EEG AND HUMAN PSYCHOPHARMACOLOGY[1,2]

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> . . . the laws of science are not man-made laws; they are the parameters of man's hypothetical vision of the orderly process of life and expendable in the first moment of inadequacy or redundancy. The scientist is always wrong; he is essentially a rebel; he only postulates his "laws" for them to be broken by himself or by others. W. Grey Walter (121)

Psychopharmacology became a clinical discipline with the appearance of new drugs that altered thought, mood, affect and memory without obvious changes in consciousness. It was logical for scientists to study the effects of these compounds in the central nervous system (CNS) as many theories suggest that the changes there are critical for the changes in behavior. But studies of the CNS in man are largely limited to scalp electroencephalographic (EEG) recordings and this limitation has been deplored for such studies "can shed little light on truly basic neuropharmacology" (15). The limitations are further exaggerated by the sensitivity of the EEG to subtle internal and external environmental changes and by difficulties in quantification.

Despite these limitations, studies of the past decade provide data for a better view of the relation of brain dysfunction to disordered interpersonal behavior. This review emphasizes reports of EEG recordings with psychoactive drugs in man. While the focus should be on the changes in CNS mediators, enzymes, and neurohumors that are the basis for both the electrophysiologic and behavioral effects of drugs, the available data do not permit more than an educated guess as to such relations. In *The Relation of Psychiatry to Pharmacology,* Wikler (126) in 1957 reviewed prevailing theories of drug action in altering behavior, especially their biochemical, neurophysiological, and psychological aspects. Despite extensive investigations of mechanisms of drug action, the theories were found inadequate to relate observed variables to behavior in a causal manner. The situation has changed little in the past decade, although the methods of observation have become more refined and the theories presented in more operational terms.

While other CNS indices may be measured, the EEG remains the single most sensitive and recordable index of brain function in intact man. As described by Brazier in her review of drugs and EEG,

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> . . . To the electrophysiologist . . . it remains a matter of astonishment that so many of the brain's secrets escape across the wall of the skull to electrodes fixed to the scalp of man. That they indeed do so is testimony to the fact that the brain's electrical activity is a most sensitive indicator of its function. (15).

The EEG is sensitive to changes in alertness, metabolism, boredom, transient stimuli, etc., and requires careful monitoring to obtain reliable, artefact free records. EEG recordings are multichannel for multilead comparisons and sampling periods are long, producing great amounts of data for analysis. The usual classification of EEG by "normality-abnormality," hand counts of frequency and amplitude, or the pursuit of unique patterns (as 14 and 6 positive spikes) are too inexact or too tedious for significant studies. Disappointment with the results of such analyses discouraged many early workers. Electronic analyzers are useful but these are frequently unstable or insensitive in important frequency bands (114). Nevertheless, interesting results have been reported using analog power spectral density analysis (1, 35, 37, 83, 84, 120), amplitude integration (28, 57) and period analysis (18, 20, 78, 79). The advent of digital computer methods markedly improved the climate (14, 16, 115, 118). Digital quantification methods have been described for each of the analog methods leading to many more systematic and more reliable studies (14, 114, 115). The digital technique has also spawned an extensive interest in the averaged evoked response (80, 113).

Technical aspects of EEG analyses stimulate much interest. In the absence of an understanding of the origins of EEG signals, dependence on prevailing electrical engineering or communication theories and the availability of electronic analog devices focuses interest on power spectral density analysis (14, 30, 31, 82, 98, 104, 114). Applications of these theories for EEG are criticized by mathematical purists who insist that stationarity is not preserved by the small samples used.

Period analysis was applied with some consistency in the mid-1950's and this technique is criticized as too dependent on fluctuations in the baseline. Averaged evoked potentials are elegant neurophysiological indices which delight the single cell and animal experimental neurophysiologists—but are also subject to the criticism of their theoretic meaning for brain function. These attitudes have led to an acceptance by many of amplitude integration as the technique of EEG quantification for drug studies—primarily because the instrumentation is inexpensive and the methods seemingly easy to apply; and to the rejection of period analysis, despite the demonstrations that for drug induced spectral changes, the method is rapid, inexpensive, reliable, and yields identical patterns of change in direct comparisons to the more expensive and lengthier power spectral analysis whether done in analog (19) or digital (114) fashions.

