Current Theories Of Psychopharmacological Phenomena

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The problem of relating pharmacological and biochemical phenomena to behavior is a difficult one. From the point of view of the biochemist there appears to be a lack of adequate behavioral postulates, the behavioral scientist having oversimplified certain physiological circuits. Thus, at this writing, no single theory is consistent with **all** empiric data. The majority of studies done on the new psychotropic drugs do, however, use as their criteria, behavioral data. Because of the inconsistencies in relating the physiochemical with psychological data, these theories must be considered as congeners for future work, rather than definitive postulates.

1. THEORIES SUGGESTED BY THE HALLUCINOGENS

A. Chemical theory with psychosis as the critical behavior.

Probably, the most extreme behavioral effects are produced by the hallucinogens. Since hallucinations frequently complement a psychosis, the hallucinogens are seen as a gateway to the understanding of psychosis and its eventual chemotherapy. In this light, the behavioral data seem very respectable at first glance, but, conceding differences between laboratory induced and clinical induced psychosis, the question remains—is psychosis the proper behavioral referent to consider?

Hoffer and Osmond have put forth a well documented adrenochrome-adrenolutin theory. Basically, many of the hallucinogens are indoles or are indolized **in vivo.** These indoles, or indolized substances, are capable of producing hallucinogens and are part of a long list of hallucinogens: LSD-25, Mescaline, bufontenin, dimethyl and diethyltryptamine, trimethoxyphenylaminopropane, and some of the Mexican Mushroom hallucinogens. They have also collected evidence which inferred that defective oxidative products of epinephrine metabolism (adrenochrome pigment of adrenolutin), in body fluids of schizophrenics were capable of producing schizophrenic-like hallucinations.

Other workers have suggested that schizophrenic patients have an abnormal amine metabolism due to a substance called "taraxine." They further postulate that epinephrine has an indole like nucleus, which is not entirely correct. In keeping with the theory of toxic indole metabolites of epinephrine, further reports state that body humors of schizophrenics are toxic in a variety of situations.

It is thought that the amine oxidation defect, mentioned above, **might** help produce schizophrenic symptoms, either directly or as part of a long chain of events. Claiming that substances acting as antagonists to psychotomimetics such as LSD-25 and adrenolutin tend to be therapeutic to the schizophrenic state. The authors conclude by mentioning that some therapeutic success has already been demonstrated with early schizophrenic patients.

Although the adrenochrome theory has been responsible for stimulating many studies, there are facts to question its validity. The report of La Brosse Axelrod, and Katy denies the biochemical basis for the theory by claiming O-methylation as the chief pathway of epinephrine metabolism in man, rather than oxidation. Additional work with high sensitivity testing methods failed to detect adrenochrome in the blood of normal controls, acute schizophrenics, or chronic schizophrenics. Other queries involve the modification of the metabolism of a schizophrenic produced through diet, activity, drugs, and even infectious diseases. Finally, there is the question of whether adrenochrome is actually a psychotomimetic drug, a question which puts doubts on the exact labelling of its effects in the subjects.

Other drugs, which do not contain indole nuclei, produce hallucinations in human subjects. Lubin and co-workers, have shown that Sernyl (phenyl cyclohexyl piperidine) has produced these effects. Sernyl was originally used as a sensory blocking agent for anaesthesia.

It must be borne in mind, that psychosis is a broadly defined syndrome and that the changes in thinking, speech, perception and mood differ in different people as do the effects of a variety of drugs. Should amine metabolism be a factor in the causation of this state, it would be well not to consider it the only one.

B. Studies of the more subtle changes produced by the hallucinogens.

The body image is the mind's model of the self in relation to the outside world. Although the image is flexible, it must

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be maintained by continuous input of relevant sensory data. In a perceptual isolation, meaningful sensory data are reduced and a disordered psychological function ensues. This may progress to a frank hallucinatory state with psychotic like episodes. Evidence exists that disturbances in the body image result from hallucinogenic drug administration, notably LDS-25. There is physiological evidence suggesting that LSD-25 can interfere with sensory input and possibly part of its effect is due to this interference with the sensory data required for full functioning of the body image.

Sernyl, mentioned above, produces a sensory impulse lack and its mechanism of action may thus be due to "a desynchrony or defect in proprioceptive feedback."

Fisher noted that in right-handed indivuals, as they mature, there is progressive differentiation such that there is a relative increase in galvanic skin responses on the non-dominant side. He found that this differentiated skin response is lacking in schizophrenics, as it is also lacking in normal subjects after administration of LSD-25.

In other studies, tests were devised to measure the dedifferentiation of the self (regressive infantile behavior) which is commonly seen in psychosis and drug induced states. It is of interest that these tests all showed significant regressive changes within the normal subjects' behavior after LSD-25 administration. LSD-25 was also shown, by Bregleman et. al., to produce a "poverty of memory", such as that exhibited by schizophrenic patients, in normal subjects. These studies were all conducted in a logically coherent framework.

2. DRUGS AND EMOTIONS

A. The influence of drugs on clinical and introspective evaluations of emotion and mood.

Since the presence or absence of psychosis and other criteria of clinical condition are too general to support an adequate theory, the understanding of drug effect in psychopharmacology is based on the examination of changes produced on emotional behavior and motivational factors.

Contrary to the studies which demonstrate an effect of tranquilizers on emotional response, Segal and Shapiro showed that a 3 week course of reserpine produced no greater therapeutic improvement than did a placebo in outpatients with anxiety states. In a study on postoperative gynecologic patients, it was found that chlorpromazine markedly effected the response to pain and that fewer narcotics were needed. In studies on hospitalized cancer patients with severe pain however, chlorpromazine had no analgesic effect, used either alone or in conjunction with morphine.

