anterior 0·37; posterior 0·44; thalamus 0·27; caudate nucleus 0·38; hippocampus 0·22; cortex 0·20; and mesencephalon 0·42. These are average values of five animals. S.D. = standard deviation of normal values.

physiological reflection of a more direct effect of the drug on hippocampal neurons.

On the basis of these data, we hypothesize that the specific dysleptic symptoms produced by these drugs are the result of a malfunction in the anatomically and functionally well-documented serotoninergic pathway running from hippocampus through the septum into the hypothalamus (Nauta and Kuypers, 1958; Green *et al.*, 1960; Heller *et al.*, 1962).

If we now recall the information-flow chart of the CNS, we can see that this pathway forms an important feedback loop between A_2 and A_1 running from the banks B_{42}, B_{32}, and B_{22} through a_2 into C_2 and C_1. Since we assigned

the function of regulating the scanning speeds of A_1 and A_2 for this loop we might conclude that the dysleptic drugs disrupt the mechanism which regulates the scanning speeds of A_1 and A_2.

If we further assume that the proper ratio of scanning speeds determines the channel capacity between A_1 and A_2 (Miller, 1956), then we have a beautiful model to accommodate most of the psychological symptoms observed and experienced as the specific effects of dysleptic, hallucinogenic drugs. These symptoms are too numerous to elaborate on here but it will be attempted on another occasion. It is sufficient to point out here that the basis for this

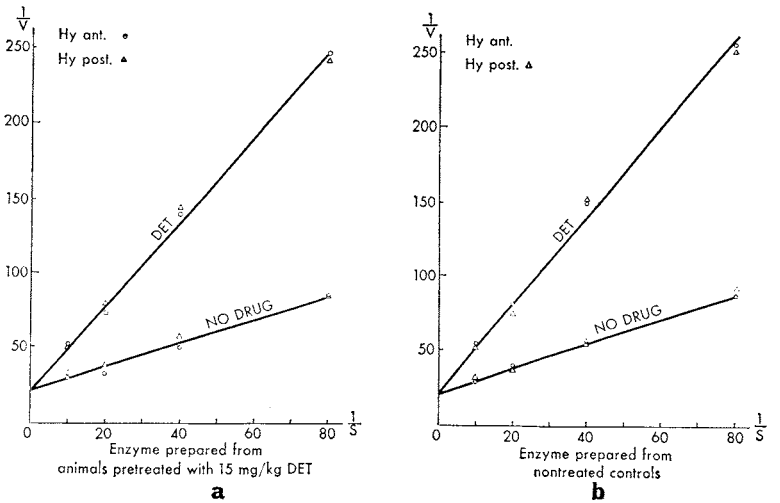


FIG. 6. Lineweaver–Burk plots showing competitive inhibition of monoamine-oxidase (MAO) prepared from the anterior and posterior part of the hypothalamus, pooled from several animals by N,N-diethyltryptamine (DET). Substrate for MAO was C^{14}-labeled tryptamine. Substrate disappearance technique was used for measuring 1/V. (a) Shows the plots obtained from enzyme prepared from animals pretreated with 15 mg/kg i.p. 15 min before decapitation. (b) Shows the results obtained with enzyme prepared from non-treated control animals.

particular symptom complex—I am referring here to the disruption of the regulating mechanism for the communication channel between A_1 and A_2—is stated in a language which can be transplated easily into the language of neurophysiology, behavioral psychology, as well as clinical psychology, so that appropriate working hypotheses can be stated and tested using usual research techniques and methods.

III. SCHIZOPHRENIA

In trying to relate the drug-induced symptom complex to that of schizophrenia we run into the problems mentioned in the introduction. It is significant, however, that the most important fundamental disturbance in

schizophrenia, the loosening of association (Bleuler, 1934), can easily be conceived in our model as a result of a disturbance in setting the proper scanning speeds between automaton A_1 and A_2 so that the associative function of tape T_4 becomes indeterminate which is another way of saying that the association is "loose". It should be noted that T_4 is the main connecting link between A_1 and A_2 and its functional connections constitute the most important channel of communication between these two Turing machines.

The cross-section of the complex psychological deficit, recently summarized by Shakow (1963), points to a basic weakening of the control center that serves the integrating and organizing function of the central nervous system and provides for the establishment of what Shakow has called "generalized" or "major sets". He refers to the world of the schizophrenics as an inefficient, unmodulated system, full of "noise", and of indeterminate figure–ground relationships. Thus, it is very tempting to speculate that this control center Shakow is referring to is functionally equivalent to our C_1 and C_2 centers

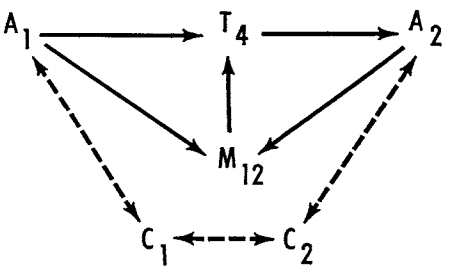


FIG. 7. The basic communication channel hypothesized to be involved in both schizophrenia and the hallucinogenic drug action. For explanation of symbols see legend for Fig. 2.

which in our model form a most important part of the feedback loop regulating the "communication channel" between A_1 and A_2. In this way, "noise" becomes more than just a figure of speech—it assumes specific meaning amenable to information—theoretical analysis and provides new approaches for experimental analysis of this basic schizophrenic disturbance.

We might conclude then that the same basic functional circuitry involved in the action of hallucinogenic drugs might also be involved in schizophrenia.