The prevailing view that power spectral density analysis is the technique of choice has limited research, especially in studies of all-night EEG sleep patterns. The volume of data recorded in an all-night session is large, and sampling is precluded by the desire to measure the pattern of the total

night's record. Power spectral density analysis, by analog or digital techniques, is expensive. In contrast, period analytic methods in real-time or twice real-time analyses discriminating up to nine stages of sleep are in daily use in the presentation of "sleep prints" (46, 50, 71, 72).

With no methods of quantitative assessment of EEG grounded in a theoretic understanding of CNS function, their immediate utility is dependent on an ability to satisfy the pragmatic question—whether the methods provide answers (even provisional) to experimental or clinical questions. Lacking at present are systematic studies of the advantages and limitations of power spectral density, period, amplitude, averaged evoked potential, pattern, and spike count methods of EEG analysis in drug research.

CNS-drug studies are also made more complex by variations in dosage, chronic and acute administrations of drugs (38), by different populations (40), and by differences in states of vigilance at the time of recording. While few studies attend to these variables systematically, the data from study to study are sufficiently consistent to allow the generalization to be suggested here.

For this review, the many relevant reports before 1950 are cited in the *Bibliography of Electroencephalography* by Brazier (13), and from 1951 to 1962 in the *Selected Bibliography of Electroencephalography in Human Psychopharmacology* (36) [In subsequent sections, it is possible to take advantage of recent excellent reviews of drug effects on evoked potentials (113), all night sleep recording (62, 63) and attention (86).] For details of the effects of individual drugs on the EEG, these citations are recommended to the reader. Other reviews, emphasizing different viewpoints of EEG-drug relations in man are those of Borenstein, Cujo & Chiva (5), Brazier (15), Domino (25), Itil (73) and Müller & Müller (88). A permuted title index by Bickford, Jacobson & Langworthy (3) and the volume *Applications of Electroencephalography in Psychiatry* (128) supplement these reports.

The Waking EEG

The waking EEG exhibits many changes in response to psychoactive drugs. These changes are frequently ignored or, at most, clinical electroencephalographers are advised not to report records as exhibiting abnormal frequencies in subjects taking psychoactive drugs.

While most studies of drug effects define the EEG changes from the "normality-abnormality" point of view, or by gross statements of "slowing," "drowsiness" or "increased sleep activity," changes in frequencies and amplitudes are the aspects usually quantified.

Frequency measures.—Early observers were satisfied to identify the induced frequency changes, noting that barbiturates and anesthetics developed or exaggerated frequencies of 16 to 30 cps (17, 23, 64) and that injections of seizure-inducing agents, such as pentylenetetrazol, were accompanied by slow-frequency burst patterns (24, 103, 116). Increased low-voltage slow-

wave activity, decreases in alpha activity, and changes in the regularity of the record, as in "synchronization" of frequencies, were reported with many drugs, but often explained as the development of "drowsiness." These expressions were not quantitative and there was little incentive for systematic studies until Wikler (125) suggested that

> regardless of the nature of the drug administered, shifts in the pattern of the electroencephalogram in the direction of desynchronization occurred in association with anxiety, hallucinations, fantasies, illusions or tremors, and in the direction of synchronization with euphoria, relaxation or drowsiness.

This formulation, augmented by changes in specific frequency bands, was the basis for many classifications of drug classes by EEG patterns. Phenothiazine antipsychotic drugs were associated with an increase in slow wave activity and in synchrony or an increase in synchrony without frequency shift. Barbiturates, meprobamate, and chlordiazepoxide were associated with an increase in fast wave activity and in synchrony while LSD, amphetamine, and mescaline were accompanied by EEG desynchronization and frequency irregularity (32–34).

Itil subdivided intravenous psychoactive drug effects into four classes according to their similarity to the patterns of sleep (66, 67). His classes were a "chlorpromazine-type," with increased alpha activity and increased synchronization (regularity) of frequencies; "promethazine-type," with decreased alpha, increased beta and low voltage theta activities; "piperazine-type," with markedly increased well-synchronized alpha activity, rapidly followed by high voltage slow waves; and the "laevomepromazine-type," with decreased alpha activity and increased fast and theta activities. Similar classifications have been proposed by Bente (2), Schneider et al. (105) and Borenstein, Cujo & Chiva (5).

