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NEUROPHARMACOLOGY AND EXPERIMENTAL PSYCHIATRY

The Evolution of a Project--A Progress Report

AMEDEO S. MARRAZZI, M.D.

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NEUROPHARMACOLOGY
University of Missouri Institute of Psychiatry
St. Louis, Missouri
1970



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13. ABSTRACT
By means of a correlative, interdisciplinary approach analyzing performance at all levels, it has been possible to gain a more insightful understanding of the uniquely comprehensive functions of the nervous system, which display man's environments translated into information signals, develop the required solutions and convert them into the necessary command signals. These studies have highlighted the capabilities of the cerebral computer for maintaining homeostasis and the devastating consequences--mental and bodily--when homeostasis or adaptation at the key level of central representation fails and constitutes mental illness. A critical communication link between brain cells is chemical, and therefore would be expected to be and is modifiable by other chemicals and drugs accounts for the amenability to analysis and to correction by drugs. It has been found that this special interneuronal chemical transmitter environment appears to be the substrate for the action of the most potent cerebral drugs.

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NEUROPHARMACOLOGY AND EXPERIMENTAL PSYCHIATRY

The Evolution of a Project--A Progress Report

The study of the operation of the nervous system in health and in disease has led the author and his collaborators through a series of adventures in research that have developed into an increasing involvement with the mind and its disturbances. The evolution of this commitment to Experimental Psychiatry, the approaches that have been required and the insights that the data obtained have afforded constitute this progress report and expression of conviction in the need for interdisciplinary investigation.

An initial exposure to the practice of medicine strengthened the belief that, at its best, it constitutes a daily clinical experiment with each patient in which drugs provide the tools for dissecting and modifying normal and disease processes. The focus on control systems with the greatest versatility in adapting to internal and external environments and with the greatest vulnerability to drugs, resulted in a convergence on the nervous system and its response to drug manipulation. Thus a neuropharmacologist came into being. In the process of developing suitable techniques and laboratories, the neuropharmacologist organized and headed two Departments of Pharmacology (Loyola Univ. and Wayne Univ.). Army Chemical Corps next provided the opportunity for exploration of the nervous system with more powerful substances both in the laboratories and in the field, and for the realization of a strong desire to reversibly reproduce and control derangements at the highest integrative levels including the mind.

The neuropharmacologist thus became a neuropsychopharmacologist who subsequently, as Chief of the Clinical Research Division, put his experiments into the context of mental disease as Experimental Psychiatry.

The need for an expansion of the interdisciplinary approach and the greater availability of clinical rather than solely man-made disease made it natural to accept the VA's invitation to set up the first National Laboratories for Research in Neuropsychiatry. As the life of this successful pioneering operation approached a decade, the lure of a similar but completely on-campus operation culminated in the Hill Foundation Research Professorship of Neuropharmacology at the University of Minnesota. After thriving for five years, the project was again lured by the fuller recognition and potentialities afforded by the new laboratories and research ward of the new Neuropharmacology Division of the University of Missouri's Institute of Psychiatry in St. Louis, where the author is presently Professor of Psychiatry and Neuropharmacology and Chief of Neuropharmacology.

The definitive orientation to Psychiatry is reflected in continued studies on the operation of the nervous system in health and disease. These are designed to examine the nature of drug influences on and regulation of this key communication and control system, which allows man to monitor and to adjust to his inner needs and to the demands of the world about him; i.e., to continuously respond adaptively to his internal and external environments. Such information has provided the basis for the use of drugs in bringing about remedial or therapeutic changes in the function of the nervous system. Equally important is its use to elicit experimentally and at will, accentuation or suppression of

particular aspects of normal function or of the distorted function otherwise exhibited by the diseased nervous system. In this way drugs can become remarkably effective tools for the analysis and better understanding of normal function and the identification of underlying processes common to selected experimental and to certain clinical disturbed states. Such experimental analogs of mental disturbance are giving us a better understanding of normal performance as well as more appropriate and therefore better ways of testing the manner and effectiveness of corrective action.

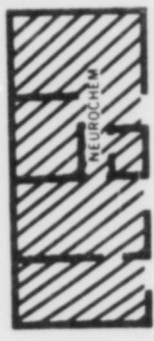
Dissection can achieve optimum results when the tools are sharp, the capabilities known and the nature of the material appreciated. Orientation of this approach to the nervous system gives us neuropharmacology and focusing on mental behavior, psychopharmacology. The successful elaboration of the strategies suggested has required a multifaceted survey and analysis, including electrical monitoring of message traffic in the nervous system as influenced by drugs, or electropharmacology, determining the underlying cellular and molecular changes responsible for them, or neurochemistry, and the resulting changes in relating to the environment accomplished by the neural control system, or the behavioral outcome, in animals and man.

The current full realization of the desired facilities and the interdisciplinary nature of the explorations they make possible are summarized by the plan of the Neuropharmacology Division laboratories and wards at the University of Missouri Institute of Psychiatry. (cf. page 3a.)