Each member of this circuitry is also a member of other circuits so that if a malfunction of any of these structures introduces noise it would not only limit the capacity of this channel but also interfere with the functions of the additional circuits to which its belongs. In the action of hallucinogenic drugs we blamed the connection $A_2 \leftrightarrow C_2$ for the basic disturbance. Of course, all the circuits of which A_2 and C_2 are members would also be disturbed at the same time. In schizophrenia the point of disturbance might be another member of this basic circuitry which would result in additional symptoms

different from those observed in the case of dysleptic drugs. This might be an explanation for the discrepancies between the two-symptom complex referred to in the introduction. It is also a possibility that the primary point of attack is the same in both cases but that there are additional functional disturbances in schizophrenia due to attacks of a hypothetical toxin on other points in the CNS. Schizophrenia might also be due to inherited or acquired functional inadequacies of the same circuit manifesting themselves in a different manner than in the case of the hallucinogenic drug effects.

A final word of caution seems to be in order. It is very easy to substitute psychological terms for the technical terms of information theory. Thus, inputs and outputs of a channel are easily and naturally translated into the stimuli and responses of the organism. Verbal recoding of this sort is not simply playing with words. It influences the choice of variables and the design of experiments (Frick, 1959). The variables, however, have to represent real measurable quantities and the network of influences among them have to be actually observed or specifically assumed in order to arrive at valid conclusions (Toch and Hastorf, 1955).

In our theoretical model we used parameters, variables and functions (like anxiety, pleasure, arousal, disturbance of function, etc.) not always quantifiable very easily. Such an analog description of function, however, matches most people's ordinary modes of thought better and is, therefore, likely to facilitate interaction between theory and experiment. As theory develops much more precision of statement and formalization of assumptions on the basis of experimental data will be in order. To accomplish this it would seem we have a lifetime program ahead of us.

ACKNOWLEDGMENT

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SUMMARY

I. An information-flow map for the central processes in the nervous system is proposed. It is characterized by:

A. Three interconnected Turing machines (automata) which are capable of functioning both deterministically and indeterministically.

B. Cortical areas are hypothesized to function as "tapes" while the reticular formation is viewed as a scanning system equivalent to the function of "tape mover" and "tape scanner" of the automata.

C. The scanning speed of the individual Turing machines is assumed to be regulated by interdependent central reticular structures.

II. Literature data and results of our experiments indicate that the specific dysleptic symptoms produced by the hallucinogenic drugs might be the result

of a malfunction in the serotoninergic pathway from hippocampus through the septum into the hypothalamus.

It is proposed that this pathway is the most important feedback loop regulating the relative scanning speeds between the sensory recognizer and comparator organizer system; malfunction of this pathway results in narrowing the capacity of the communication channel between the two systems.

III. The psychological deficit in schizophrenia is viewed as the result of a disturbance in the same basic circuitry subserving the communication channel between the sensory recognizer and comparator organizer system. The possible difference in the mechanism of disturbance could account for the discrepancies between the drug-induced symptom complex and schizophrenia.

ADDENDUM

A short review of the author's earlier work with hallucinogenic drugs follows.

Interest in the possible hallucinogenic activity of N,N-dimethyltryptamine (DMT) stems from the report by Fish, Horning and Johnson (*J. Am. Chem. Soc.* **77**, 5892, 1955) who found DMT, together with bufotenin, in snuff powder prepared by Haitian natives from *Piptadenia peregrina* seeds which the natives used in their religious ceremonies to produce mystical states of consciousness.

In 1956 the hallucinogenic action of bufotenin was reported by Fabing (*Am. J. Psychiat.* **113**, 409) but no information whether DMT had similar psychotropic activity was available. We prepared DMT by chemical synthesis and tested its activity on animals and humans. It was found that it produced mescaline- and LSD-like symptoms lasting for a surprisingly short period of time (45 min–1 hr) after intramuscular injection of about 1 mg/kg dose of the drug (Szara, *Experientia*, **12**, 441, 1956).

Because of the very short action of the drug, we turned our attention to the study of the metabolism of DMT in animals and in man. A new pathway —6-hydroxylation of the indole ring—was shown to be a major route for the metabolism of DMT and DET in animals (Szara and Axelrod, *Experientia*, **15**, 216, 1959; Szara and Hearst, *Ann. N.Y. Acad. Sci.* **96**/1, 134–41, 1962), but in human subjects only a small portion (5–15%) of the administered drug could be recovered from urine as 6-hydroxy metabolites (Szara and Rockland, *Proc. IIIrd World Cong., Psychiatry*, **I**, 670, 1961). In spite of this latter finding it was felt that the 6-hydroxylation pathway is pharmacologically important for two reasons. First, a strong correlation was found between the individual ability of a subject to hydroxylate DET and the LSD-like symptoms (perceptual distortion, paranoid ideation, etc.) produced by a 1 mg/kg dose of the drug (Szara, Rockland, Rosenthal and Handlon, submitted for publication). The second reason, mentioned also in the formal paper given in this symposium,

is that if 6-hydroxylation is prevented by a substitution of the 6-position of the indole ring by a fluoro-atom, the resulting derivative, 6-fluoro-N,N-diethyltryptamine, is not hallucinogenic any more although it retains some of its non-specific, autonomic effects in man.

It might be of interest to mention here that Axelrod has found an enzyme in mammalian organisms which can methylate serotonin and tryptamine to psychotomimetic bufotenin and DMT (*Science*, **134,** 343, 1961). But, as we already mentioned in the formal paper, all attempts to find bufotenin or DMT in schizophrenics' urine have failed. This is not discouraging, however, since DMT, if it would be formed, would be metabolized so very fast that chances of finding it unchanged in the urine would be slim.

Research is under way to explore the metabolic fate of these tryptamine derivatives in the hope that among the unknown metabolites we may find perhaps some which will prove more useful in understanding the mechanism of the hallucinogenic action and thus possibly help us to understand the etiology of schizophrenia.

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