But these classifications did not anticipate anticholinergic hallucinogens, deliriants, and antidepressants, associated with increases in both slow and fast frequencies and with desynchronization; or the minor tranquillizers associated with rhythmic fast frequencies. In a review of quantitative EEG data, I was able to assign the known psychoactive drugs into a classification of four principal patterns and five subtypes based on changes in frequency (Table I). Changes in amplitude and in burst patterns were used as subsidiary discriminants. The sedatives, tranquillizers, and antipsychotic drugs most useful in clinical psychiatry were those associated with EEG slowing or increased alpha activity, while those compounds used as hallucinogens, deliriants, stimulants, and antidepressants were associated with increased beta activity and desynchronization of the record (41, 42).

Common psychoactive compounds can be classified by their EEG characteristics emphasizing their most general EEG effects, usually after intravenous administration and in dosage ranges best approximating the usual clinical doses if the data are available. (Table II). (Where the data are unsatisfactory or ambiguous, a suggested classification is stated in parentheses.)

TABLE I

EEG PATTERNS OF PSYCHOACTIVE DRUGS

Class	EEG Pattern	Frequency (cps)						Amplitude Integration	Amplitude Variability	Burst Activity	Spikes
		Δ (0–3.5)	θ (3.5–7.5)	α (7.5–13)	β_1 (13–22)	β^2 (22–33)	Variability				
Ia	Slowing	+	++	±	0	−	−	+	0	+	+
Ib	Slowing with alpha	+	++	++	0	±	−	+	−	0	0
Ic	Slowing with seizure activity	+	+	−	0	0	±	+	−	+	+
IIa	Fast activity, increased amplitude	0	+	0	++	+	−	+	−	0	−
IIb	Fast activity, decreased amplitude	0	−	−	+	++	+	−	+	−	+
IIIa	Fast and slow activity	++	+	−	+	++	+	−	+	−	±
IIIb	Fast and slow activity, with seizure actvitiy	+	++	−	+	+	+	−	+	+	0
IVa	Alpha variation, increase	0	+	0	0	0	−	+	−	±	0
IVb	Alpha variation, decrease	0	0	0	0	0	+	−	0	0	0

Legend: + increase; 0 no effect; − decrease; ± variable.

A second classification is indicated for some compounds reflecting changes reported with dosages outside the usual clinical ranges or in special populations.

Normalizing the data of drug-induced changes is a technical contribution of the analysis of frequency changes by digital computer programs. In single administration studies, the ease of analyzing multiple samples before drug administration allows the measurement of the mean variance of any frequency band. The changes after drug administration can be observed both as direct values of the power or the percentage time in a band, or the values may be converted to changes from the pre-drug mean using the variance as a weighting score. Such conversions make possible the comparison of changes induced by drugs among subjects with different pre-drug EEG waking patterns (46, 78, 79, 114).

Amplitude integration.—Other observers have measured amplitude and amplitude variability changes, and while they have not presented as exhaustive or detailed a classification, the data are consistent with frequency-derived data. Drugs having stimulant subjective and behavioral effects such as caffeine, LSD-25, and dextroamphetamine are associated with a reduction in the electrical energy and in the variability of the energy of the EEG (29,

57, 58, 60, 61, 93–97, 117). Drugs having depressant or hypnotic behavioral effects, such as chlorpromazine and pentobarbital, are associated with an increase in both the electrical energy and variability. Drugs having antianxiety effects, such as glutethimide, meprobamate, low doses of pentobarbital, diphenhydramine, and aspirin are associated with a decrease in mean electrical energy and an increase in variability.

These patterns are related to the behavioral effects of the compounds, varying with dosage (29, 58, 94, 96) and also with subject populations, for different EEG changes are reported in normal volunteers (57, 61, 93, 96)

TABLE II

CLASSIFICATION OF DRUGS BY EEG CRITERIA

Slowing of EEG Frequencies		
Ia	**Ib** Increased Alpha	**Ic** Increased Seizure Activity
chlorpromazine	butaperazine	reserpine
chlorprothixene	fluphenazine	cycloserine
haloperidol	perphenazine	diphenhydramine
pinoxepin	thioproperazine	prochlorperazine
thioridazine	trifluoperazine	promazine
thiothixene		(amitriptyline)
trifluperidol		(bemegride)
triflupromazine		(promethazine)
(bromides)		
(fluphenazine)		
(lithium)		
(tetrabenazine)		