By means of such a correlative, interdisciplinary approach analyzing performance at all levels, it has been possible to gain a more insightful understanding

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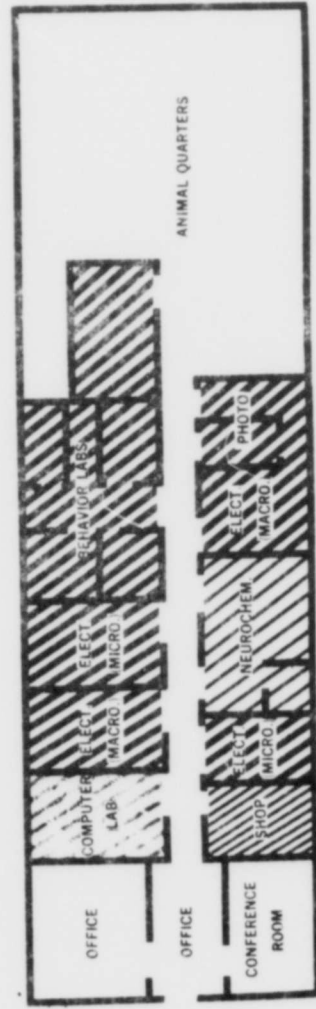
CLINICAL LABS.



5th Fl.



BASIC LABS.



Base.

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of the uniquely comprehensive functions of the nervous system, which display man's environments translated into information signals, develop the required solutions and convert them into the necessary command signals. The studies have highlighted:

1. The exquisite capabilities of the cerebral computer for maintaining homeostasis and the devastating consequences--mental and bodily--when homeostasis or adaptation at the key level of central representation fails and constitutes mental illness.

2. The fact that a critical communication link between brain cells is chemical, and therefore would be expected to be and is modifiable by other chemicals and drugs accounts for the amenability to analysis and to correction by drugs. We have found, in fact, that this special interneuronal chemical transmitter environment appears to be the substrate for the action of the most potent cerebral drugs.

Electropharmacology

By tapping in* on the brain circuits, we have been able to record effects of communication between nerve cells or synaptic transmission. This is accomplished by recording the output messages (evoked potentials) from terminal cells in a neuronal chain, in response to test inputs initiated by weak electrical shocks to the beginning of the chain^(1,2,3). When a drug, introduced into

*i.e., Leading off the minute electrical signals that are an inseparable part of nerve impulses, amplifying them and displaying them on the surface of a cathode ray tube for photographic recording.

the blood stream to the brain, succeeds in altering the chemical synaptic environment, this results, depending on the direction of the change, in an increase or decrease in the output messages.

This sensitive, direct technique has enabled us to show with almost complete conclusiveness that chemicals, e.g., acetylcholine, known to be liberated from the ends of excited brain cells at their junction with others, act as the messengers to bridge the microscopic junctional gap separating them and to transmit the nerve impulse. The chemicals belong to a cholinergic family (1,4,5,6,7,8) that excites the next cell reached and to adrenergic (1,4,8,9,10) and tryptaminergic (7,8,10,11,12) families that inhibit it.

The classical criteria for a neurohumoral mechanism require a demonstration of the liberation of the candidate substance in response and in proportion to activation. We accomplished this in the cerebral cortex of the cat by introducing tritium labeled choline intracortically and demonstrating the presence (release) of labeled acetylcholine in response and in proportion to electrical and to nerve impulse activation (13). The labeled material was both measured in the cortex and collected from an overlying McIntosh cup filled with ringer/solution containing anti-cholinesterase and atropine. This supplies long needed support for a critical point in the working hypothesis that cerebral synapses contain a cholinergic (1,14) excitatory mechanism which can be demonstrated and controlled by drugs. The complementary aspects of this hypothesis, viz., that the excitatory is in equilibrium with an inhibitory mechanism in which biogenic amines are the neurohumoral operators requires similar data. Such data in conjunction with the demonstrated

existence of the candidate substances and the associated enzymatic systems for their synthesis and destruction would provide the requisite basis for our hypothesis that there is a neurohumoral homeostasis at cerebral synapses which makes possible physiological transactions and their modification by drugs. (15, 16, 17, 18, 19)

It is clear that there is a labile, push-pull type of balance between continuously active "stop and go" or inhibitory and excitatory chemicals liberated by the stream of impulses arriving at the synapses as a result of the constant sensing of the body and the world it is in. A sufficient change in the composition of the input; i.e., a change in the ratio of excitatory to inhibitory impulses, tips the balance in favor of an appropriate increase or decrease in transmission with, normally, a rapid restoration to the normal equilibrium state.

This labile equilibrium, chemically maintained by the competing messengers produced by the brain cells, is by its nature susceptible to other chemical influences; and this has presented a key to the mechanism of cerebral actions. We have been engaged in unlocking these particular brain mechanisms which form the basis for the effects of the most powerful drugs that affect the brain and whose consequences and implication we are fully exploring and utilizing in gaining further insight into the operation of the brain and mind. (20)