Beecher has postulated the "reaction component" in connection with subjective responses to pain. He feels that drugs such as morphine do not affect the sensation of pain or the pain threshold, but rather the individual's reaction to the pain, based on an interpretation of its significance. In the instances where chlorpromazine had its analgesic effect, there was some physical basis for the pain, i.e., vomiting and muscle spasm. Chlorpromazine, thus acting as an antiemetic and antispasmodic, relieved the symptoms, secondarily decreasing anxiety and pain. In like manner, chlorpromazine may have a benefical effect on anxious patient with concomitant physiological symptoms which arise from, and are synergistic with, the anxiety.

Benactyzine, as reported by Kinross-Wright and Moyer, has as its main action the "reduction of emotional reactivity to stress." In this study, placebo administration was also used for control purposes.

Although reports of specific reduction of anxiety by drugs are scarce, euphoria induced by drugs is seen frequently. With the production of euphoria, there appears to be a reduction in anxiety; the reverse situation is also obtained. Drugs which may produce euphoria or anxiety may be found in both the stimulant and depressant groups of drugs; the amphetamines, LSD-25, barbiturates, opiates and ethyl alcohol. One study reported euphorigenic effect in patients administered cortisone and ACTH. The significance of euphoria as an emotional response is not clear, although recent work on "reward" or "pleasure" centres in the brain may be further investigated.

In the field of introspective evaluation, Wendt and associates, of the Univ. of Rochester, have devised a method of measuring subjective (introspective) responses in an objective way. After administration of the drug, the subjects were requested to self-rate themselves, thus testing the emotional effects of the compounds. They are presented with an adjective check list of 100 to 200 adjectives. In each response, four response options were permitted the subject, from which he was to choose the most appropiate to describe his subjective feeling at the moment. For example, Dramamine produced a marked increase in checking of such words as "tired", "drowsy", "detached"; and a decrease in the checking of such words as "business-like", "genial", "industrious". The opposite effect was obtained in subjects given benzedrine.

Clinical studies, thus seem to show that tranquilizer drugs do reduce clinical anxiety, although the means by which their effect is brought about is still questioned. In objective tests depressant or stimulant syndromes are seen. The most outstanding fact observed was that the subject's prevailing social situation can produce reversals in drug effect.

B. Drugs and bodily changes that accompany emotion.

Of the many papers dealing with bodily changes which occur during or following emotional reaction, some of the more interesting are cited below.

The galvanic skin response (GSR) was used to evaluate responses of leukotomized (surgical severence of white matter) patients to painful stimuli. Results were that while the anticipatory fear response was lessened, the response to actual pain was unchanged as compared with the response of control subjects.

In another study, increased myographic potentials, occuring in the half second after each loud sound, were reduced by amyl nitrate, nerve gas, and methamphetamine. The reduction seen here is concluded to be a reduction in emotionality.

Heart rate assessment may be used as an index of autonomic response. No studies of heart rate change in humans, in response to emotion provoking stimuli after drug administration, have been reported. A deduction may be made, however, from a study which reported a conditioned bradycardia during an emotion producing stimulus in man. This would seem to indicate that the autonomic component of emotional response is not always effected by drugs, as may be foreseen from their effects on the resting autonomic nervous system.

Another study found that a seven day administration of benactyzine led to general decrease in autonomic response of psychoneurotic subjects during stressful interviews. Further studies of the sympathetic components reveal that in 15 healthy subjects, chlorpromazine increased and prolonged the hypotensive response to mecholyl. This coincides with the hypothesis that chlorpromazine reduces central sympathetic activity and thus paves the way for relative parasympathetic domination. This theory remains tenuous.

Arousal response to drugs appears to be a fractionated rather than united response. In one study, it was found that morphine had a selective depression on the arousal response produced by painful stimuli, but it did not influence the arousal to non-painful sensory stimuli. On the other hand, scopolamine and pentobarbital blocked sensorial arousal more than the nociceptive arousal. Thus, three different arousal systems are postulated; based on sensory input, painful input, and conditioned emotional input.

Cleghorn and others found that anxious patients showed decreased eosinophils (release of adreno-cortical hormones) and lymphocytes and an increased neutrophil count and uric acid/creatinine ratio, in comparision with anxious patients. In regard to the eosinopenia, it has been demonstrated that chlorpromazine and reserpine elevate plasma levels of 17-hydroxycorticosteroids under resting conditions and in response to emotional stress. It is unlikely that these drugs would depress an already emotionally induced eosinopenia.

Broadly speaking, it is seen that using physiological criteria as indexes of emotional response, the tranquilizing and anxiety reducing compounds produce a general parasympathetic shift in the resting state of the nervous system. Drugs of the stimulant and antidepressant groups have the exact opposite effect. When studied in detail, these systems must be considered in the light of the graduations and complex interrelationships which do exist.

Thus, there is no one "rule" when dealing with drugs and body emotions, as the drug may modify the effect of emotion on the bodily change without influencing the emotion itself. Bodily changes, as indexes of drug effects and usefulness, are necessarily limited.

3. CONCLUSION

It must be continually kept in mind, when dealing with the theories mentioned above or postulating new ones, that psychopharmacology deals with behaviour and that behavioural hypotheses are more often treated as "black sheep" while physicochemical theories are given the "right of way". This is, no doubt, partly due to the greater definitiveness of physicochemical concepts. Most psychological theories used in psychopharmacology are, in comparison, vague and limitless.

The behavioural scientist, on the other hand, must not oversimplify physiological concepts e.g., referring to the reticular formations as having one absolute physiologic function, and arousal as an absolute state of the central nervous system.

With cooperation from both groups, the new psychotropic drugs can serve as an invaluable class of independent variables to help in the development of newer and more satisfactory theories.

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