Increased Fast Activity	
IIa Increased Amplitude	IIb Decreased Amplitude
amobarbital	amphetamine
chlordiazepoxide	bemegride
diazepam	dimethyltryptamine
ethchlorvynol	di-ethyltryptamine
glutethimide	epinephrine
meprobamate	lysergide (LSD-25)
methylpentynol	mescaline
pentobarbital	methamphetamine
phenobarbital	methylphenidate
secobarbital	phenmetrazine
thiopental	psilocybin

TABLE II (*continued*)

Increased Slow and Fast Activity	
IIIa Maximum Amplitude Decrease	IIIb Little Amplitude Decrease
atropine	amitriptyline
benactyzine	cyclazocine
diethazine	imipramine
Ditran	levomepromazine
scopolamine	nalorphine
(phencyclidine)	promethazine
Alpha Variation	
IVa Alpha Increase	IVb Alpha Decrease
alcohol (ethyl)	benactyzine
heroin	iproniazid
morphine	pipradrol
methadone	(azacyclonol)
(hydroxyzine)	(deanol)
(sulthiame)	(isocarboxazid)
	(isoniazid)
	(nialamide)
	(tranylcypromine)

and schizophrenic patients (57, 58, 60, 61, 95, 97, 117). The behavioral associations are considered so specific that one EEG pattern is defined as "anti-anxiety." Implicit in these reports is the suggestion that the behavioral effects may be related more to the individually-induced EEG changes than to the general patterns produced by each drug. Goldstein et al. (58, 60), summarizing studies of stimulants, note that amphetamine, caffeine, LSD-25, and deanol are associated with a decrease in mean energy content, but that for the first three drugs (not deanol) the effect is accompanied by a reduction in EEG variability. The unsatisfactory performance of deanol in clinical trials may be related to its indistinct central effects.

A major technical contribution is their emphasis on changes in variability of the amplitude-integrated signal as a measure of drug effect (57, 58) and the application of von Neumann's "mean square successive difference" to exhibit trends over time (61). Regression analysis has also been applied to these problems (21).

Recently, some amplitude integration studies have been supplemented by frequency measures, suggesting that the limits of discrimination by amplitude integration methods alone may have been reached (89, 90). In period

analytic studies using modern digital computer methods, amplitude integration and variability are readily derived measures and add discrimination power to the frequency measures (46, 50, 78, 79, 114). This may be best seen in the digital analyses of sleep stages (46, 50, 71, 72).

Averaged evoked potentials.—The development of a small computer for averaging EEG transients has led to extensive studies of the effects of sensory stimulation. The effects of drugs on evoked patterns have been measured in humans and animals, and Shagass (113) has written an extensive review of the effects of psychoactive drugs.

After emphasizing the importance of adequate instrumentation and the need for calibration, he lists many sources of variations including the lack of adequate controls for sharply defined stimuli; population differences in age, sex, psychiatric status, alertness, and recent drug intake or treatment; extracerebral signals (artefacts); differences in the background EEG; and the problems of adequate measurement of the recorded averaged responses. Despite these difficulties (which are generic to all neurophysiologic studies in humans and not specific to evoked potentials) changes in evoked responses have been described which seem characteristic for the drugs studied, or the populations, or both.

Variations of latency, amplitude, and rhythmicity are the principal measures studied but these are difficult to catalogue and appear only at dosages outside therapeutic ranges. For barbiturates, Domino (26, 27), Shagass (113), and Rosner (100) describe increases in the amplitude of the late components of the evoked responses, but such changes are seen only with anesthetic doses. The effects are not related to the usual clinical classifications since Shagass indicates that the "effect of amobarbital does not appear to be specific since it may be observed in the same subjects after the administration of intravenous methamphetamine and when the patient has been receiving imipramine in therapeutic dose . . ." He also reported that the somatosensory response was not significantly altered by intravenous amobarbital in doses sufficient to cause dysarthria. The effects of other psychoactive drugs appear to be as nonspecific as the sedative drugs. Often the changes in the resting EEG are more prominent than the changes in the evoked responses.

As yet, the evoked response is as complex a neurophysiological signal to record and analyze as the spontaneous EEG, and the data are too sparse to provide a useful classification scheme.