The explorations have pursued several parallel paths. Thus, to examine further the cogency of the above thinking, we have continued to investigate its applicability to other strategic areas of the brain in order to test the validity of the basic generalization that internal communication in all parts of the brain is carried on by the same kinds of messengers in varying proportions and with

varying responsiveness of the brain cells to their influence⁽²¹⁾. For example, we are filling out more completely the table I summarizing our supporting findings that the interneuronal messengers and their chemical cousins, as in the case of certain mind disturbing drugs (first cousins in the case of mescaline and distant cousins in the case of LSD), as well as their characteristic antagonists⁽²²⁾ have the same kind of effects though with differing intensities at all these sites⁽²²⁾. This includes intensifying our analysis of the effects in the brain stem, through which funnel and cross-connect for supplementary and wider interaction the main incoming and outgoing lines. So far, we have found that serotonin, the most potent synaptic inhibitory messenger acts on the brain stem electrical signals (evoked potentials) in the same way as we have previously found it to act at other synapses of the brain and that norepinephrine and LSD do likewise, while the tranquilizer, chlorpromazine, here as elsewhere in the brain, characteristically prevents or blocks these effects^(5,7,8). Acetylcholine in small doses produced an increase in the mesencephalically recorded potentials evoked by pontine electrodes. In the same animal acetylcholine in larger doses produced a secondary paralytic effect⁽⁷⁾. The parallelism so far is complete lending support to the tentative generalization that cortical and subcortical, including brain stem, synapses are qualitatively alike, though they may have different thresholds as indicated by drug response. Since we believe this drug responsiveness is due to an interaction with the neurohumoral environment; i.e., that the latter is the substrate for the drug action, we are implying that the neurohumoral mechanisms are alike in kind though perhaps not in detail at various types of synapses that we have explored. Thus far, our generalization that cerebral synapses are qualitatively alike in response to drugs,

GENERALITY OF CEREBRAL SYNAPTIC DRUG RESPONSE

SITES EXAMINED

REGION	RECORDED FROM	EVOKED THRU
CORTICAL	1° SENSORY OPTIC AUDITORY ASSOCIATION	OPTIC RADIATIONS AUDITORY N. (CLICKS) COMMISSURAL FIBERS A) TRANSALLOSAL OR B) TRANSCYRAL
	LAT. GYRUS SUPRASYLVIAN G.	
SUBCORTICAL	LAT. GENICULATE	OPTIC TRACT
BRAIN STEM RETICULUM	MESENCEPHALIC PONTINE	PONTINE RETIC. SCIATIC NERVE
	PHRENIC NERVE	SPONT. RESP.
MEDULLA		

TABLE I

holds, to be further challenged by additional experiments including:

- a) Testing of more synapses.
- b) Testing of more drugs.
- c) Intracellular recording.

The complete and direct specification of such actions requires intracellular recording in order to obtain the corresponding excitatory postsynaptic potentials (EPSP) and inhibitory postsynaptic potentials (IPSP).

We have not, then, as yet, found an exception to what becomes a fundamental observation. More detailed examination of such drug response properties and expansion of the survey to additional critical sites continue the testing of the generalization. The generality found supplies an explanation of why drugs cannot be expected to act exclusively or uniquely at particular sites, but only with a relative discreteness, which can be overcome by larger than minimum amounts of drugs producing an undesired degree of extensiveness, then becoming toxicity.

The blocking action of chlorpromazine, and the same is demonstrable in varying degree with all the phenothiazine tranquilizers as well as with reserpine and meprobamate, turns out to be a competitive inhibition for the same receptors. In other words the tranquilizers are actually operating as weak mind disturbing drugs or psychotogens, which offer protection by preempting the site of action with a weak substance and thereby substituting a weak for the action of a strong substance.^(20, 23, 24)

It then follows that at a critical strength of tranquilizer, there could be an additive effect making matters worse; and we have, in fact, been able

(25)

to produce this aggravation experimentally. We believe this accounts for the occasionally reported aggravation of drug induced or "trip" symptoms by chlorpromazine. Similarly, inordinately large doses of the weak psychotogen-- in this case the tranquilizer--could produce a disturbance by itself; and this is also observed clinically as a drug induced, toxic psychosis.

Direct observations of the kind we have been describing must necessarily be done, for the most part, in subhuman species. Even before human experimentation becomes feasible, the relevance of the preliminary information can be judged by comparing the results across the animal kingdom, in a series ascending the evolutionary scale, through a subhuman primate, to man. We have added to our previous work on the rat, cat and dog the corresponding data in the monkey, where we have gotten the same kinds of effects for the various drugs used. This has led us to conclude in a paper presenting the monkey and summarizing these findings that they suggest "an orderly, parallel relation in a series that progresses through a subhuman primate to man." & "Comparative neuropharmacology can go beyond pragmatic opportunism to provide an instructive display of unifying similarities and clarifying differences among the species as they approach man in cerebral development. Thus we seriously entertain the possibility of similar mechanisms accounting for the phenomena induced by psychotogens in man." (22)

As correlates of a neurohumoral synaptic inhibitory mechanism accounting for our observed effects of serotonin, noradrenaline, mescaline, LSD, etc., such an action should be demonstrable in varying degrees throughout the members of the cerebral biogenic amine series participating in the natural cerebral amine

metabolic cycle as well as in their analogs*. Accordingly we have demonstrated the varying inhibitory potencies of dopamine, DMPEA (dimethoxyphenylethylamine),^(26, 27, 28) and other ring methoxylated analogs.