The Sleep EEG

Much interest in the relation of EEG changes and behavior has been generated by observations of different "sleep EEG" patterns and their relations to dreaming, eye movements, and psychophysiological variables. The identification of stages in the sleep EEG with characteristic periodicities and durations, varying with emotional state, sleep deprivation, and psy-

choactive drugs led to widespread interest in all-night sleep EEG recordings or "sleep-prints."

The recording and analysis of these EEG signals face the same problems as the waking EEG. Sleep recordings provide extensive data which are usually classified visually using the grossest frequency changes and their correlation with rapid eye and muscle movements, heart rate, and other psychophysiological measures as criteria. For such reasons as complexity of analyses, difficulties in obtaining artifact-free records, and expense, the available data of drug effects are fragmented and inconclusive. Hartmann has reviewed the studies in man, describing the effects on total sleep time, sleep latency, total D-time (REM time) and D-latency, and stage 4-time (62, 63).

Sleep studies are usually carried out in normal volunteers, and only recently have the differences between various psychotic populations received attention (85). The initial data suggest that the sleep patterns vary markedly during illness and recovery and in depressive and schizophrenic states.

A few studies assess the impact of drugs on total sleep time—a specially difficult measure in normal subjects who may be presumed to be sleeping their maximum time. Single doses of pentobarbital, chlordiazepoxide, and the experimental compound RO-5-6901 are credited with increasing, and amphetamine with decreasing, total sleep time.

Sleep latency is decreased by hypnotics and minor tranquillizers, and may be increased by amitriptyline.

The D-state (paradoxical sleep stage) has been studied extensively, but a lack of adequate analytical methods has contributed to a paucity of consistent results, for each observer has different methods of analysis and describes the observations in idiosyncratic terms. The duration of the D-state and the D-time percentage are reduced by almost all clinically active agents, including barbiturates, phenothiazines, dextroamphetamine, monoamine oxidase inhibitors, and tricyclic antidepressants. Only reserpine, L-tryptophan, and 5-hydroxy-tryptophan have been associated with an increase in D-time.

The effects of drugs on D-latency (time from sleep onset to first D-period) are similar to that of D-time percentage, with most drugs reducing the latency, and only reserpine and methadone being associated with a delay in onset of the D-state. Stage 4-time is increased by hypnotics, phenothiazines, and antidepressants, and decreased by amphetamine.

Sleep studies are complicated by the problems of the initial interference with sleep in a novel laboratory setting (first night effect)[3] and the alterations in these measures on repeated trials. The effects on D-time, D-latency, and stage 4-time are observable for the first few nights only, for thereafter,

[3] This observation is also true of waking records. In repeat studies in volunteers, we observed that the initial record was significantly different from all subsequent records, and have since discarded the first record in systematic studies (46, 47, 50).

with repeated administrations, the measures approach baseline (control) values, only to exhibit a "rebound" on the nights immediately after drug intake ceases. This has been reported in studies of barbiturates, chlorpromazine, alcohol, and amphetamine.

The study of the sleep EEG has recently been augmented by detailed digital computer analyses of all-night sleep, described as "sleep-prints" Itil & Shapiro (46, 71, 72). They report changes in EEG amplitudes and individual frequencies, length of REM periods, and numbers of single REM and of REM bursts which appear drug-specific, but they have not yet described a simple classification of psychoactive drugs such as Itil accomplished on the basis of thiopental recordings (66–68) or the resting EEG (66).

As yet, sleep studies do not provide a satisfactory classification of drug effects. As with averaged evoked potentials, sleep records have technical aspects as complex as waking EEG records. The methods are still gross and only the most obvious changes in amplitude or of single frequencies have been studied. The dependence of the changes on the resting EEG pattern has been ignored, as has the importance of dose and duration of drug administration.

Technical Aspects

Acute and chronic administration.—The effects of psychoactive drugs depend on dose, duration and route of administration, and the state of the organism (39). It is impressive that the CNS changes under these different conditions vary in degree but not in quality. Different oral doses of amobarbital (46, 47, 50), phenobarbital and pentobarbital (57), diphenhydramine and other antihistamines (59), LSD (57), and different formulations of aspirin (94, 96) produce similar EEG changes but with differences in time courses and levels of significance. These studies include single oral dose studies and repeated administrations.

In single intravenous dose studies, thiopental (67–69), amobarbital (46, 50), and atropine and Ditran (70, 74, 75), exhibit similar patterns of change in frequency and amplitude with different doses, although varying in time course.

Studies of drug-specific patterns rarely compare the effects of oral and intravenous administration, for most observers are satisfied that the descriptions are sufficiently similar and characteristic and ignore direct comparisons. In one direct comparison of oral and intravenous chlorpromazine and of imipramine the EEG changes were drug-specific, with the changes more marked after intravenous administration (37).

The state of alertness or vigilance of the subject is perhaps more critical than the route of administration and dose of drugs for the recording of consistent EEG patterns. Spontaneous drowsiness, sleep, hyperventilation, frequent eye-opening, or problem solving, alter EEG recordings as much or more than threshold doses of psychoactive drugs, and failure to provide ad-

equate controls contributes much to variations in the reported data. Some of the enthusiasm for sleep recording may be related to the apparent control of vigilance, reduction of responses to external stimuli, and systematic nature of the recordings. The similarity of the observations in sleep EEG to thiopental studies has been described (71, 72). In retrospect, the importance of thiopental administration may not have been in a specific drug effect or interaction with the psychoactive compounds under study, but the ritual of administering thiopental at a set rate may reduce the variability of the record by decreasing responses to random external and internal stimuli. In some rigorous EEG quantitative studies, threshold drug effects were observed when a simple reaction-time task was periodically introduced with the EEG frequency and amplitude changes measured immediately after correct performance of the task (46, 47, 50). These tasks and their relation to EEG changes have become specific objects of study by Mirsky & Kornetsky (81, 86). They observed that omission errors on continuous performance tasks are associated with slowing of EEG frequencies as with chlorpromazine, while commission errors, observed after high doses of secobarbital, are associated with higher voltages and increased fast frequencies.

Dissociation of EEG and behavior.—Early expectations of simple relations between psychoactive drugs and brain function in man have not been fulfilled, and it is not surprising, in this complex interplay of subject, recording, drug, and analytical methods, that opinions are divergent. In a review of the human pharmacology of antipsychotic and antidepressant drugs, Hollister (65) observed that, "Desirable as it might be to have a physiological predictor of clinical response as simple to obtain as an EEG, this hope is still not realistic," and continues, "In practice, EEG studies have not been very useful, at least in my experience, in managing individual patients because of variability of response of individual patients to drugs."

Another criticism of these studies is found in the recurrent argument of the dissociation of EEG and behavior with psychoactive drugs, especially anticholinergics. Reference is frequently made to Wikler (124, 127) who reported ". . . dogs that had been given fairly large doses of atropine (7.2 mg/kg) exhibited EEGs characterized by continuous high voltage slow activity interrupted by spindlebursts, regardless of whether they were quiet and appeared to be dozing or whether they were barking and struggling." Similar observations were reported in other species by Bradley & Elkes (12), Funderburk & Case (51), and Rinaldi & Himwich (99). In reviews of these observations, the apparent dissociation was related to inadequacies in the observations of behavior and in the measurement of EEG changes. In examining the behavior of animal species the usual gross observation of "awake" or "asleep" is insufficient to describe the subtle changes which occur in these states, which are readily observed in man. The different states of behavior can be observed also in animals trained to carry out specific tasks, as in the reports of Elazer & Adey (31), Rougeul, Verdeauz & Gogan (102), and White et al. (122, 123). The controversy also results from

a simplistic view of the EEG of sleep. As more quantitative EEG sleep studies discriminate between different slow-wave stages (i.e., with or without fast frequencies) and different low-voltage fast frequencies (i.e., with or without rapid eye movements), the oversimplification of "dissociation" becomes less likely and the question changes to the kinds of EEG patterns associated with different behaviors.[4]

Changes in EEG are related to behavior following single drug administrations. Atropine and Ditran elicit both slow and fast EEG activity, and these changes are accompanied by confusion, memory loss, excitement, and restlessness (70, 74, 75).

Chlorpromazine given after atropine or Ditran reduces fast EEG activity and increases slow wave activity. At such times the subjects are stuporous or even comatose. Yohimbine given after atropine or Ditran reduces slow EEG activity and increases fast activity. The subjects are more alert and better oriented but exceedingly restless. The addition of tetrahydroaminacrin (THA) reduces both fast and slow EEG frequencies and subjects return to the pre-atropine or pre-Ditran types of behavior.