The use of drugs as tools and the growing support for the concept that many of the highly active cerebral drugs exercise their effect on the neurohumoral synaptic substrate, in each case altering the equilibria between excitatory and inhibitory transmitters that are continuously operating, is borne out by the cerebral actions of the several dozen drugs listed in Table II, "Drugs Modulating Cerebral Synapses." Recalling that we have been postulating a cholinergic excitatory mechanism and adrenergic and tryptaminergic inhibitory mechanisms, we examined natural and unnatural cholinergic, adrenergic, tryptaminergic and related substances and their preservatives, and blockers. Each of the tabulated cases lived up to the expectations that are consequent to our interpretation.⁽²⁹⁾

This kind of thinking relates readily to classical pharmacology, which points out that for reversible drug effects, there really can only be two kinds of actions, viz., an increase in the functions of a cell or excitation and a decrease in its function or inhibition. From these two changes at the site of drug action and depending upon the complexity of the circuit into which the cell is "plugged" stem the complete repertoire of effects. These are schematized in Table III, which presents the "Continuity of Inhibitory Effects" and "Continuity of Excitatory Effects." In each case there is a progression of effects charted from left to right. The solid black bars indicate the desired effect in each instance and the dashed continuation, the "toxic" effects that result in each case

* Of more than passing interest to mental disturbance is that histamine is also a very potent cerebral synaptic inhibitor.⁽⁵⁶⁾

DRUGS MODULATING CEREBRAL SYNAPSES

		ACCUMULATORS (Preserve, Release, Inhib. Reuptake)	BLOCKERS
EXCITORS			
Cholinergic (Natural)	Acetylcholine	Antiche.	Atropine Curare TEA
Others (Unnatural)	Pilocarpine Nicotine		Atropine
INHIBITORS			
(Natural) Adrenergic	Adrenochrome Dopamine Norepin. Epin. Nor metaneph. Metaneph. DMPEA	MAOI Amphet. Ephed.	CPZ
Tryptaminergic	Serotonin	MAOI	
Other Amines	GABA	Dilantin	
	Histamine		Triplennamine
"Peptides"	Bradykinin		
	Taraxein-like		CPZ
(Unnatural) Amines			{ Phenothiazines Reserpine (BOL vs. LSD) (LSD vs. Serotonin)
Catechol	Mescaline		
Indole	Bufotenine Harmine Psilocybin LSD BOL		

CONTINUITY OF INHIBITORY EFFECTS

	DISSOCIATION <i>(Release)</i>	SEDATION	HYPNOSIS	ANAESTHESIA	COMA
Tranquilizers	██████████	██████████	██████████	██████████	██████████
Psychotogens	██████████	██████████	██████████	██████████	██████████
MAO Inhibitors	██████████	██████████	██████████	██████████	██████████
Alcohol	██████████	██████████	██████████	██████████	██████████
Narcotics	██████████	██████████	██████████	██████████	██████████
Sedatives	██████████	██████████	██████████	██████████	██████████
Hypnotics	██████████	██████████	██████████	██████████	██████████
Anaesthetics	██████████	██████████	██████████	██████████	██████████

CONTINUITY OF EXCITATORY EFFECTS

	DISSOCIATION <i>(Local Stim.)</i>	GENERALIZED STIMULATION	ANALPESIS	CONVULSION	POST CONVUL DEPRESSION
Antidepressants <i>(Non-MAO Inhib.)</i>	██████████	██████████	██████████	██████████	██████████
Analeptics	██████████	██████████	██████████	██████████	██████████
Convulsants	██████████	██████████	██████████	██████████	██████████

Desired
 Undesired

TABLE III

from increasing the dose. It becomes clear, then, that by suitable control of dosage that any portion of the range of effects can be obtained. It is to be noted that the first column or "dissociation" is obtained in the case of the inhibitors and depressants by a disinhibitory effect or release phenomenon and in the case of the excitors, by the imbalance resulting from the earlier or greater activation of low threshold areas preventing otherwise natural synchrony. In the context of this formulation the specificity of action becomes simply an ease in eliciting the desired fraction of the effects devoid of the remainder, which surely follows when the dose is increased⁽³⁰⁾. Accordingly by careful control of the dose, it is possible to obtain "specific" effects, such as tranquilization with simple sedatives or even anesthetics. The use of alcohol for this purpose is a case in point.

Continued refinement of our tools and techniques has added strength to our analysis. Thus, our interpretation of a changed output in response to an unchanged input rested on recording directly from output cells, but only remotely from the input ones. We have confirmed the findings by recording both input and output directly and simultaneously--the output as before and the input through another set of electrodes inserted into the input path. Under these conditions, again, drugs can change the output although the input remains unchanged⁽³¹⁾.

The necessity for demonstrating an independence of cerebral drug effects from possible vascular changes the drugs could also induce has been satisfied by demonstrating the absence of significant changes in local oxygen availability, as indicated by an oxygen electrode placed alongside the electrode recording evoked potentials⁽³⁾. The same synaptic effects were gotten in unanesthetized animals. Isolating the cortex under the recording electrode from the rest of the brain by undercutting or by lifting out an island that included the cortex demonstrated that, although the effects are exercised throughout the brain, they could also be restricted to the terminal synapses in the cortex. (21)

The analysis will be carried to the level of the individual units or single nerve cells that make up the discharges of brain activity we have been sampling, and we will then be able to correlate the activities of populations of neurons, which is the usual mode of operation of the nervous system, with the constituent units that must be artificially separated for study. It will thus be possible to understand the degree of heterogeneity that may be represented by the field potential emitted by the population.

The individual measuring of the responses to the test shocks, which are delivered every two seconds for two hours, becomes very time consuming and, because of the fatigue of the individual reading the records, precision may be lost. We have, therefore, developed a computer program now being checked, designed to machine read the records, especially those, which, because of variability, are more subject to the reader's judgment and to variations arising from the fact that the reader's judgment is not precisely formalized as readily as is achieved by the computer program.

Neurochemistry

The crucial nature of the chemical messenger operation as a synaptic transmission mechanism and as a substrate for drug action has made it vital to determine the full details of the production, liberation and destruction (to prevent a "line busy" effect) of the neurochemical mediators. The collection of liberated chemical transmitters has been done with relative ease for transmission sites outside of the brain and spinal cord, but the brain lends itself less readily to tampering with for this purpose. However, by use of radioisotope labeling

techniques, we have demonstrated that synthesis of the "go" (excitatory) messenger, acetylcholine can be achieved from a radioisotope labeled "supply material," choline, which then becomes acetylcholine and is freed in amounts proportional to the intensity of nerve activation of the surface layers of the brain (cortex) into which the precursor had been previously introduced. Separation of the cellular constituents has allowed us to see that the labeled acetylcholine is concentrated in a region corresponding to the ends of the neurons from which it is liberated. The rise of the labeled acetylcholine, determined by chemical analysis of the tissue, can reach such proportions that an "overflow" can be collected in a special cup fitted on to the surface of the brain overlying the stimulated region and revealed by the very sensitive radiation counting techniques (13) Similar approaches are to be followed in obtaining the corresponding necessary details of the "stop" systems.

We had previously shown that drugs producing such symptoms of the disturbed mind as hallucination and attendant anxiety, etc., like LSD, mescaline, the drug obtained from the cactus "bean" and used as a sacrament of the Indian "Native American Church," tend to interrupt cerebral communication and that tranquilizers offset this action. (20,23) We had also shown that the substance extractible from human blood and present in greater amounts in the blood of some schizophrenic patients behaved in the same way. (32, 33, 34) We have established similar data for a substance dimethoxyphenylethylamine (DMPEA), that is reported by some to be extractible from the urine of the sickest of such patients and of others with a nervous system damage known as Parkinsonism. (26, 28) The substance is chemically related to

mescaline and is likewise offset by a typical tranquilizer. It then would have the attributes of a mind disturbing chemical and its production in the body might, indeed, be a factor in the causation of some types of cerebral and mental illness. Aside from this important possibility, its chemical similarity, on the one hand, to mescaline, the poison from the cactus, and, on the other hand, to substances natural to the brain and instrumental in the interneuronal communication process; i.e., the biogenic amines provides a link allowing the arranging of a series of compounds from the hallucination producing mescaline to related chemicals natural to the brain. The members of this series differ from each other in a stepwise fashion according to the presence of increasing numbers of a constituent group (the methoxy on the phenyl ring) and show a graded increase in the synaptic communication and mind disturbing effects that suggest the importance of this group in these functions. Valid relations between chemical structure and the actions on the brain open the possibilities of tailoring other chemicals to offset the action, in this case undesired, and would constitute a chemotherapy of the mind. The relation to the chemical messengers of the brain supports our contention that cerebral chemotherapy could be profitably focused on the synaptic communication process.

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The distortion of the resting state equilibrium between "stop and go" mechanisms achieved by drugs can, as we have seen, also be produced by abnormal products of chemical processes natural to the body. The exact chemical nature of an example of such a substance that we have found in the blood, is therefore, of great interest both in illuminating the naturally occurring pathological process and in offering a point of attack for chemotherapy of the brain.

We have shown that this particular substance is carried adsorbed to normal blood proteins. Electrochemical (electrodialytic) separation from the protein and the preliminary identification of the small fraction actually responsible for the brain effect is being carried further/⁽³⁴⁾

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Behavior and Psychopharmacology

The final and most important outcome of neuronal messages is behavior or the means of relating man to his world. The ultimate significance, then of our findings is to be found and needs to be expressed in behavioral terms and experiments. We have carried these out in animals and in man. Indeed, LSD has achieved notoriety in the lay press because of the social consequences of the changes in behavior it induces. We have for years been utilizing it and similar and related chemicals in the serious study of behavior.

Having determined its effects on intracerebral communication, we have proceeded to analyze the resulting behavior (Psychopharmacology) to determine whether correspondence with its neuropharmacology and neurochemistry justifies our interpretations and the strategies of further analysis and of therapy which they suggest. Table IV summarizes some of our results and shows that the synaptic transmission or communication effects of the natural cerebral chemical, serotonin and of LSD are the same and that various samples of behavior are as a result, hindered as would be expected/⁽³⁰⁾ In fact the behavioral effects of the cerebral synaptic inhibitory amines and the related or interacting compounds turn out to be reasonable counterparts of inhibition, first--in the smaller doses-- a inhibition of inhibition producing a release phenomenon and then as the dose

TABLE IV

COMPARATIVE NEUROPHARMACOLOGY

SPECIES	MODE	SEROTONIN	LSD25	CPZ PROTECTION VS
Rat	Synaptic* Behavioral	Inhibition(40)	C. Ap. L ↑(12,17) C. Av. L ↑(12,17) Diff. ↓(12,17,38) Intersignal responses ↑(38)	LSD25 C. Ap.
Cat	Synaptic Behavioral	Inhibition (12)	Inhibition (12) Intersignal responses ↑(38) (No. of responses)	Serot. (12); LSD25 (12,24)
Dog	Synaptic	Inhibition (39)	Inhibition (39)	
Monkey	Synaptic Behavioral	Inhibition	Inhibition C. Ap. L ↑(37) Diff. ↓(37) Intersignal responses ↑(37)	Serot.; LSD25 LSD25 on C. Ap. (37)
Man	Synaptic Behavioral		Inhibition (41) Hallucination (42,43) Perceptual assoc. ↓(20)	LSD hallucination (42,43)

↑ -increased; ↓ -decreased; C. Ap. L. =conditioned approach latency;
C. Av. L =conditioned avoidance latency; Diff. =differentiation (tone or time).