Changes in EEG are also related to changes in behavior on repeated drug administration and treatment. At a symposium at the 1961 World Congress of Psychiatry, various observers reported that failure to observe EEG changes during the treatment of schizophrenia is a poor prognostic sign, suggesting that the changes in brain function are necessary to improvement (34). The data in depressive illnesses were less secure, however, and this was related to the difficulties in separating spontaneous recovery from a pharmacological result. More recently, Sugerman et al. (117), in a double-blind study in chronic psychotics reported consistent changes in EEG amplitude integration and in clinical behavioral ratings with placebo, deanol, chlorpromazine, or perphenazine. Itil, Keskiner & Fink (76), reported similar time course changes in chronic psychotics treated with butaperazine.

These relations are more clearly defined when the techniques of activated EEG are applied. Changes in EEG after intravenous thiopental have been related to behavioral improvement with electroconvulsive therapy (101) and drug treatment (53–55, 67, 68). Itil (67, 68) has emphasized the changes in the duration of post-narcotic sleep, and Goldman (53–55) the amount of beta spindling and the time of its appearance. These techniques are sufficiently similar to indicate that improvement in behavior with antipsychotic drugs is related to increases in EEG show wave and alpha activities, a decrease in EEG variability, and an increase in amplitudes. Monroe has made similar suggestions using a chloralose-activation test (87).

Association of EEG and behavior.—While the number of studies are few and the data scanty, the weight of the observations of the past decade

[4] The controversy of dissociation of EEG and behavior has recently been reviewed in *Anticholinergic Drugs and Brain Functions in Animals and Man* (edited by P. Bradley and M. Fink, *Progress in Brain Research,* Vol. 28, Elsevier, Amsterdam, 184 pp. 1968).

favors a theory of association of EEG and behavior with psychoactive drugs.[5] In part, this is based on the studies described here and on the classification of EEG changes produced by drugs (Table I).

In reviewing this classification, the EEG changes resulting from the drugs are not haphazard with respect to clinical data but appear in systematic relation to the conventional clinical usage of the drugs. It is possible to extend earlier classifications of drugs in man and to define five theorems of EEG-behavioral relations, regardless of the class of psychoactive drug administered.

Three changes in EEG patterns are associated with clinical "tranquillization": (*a*) Increased slowing of the EEG is associated with sedation, drowsiness, relaxation, a decrease in psychotic ideation (as in illusions, hallucinations and delusions), an inhibition of psychomotor activity, or an increase in confusion, memory loss, and confabulation; (*b*) Increased abundance of fast activity in the EEG with increased rhythmicity (decreased variability) of frequencies is also associated with sedation, drowsiness, and relaxation; and (*c*) Increased abundance of alpha waves in the EEG with decreased variability of frequencies is associated with euphoria, relaxation, sedation, a decrease in psychotic ideation, and an inhibition of psychomotor activity.

Two EEG patterns are accompanied by behavioral excitement: (*a*) Increased fast and slow activity in the EEG, usually with increased variability of frequencies and amplitudes, is associated with euphoria, increased psychomotor activity, alertness, and irritability; greater degrees of EEG change are associated with confusion, memory defect, illusions and thought disorder, confabulation and delirium; increasing the slow wave component is associated with increasing stupor and decreased excitement, while increasing fast activity is associated with greater psychomotor activity and irritability; and (*b*) Increased fast frequencies and amplitudes in the EEG with decreased alpha activity are associated with illusions, fantasies, hallucinations, anxiety, increased motor restlessness, or increased speech production.

These views are based primarily on acute intravenous studies, although the data from chronic oral studies are generally consistent. Various applications are now under study and some reports have already demonstrated clinical utility. In some laboratories, notably those of Itil (69–77), Pfeiffer & Goldstein (57–60, 93–97), Borenstein (5–11) and my own (35–50), the EEG profile is used to identify clinical applications of new agents and to classify centrally active drugs. This approach has been successful in identifying the antidepressant activity of the narcotic antagonist cyclazocine (48, 49), and the sedative properties of fenfluramine in waking EEG records

[5] Theories of "dissociation" and of "association" of EEG and behavior have been formulated in relation to the effects of psychoactive drugs. The possible associations of the spontaneous waking or sleep EEG to clinical behavior, diagnosis or personality are not encompassed in these views.

(47) and in sleep EEG (91); in demonstrating effects of smoking (90) and of different dosage forms of aspirin (94, 96); in the classification of different classes of hallucinogens with different antidotal characteristics (44); and in the classification of antidepressants (43).