*Synaptic in his table refers to transcallosally except (41) activated cortical synapses. However, as indicated in the table of "Generality of Cerebral Synaptic Drug Response" that we have published (21), synaptic inhibition by serotonin and LSD25 is obtained at a variety of cerebral synapses, including cortical, subcortical and brain-stem.

is increased a reduction in behavior. It further shows that the tranquilizers, represented in this case by chlorpromazine, do protect against the communication (25, 34, 35, 36, 37, 38) impediment and the behavioral consequences.

The behavior is quantitatively measured by conditioning the animals to respond to the correct identifying signals by pressing levers to obtain food or to avoid an electric shock to the feet. The behavioral tasks are of increasing complexity; e.g., performing a series of acts in correct sequence to obtain a reward. The more complex tasks have proven easier to disrupt, requiring smaller doses of LSD than the simpler ones, in agreement with the fact that the complexity resides in more elaborate communication involving more connection points where drugs can act thereby adding up to greater total.

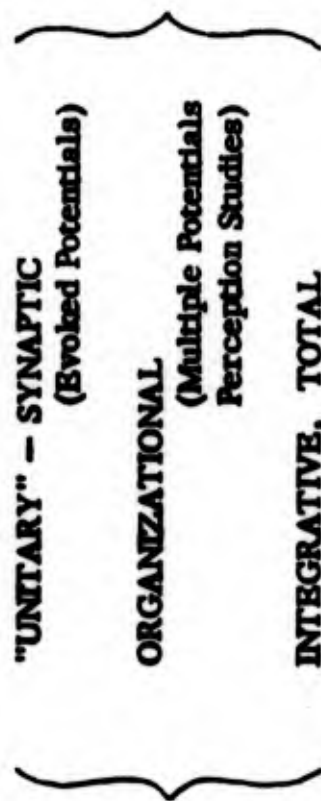
On the strength of the agreement among the results of the interdisciplinary examination, showing that at the molecular or neurochemical, the cellular or electropharmacological and the organizational or behavioral levels, mind disturbing or psychotogenic drugs act in a consistent manner and are offset in a similarly consistent manner by tranquilizers, we have come to a new concept of the action of these drugs. This says that distortion of the communication process within the brain is the fundamental difficulty that psychotogenic drugs^{and chemicals} induce and that the tranquilizers, by interfering with their effectiveness, tend to restore equilibrium of message control and the status quo or homeostasis of the brain and the organism it serves. This situation along with some of the means of investigating its principal levels and ramifications is charted in Table V on "Cerebral Adaptive Systems." (20)

A critical testing of some of its important implications for the operation of the brain in health and disease in man has been brought to fruition and will now be discussed.

CEREBRAL ADAPTIVE SYSTEMS

LEVELS - FUNCTIONAL & EXPERIMENTAL

Successful
ADAPTATION
or
HOMEOSTASIS



HETEROSTASIS
or
Failure of Adaptation

1. IMBALANCE
at all Levels

2. MALADAPTATION
Overcompensation
Undercompensation

3. LEARNED
PATHOLOGY

MENTAL HEALTH

PSYCHOSIS

THERAPY / DISEASE
(TRANQUILIZERS) / (PSYCHOTOGENS)
etc.

Plate 1.

Research Ward

Progress in the following studies with mentally disturbed patients has been made uniquely possible by the University of Missouri Institute of Psychiatry. All of the patients in the Institute are selected and admitted for study of specific problems, and they are assigned to the corresponding wards as needed.

Thus a 15 to 20 bed ward is part of the Neuropharmacology setup, it is operated by Neuropharmacology with its own resident staff that interacts daily with the personnel in the other experimental disciplines constituting this Division's approach to the study of the operation of the nervous system in health and in disease.

Presently, this ward is devoted to therapy resistant chronic schizophrenics and is soon to admit acute schizophrenics. The further aspects of mental disease to be subsequently represented on this ward will depend upon the various aspects of the problems that are being considered.

In addition to the procedures to be described below, we have presently instituted weekly ratings of each patient independently by nurses and by the resident staff, using forms that can be readily computerized so that the resulting profiles over extended periods of time can be compared to the reflections of the fluctuations so characteristic of mental disturbance as seen and formalized in the rating scales and in the objective, instrumental determinations to be described.

Although it is easy to comprehend that a delicately balanced system will be upset by either unrestrained or excessively restrained activity of one or more of its components, when the exaggeration exceeds its self-correcting capabilities, it is essential to be able to see how this might generate the actual clinical pictures encountered. This requires identifying a typical feature of the clinical picture and quantitatively testing the ability of the drug to match it.

Mental illness is said to fill every other bed in our hospitals. The striking derangement shown by these people features, in some of its most frequent forms, hallucination and an overpowering anxiety. Both of these, to lesser degrees, can be produced at will in normal subjects by giving them LSD, mescaline, amphetamine or related substances. Furthermore, these symptoms can be controlled by tranquilizers. The situation parallels the electropharmacological, neurochemical and behavioral findings with these drugs in animals, suggesting that the kind of action observed in animals is the kind responsible for the symptoms in man. Clarification of the action that might be responsible for the symptoms has resulted from our finding that the hampering effect is most marked in the parts of the brain that are believed to store information and experience. It seemed to us that a very likely outcome of such interference with memory, making past experience less available, would be a reduced ability to interpret new information in the light of past experience or an impaired perception. A sufficient impairment we believe leads to hallucination. If this concept checks out, it would mean that the dissociation resulting from undue reduction of activity of one of the parts of the brain is, indeed, at the basis of the mental illness exhibiting these

symptoms and, further, that a fundamental fault in function in psychosis is
an inability in overall coordinated action of the brain.^(44, 45)

Our accumulating evidence indicates that this is the case. We have devised a test of perception that can measure instrumentally by requiring the subject to track* the distortion induced in the appearance of a room by wearing special lenses. Distortions of this kind are normally limited by the checking we all do with our stored previous experience, in this case of the customary shape of rooms. Reasoning that the mentally sick of the type considered would find it more difficult than the normal, because of the already existing dissociation, to overcome the further dissociating influence of the challenge to perception offered by LSD or similar drugs in doses small enough not to produce other symptoms, we developed a test procedure that takes advantage of this. It uses a dose, inadequate to alter the situation in normals, but adding sufficiently to the difficulty in perception already present in the mentally ill to greatly increase the distortion, revealed by the sensitive test even though ordinarily no overt symptoms are produced.⁽²⁰⁾

The success of this test comparing normal students to hospital patients supports our interpretation of the nature of the cerebral difficulty and also provides for the first time an objective, quantitative measure or "clinical yardstick" to help make diagnosis and assess the intensity of illness and degree of relief obtained by treatment. We believe it can be utilized to detect in a population

* Rotating a bar so as to keep it parallel to the wall or floor which gradually appears to slope.

those individuals with less than normal correlation of brain activities, even though they may never have been actually sick. Such individuals should have preventive therapy and should live more sheltered lives. (19, 46, 47, 49, 50)

Further support has come from similar results in behaviorally disturbed children where we have used amphetamine as the challenging agent. (48, 50, 51)

Confirmation and particularly relevant clinical testing, since auditory hallucinations are commoner than visual, has been obtained by challenging auditory association in a manner analogous to the visual. This makes use of the fact that normal speech is dependent on the monitoring of the spoken word and continuously checking it against the stored memory of intended speech. Interference with this process results in impairment of speech. Testing is accomplished by repeating a test passage into a microphone which records it on tape and feeds it back into headphones worn by the subject. The amount of delay* that is tolerated before speech impairment occurs is a measure of the associative power involved. The same challenging doses by interfering with ease of access to auditory information reduced the amount of delay tolerated in auditory feedback without speech impairment. The reduction in maximum tolerated auditory feedback delay measured by the difference between pre and postchallenge delay, is a quantitative indication of the degree of dissociation induced. Such data parallel the visual perception data in identifying impaired association and in the effectiveness of a tranquilizer, chlorpromazine, in preventing these effects of the challenging agent. (51)

Improper meshing of the machinery of the brain is also recognizable as a major fault in other manifestations of brain disease spanning the whole range

* Achieved by separating by a scaled distance the playback from the recording head of the tape recorder.

of life, from the mentally retarded child to the senile. Inadequacy of pertinent channels can be due to failure to mature properly or to the interruption by brain damage resulting from injury or tumor growth. We are applying our "clinical yardstick" to these conditions as well and are gaining better understanding of the potentialities of the measuring device.

A particularly fascinating aspect of this line of thinking has been the pharmacological approach it offers to the process of information recall and, more generally, to memory and learning. An important result of these efforts has been the development of a novel formulation of the cellular nature of the information storage processes as a facilitated transmission, depending on the formation with continued use of specially sensitive receiving points on the nerve cells, analogous to points of this kind, called receptors, that account for the special sensitivity to chemicals and drugs like LSD. We propose to put this theory to experimental test by direct recording of the changes in sensitivity that might be expected to accompany the long-enduring effects of messages, this is the storage of information and learning of appropriate responses⁽⁵²⁾.

We have also written a screening program designed to assist the search for new tranquilizing drugs by a modification of the perception test. It uses a small subclinical but distorting dose of LSD or other dissociating substance and determines whether a small dose, not itself producing symptoms, of a proposed new compound prevents the effect.

Plans

A great value of a concept is its built-in demand for continued experimental checking leading either to further verification or to more appropriate

possibilities to be pursued. Thus our current plans include:

Neuropharmacology

Fulfilling the obligation, incurred by every generalization, to search for and evaluate possible exceptions. To realize the value of the idea of similarity of kind of response given by various parts of the brain to a particular drug, limitations that may appear must be resolved or the generalization abandoned. Major parts of the brain that are still to be electrically monitored for drug actions of this kind are the older parts of the brain such as the hypothalamus, amygdalae, hippocampus, etc., and the major, accessory, motor coordinating "little brain," the cerebellum.