An interesting application of these associations is in the classification of subpopulations of the mentally ill. The best known studies measure the beta EEG response to intravenous barbiturates, as in the sedation threshold studies by Shagass (106–112). These have been supported and amplified by many workers, Claridge (22) being the most recent and most successful. Itil (67, 69, 76) suggests that subjects that fail to develop a beta response to defined amounts of barbiturates would be unusually resistant to therapy. Goldstein and his associates (60, 117) attempt the identification of psychotic populations by the integrated EEG, indicating that subjects having waking EEG characteristics similar to the LSD-induced pattern are more likely to be classified as schizophrenic. Glueck, Boelhouwer & Henry (4) have reported differences in response to diphenylhydantoin and trifluoperazine of adolescents with and without EEG spike activity or posterior slowing. Applications of these views to the management of individual cases, as used by Itil (76), Sugerman (117), and Borenstein (5, 7, 9) have already been described.

L'Envoi

The widespread clinical successes of psychoactive drugs, the stimulation of biochemical theories of schizophrenia, mania, and depression, the awakening interest in sleep and the physiological concomitants of dreaming, and the explosive advances in the understanding of the role of brain function in memory, learning, emotion, and behavior all contribute to today's active ferment in biological psychiatry. The neurophysiological relations of psychoactive drugs, neurohumors, and enzymatic substrates and precursors receive less attention, in part because the techniques in man are complex and difficult and, in part, because the prevailing views of neurophysiologists, accustomed to the liberties and generalizations of animal experimentation, favor a dissociation theory. The unbridled enthusiasm for EEG studies of sleep, in normal adults and patients, with psychoactive drugs in many experimental situations, is symptomatic of the potentials in interest that can be tapped by a single theory relating brain function to behavior.

In this biological ferment, we can picture strategies for continued research. The arousal theory of schizophrenia has received preliminary support from the comparisons of the EEG's of schizophrenics to the LSD response in amplitude-integrated EEG measures. The extensions of the sedation threshold and the interest in the associated galvanic skin reflex inhibition threshold (92) are examples of continued interest in this concept.

Many observers have viewed schizophrenia as of dual origin—a biological or genetic "process" type and a psychological "reactive" type. Observations that the EEG response to barbiturate is absent or very slight in

schizophrenics who fail to respond to treatment provides an approach to this classification problem.

In biochemical studies of mania and depression, periodic chemical changes are related to changes in mood. The excellent studies of Margerison, Anderson & Dawson (1) relating EEG changes, behavior, and blood chemistry are examples of a fruitful collaboration. Disorders of sleep are observed in depressive states and these are ameliorated in successfully treated manic-depressive patients (62, 63, 85). Antidepressant drugs and convulsive therapies induce different and characteristic CNS biochemical changes, while sleep prints and the waking EEG provide neurophysiological measures for clinical and chemical correlation studies.

The data of EEG changes with psychoactive drugs are sufficiently consistent and the techniques of EEG quantification sufficiently advanced to complement these strategies for a rapid advance in our understanding of the pathophysiological changes of these disorders.

Summary

Psychoactive drugs affect behavior through biochemical alterations of the central nervous system. The methods of measuring changes in CNS activity in man are limited to measures applicable to the intact organism so that most studies have been focussed on the scalp-recorded EEG.

Problems of dosage, route and duration of drug administration, location of electrodes and qualities of amplifiers, state of vigilance of the subject, and the methods of neurophysiological analysis provide great variations in the data. Changes in frequency, power, and amplitude of the waking and the sleep EEG are the principal parameters studied. The averaged evoked response to sensory stimulation is also frequently studied.

Despite variations in methods and populations, psychoactive drugs induce characteristic changes in the human scalp EEG which bear direct relations to the associated behavioral changes. Reports of "dissociation" of EEG and behavior with anticholinergic drugs are special instances of insufficient definitions of behavior and EEG in animals, and when these drugs are studied in man with better definitions of the relevant variables, dissociation is not evident.

The EEG-psychoactive literature is consistent with a theory of association of EEG and behavior. Applications are described in the classification of psychoactive drugs by EEG criteria, in the identification of compounds for clinical trial, in providing biological models of classifications of mentally ill populations, and in studies of the pathophysiology of disordered mental states.

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