Since the message system is used as the key to drug and chemical influences on the brain, a search for other chemical messengers that might participate becomes critical and will, therefore, occupy a considerable part of our efforts. Trial of potential means of altering new aspects of the transmission process will serve to suggest new ways of modifying at the same time as supplying indirect evidence as to the operation of new brain chemicals that are thought to operate as messengers.

In connection with the above, particular attention will be given to the possibility of developing both better and new kinds of tranquilizers and so-called "brain energizers" or, more properly speaking, antidepressants. Preliminary ideas as to the detailed

manner in which the group of drugs known as antidepressants can affect the nervous system will be carried to the stage of offering a definitive concept that relates to the parallel concept of the action of psychosis producing and psychosis preventing drugs. (53)

Physical (electroshock) and drug means of perhaps "erasing" abnormal communication operations will be investigated by determining the effects of such procedures on the electrically monitored transmission and chemical messenger functions.

As soon as suitable computer programs for analysis are achieved, electrical changes in unanesthetized animals recorded from electrodes permanently placed in their brain will be compared to our previous experiments. The capability provided by the computer analysis will allow successful discrimination of evoked potentials in man from scalp electrodes. This in turn will permit the conduct in humans of experiments paralleling those which, in laboratory animals, have given us some basic understanding of the pharmacology of the mind and are doing likewise with the pharmacology of learning. (54)

Neurochemistry

Identification of the "stop" system chemical messengers or transmitters and determining their life cycle.

Identification of possible new transmitters and of their life cycles.

Determination of the chemical nature of the active small fraction of material carried by proteins in the blood stream and

able to exercise profound disorganizing effects on the brain.

Extension of the correlation between chemical structure and activity of the hallucination producing compounds related to mescaline, by adding additional members to the series representing changes in position and nature of the groups that are substituted on the nuclear ring skeleton⁽⁵⁵⁾

If the nerve membrane studies succeed in locating critical spots involved in learning, we will want to attempt to determine the chemical nature of these, which would then be the first chemical links in the learning process.

Behavior and Psychopharmacology

As soon as practical, electrical recording will be combined with the behavioral and in some cases also with the neurochemical.

The special wave recorded from the scalp at the vertex and correlated with attention and learning, as reported by Grey Walter, will be investigated and correlations will be attempted with the knowledge we already have accumulated of other electrical changes associated with drug modification of the processes involved.

The sampling in the same animal of approach and avoidance; i.e., the major behavioral patterns elicited in random sequence, will be used to assess the balance between the two and the influence of disrupting chemicals and drugs and of protective ones. Preliminary data suggests that behavior combined in this way reveals important differences not otherwise apparent.

It is hoped to carry out analogs of the lever pressing experiment in the same human subjects who are participating in the perception studies.

The "clinical yardstick" of integrative brain function provided by the taxing of the association processes in perception by tiny test doses of dissociating drugs will be exploited more fully by the use of more patients with more forms of mental illness and the use of normals over a wider personality range.

To make the above more feasible, a miniaturized version of the test room in the form of a small, portable viewing box will be developed. Such equipment could be used almost anywhere and taken to the subject rather than bringing the subjects to the laboratory.

To add further ease and convenience to the testing, a shorter acting dissociating chemical; e. g., dimethyltryptamine, whose action is completed in about one hour, will be tried.

More attention will be devoted to the use of the perception test in screening populations to determine subclinical mental disturbance or tendency to it.

Perception testing will be used to gain insight into the mental make-up of drug abusers and the consequences of drug abuse.

The use of larger doses of LSD to train patients to cope with the psychosis-like effects and to their own symptoms that resemble these will be explored. The procedure would offer a form of therapy to be evaluated.

The strategies of therapy that logically follow from the concept of the pathological physiology of psychosis as diagrammed in Table V will be tested in the therapy of the patients on our research ward. As suggested by the Table, therapy will be directed not only to counteracting the basic imbalance, but also to removing the overlay of secondary symptoms resulting from maladaptation and to eradicating the "learned pathology," this is the entrenched maladaptive patterns. Some form of conditioned therapy designed to promote extinction of such patterns will be required.

(cf. next page)

SUMMARY

1. Interdisciplinary basic and clinical laboratories and a research ward have been set up to study the operation of the nervous system in health and disease at the molecular, cellular, organizational and behavioral levels, using drugs to analyze and to correct.
2. A fundamental theory of the manner in which drugs can be expected to and do act on the brain has been evolved and has received support from experiments in animals and in man.
3. The application and appropriate testing of this idea in mental disturbance has resulted in a basic concept of the nature of the disturbance.
4. The findings with mind disturbing and mind correcting drugs have led to a new and productive view of their actions that is consistent with the above.
5. A practical application of the theoretical framework we have constructed has been the devising and testing of a rational, objective (instrumental), quantitative test--a "clinical yardstick"--of mental health and illness and its responsiveness to therapy, that could bring to clinical practice the precision of the experimental laboratory.
6. A new concept of the cellular nature of the learning and memory process has been proposed and awaits test.
7. Continued progress along the lines that have been pursued and the emphasis on investigating the brain cell membrane as the triggering

site of cell functions and of their modification by nerve messages
and drugs, promises further insights into the brain and mind, better
brain drugs and methods of tailoring them, and improved understanding
and care of disorders of the brain and mind.

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