EFFECTS OF SOME PSYCHOTROPIC DRUGS UPON BRAIN ELECTRICAL ACTIVITY *

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ABSTRACT

In this article, a table is presented in which the effects of the main classes of psychotropic drugs upon the electrical activity of the brain are summarized. In the text, a number of clinical and physiological points are discussed which arise in this connection.

In trying to summarize some of the electrophysiological effects of psychotropic drugs we are faced with a number of difficulties which are due to the fact that workers in this field have approached this subject with different methods, concepts and goals. The evaluation of their results, mainly with respect to what is more important and what less so, depends frequently upon the mentioned factors. Also, there are some contradictory results. At this time, it is sometimes not yet possible to reconcile divergent viewpoints even about the basic mechanisms of action of some drugs. Nevertheless, a certain amount of agreement seems to emerge which allows an attempt of the kind which we are about to undertake.

First a few words about the place and about the methods of electrophysiology in the study of psychotropic drugs. Both from practical and theoretical viewpoints this field can be viewed as "in between" biochemistry on the one side and psychological studies on the other. Within the field itself, several levels of function can be distinguished which also are investigated by different methods. Electrical depth recordings and microelectrode techniques do not lend themselves easily to the study of clinical questions; instead one has to rely upon animal experiments. Since, in the study of drugs, the clinical questions provide the main incentive for research, it is not surprising that the greatest amount of information is available in that area.

There is a fair amount of information available about *EEG changes during drug therapy*, (see for instance the recent summary by Fink[19]), but it is not always easy to draw conclusions from the data. Bente[4] has emphasized some of the difficulties inherent in such work. Only a part of the phenomena of importance can directly be transformed into numbers for statistical analysis, while others, of equal importance, depend upon gestalt perception by the interpreter. EEGs are commonly interpreted according to whether they are within normal limits for waking or sleep records; during drug treatment this may become difficult; for the assessment of drug effects in their own right this is certainly only one question among others.

Another method of investigation, the study of specific brain responses to peripheral

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FUNCTIONAL LEVEL	METHOD	INFORMATION NOW AVAILABLE	CLINICAL STUDY POSSIBLE
(Changes in Psychol. Function)	Clinical, Psychological, Psychophysiological	Adequate	Yes
Changes in Resting and Reactive Patterns of CNS as a Whole	Electroencephalogram	Fair	Yes
	Evoked Responses (Surface)	Little	On Small Scale
Changes in Interaction Between Various CNS Areas and Levels	Depth Recordings	Little	Rarely
Changes of Electrical Macropotentials in Circumscribed CNS Areas	Depth Recordings	Some	Rarely
Changes of Electrical Cell Phenomena	Microelectrode Studies	None	No
(Changes in Cell Metabolism)	Biochemical	Some	Indirectly
↑ Drug Application			

TABLE I

Place and methods of electrophysiology in the study of psychotropic drugs.

stimulation has, in psychiatric patients, mainly been utilized by Shagass and his co-workers. Because these responses are of small amplitude they are added electronically or photographically, and the resulting average response is evaluated. Shagass found, mainly, that somato-sensory specific evoked responses in patients with psychosis (paranoid or depressed), are altered with respect to two measures: First, the cortical cells show a higher degree of refractoriness after a response than normally (this is measured by the effect of a second peripheral stimulus which is given a short interval later); and second, the amplitude of the responses is greater than normal. [47] There is some evidence that the cortical refractoriness depends upon the state of function of the reticular formation. [41] Recently, Shagass has also investigated the effects of drugs upon these measures. [47]

I.

In the following, *results of clinical electroencephalographic investigations* will be summarized.

In correspondence with the literature, Fink [19] and Bente [4] find that all antipsychotic drugs produce changes in the EEG, with single doses as well as during chronic treatment, but the latter usually produces stronger effects. Drugs of similar chemical constitution may sometimes produce different EEG effects, even if they are given in comparable doses. Furthermore, it is the rule that drug induced EEG changes are more marked at the beginning of treatment than later on, although the drug dosage remains the same. The modifications of the effects by changes in the patient's mental state are discussed below.

Phenothiazines show in *acute intravenous application*, according to Bente's [4] observations, a parallelism between the degree of extrapyramidal effect and an early slowing in the EEG. Anticholinergic substances are liable to prevent such slowing effects (this is also true for post-electro-shock slow waves. [17, 52] During *chronic medication* with phenothiazines and similar substances, such as butyrophenones, there are three types of changes: [4] First, phenomena similar to the

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
	DRUG (DRUG CLASS)	PSYCHIC EFFECT	CLIN. E.E.G.			EPILEPSY	ANIMAL BEHAVIOR			DEPTH RECORDINGS							
							Arousal		Other					Limbic Syst.			Other
			Acute I.V.	Chron. P.O.	With-drawal		RETIC. STIM.	EXT. STIM.		Retic.	Post. Hyp.	Thal.	Cortex	HIP.	AMYG.	SEPT.	
A	Reserpin	Anti-Psychotic	(S)	S		+	−	−	Parasymp	O				+			
B	Chlorprom. (Phenothiazines)		S	S	O	+	(−)	−	Energy Expend. ↓ Habituation	− Input ?	−EEG −mot			+			
C	Imipramine	Anti-Depressive	(S)	(S) (F)		+		−		−				+	+	−	
D	Iproniazid Tranylcypromine (MAO-Inhibitors)			(S)					Prevents sleep in pontine lesion animals.	O				(−)	+	+	
E	Meprobamate	Minor Tranquilizer	F	F	E	(−)			Suppr. vicious behavior	−				−	−	−	
F	Chlordiazepoxide Diazepam (Benzodiazepines)		F	F		−			Suppr. vicious behavior					+ ?	−	−	
G	LSD 25	Psychotogenic	F			−	O	+	Dehabituation	+ Input ?							Facilitation at each synapse of input ?
H	Sernyl		S														
I	Amphetamine	Stimulant	(F)	(F)		(−)	+EEG +mot	+		+			(+)	(−)			
J	Pentobarbital	Sedative	F S		E	−	−EEG −mot	−		−		−		(+) −			
K	Physostigmin (Cholinergic)	(Autonomic)					+EEG O mot							+			
L	Atropin (Anticholinergic)						−EEG O mot				−EEG O mot			−			
M	Morphin	Analgetic	S	(S)													Depression of lat. mid brain area.

TABLE IIa

Electrophysiological effects of psychotropic drugs (paradigmatic). S = production of slow waves, F, of fast activity. E = epileptiform activity upon drug withdrawal. + indicates increase of excitability, — indicates decrease of excitability, except in the column "Epilepsy" where + or — indicate increase or decrease of epileptiform activity. The arrows indicate secondary electrophysiological effects upon another brain structure.

	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
A	6 7	6 7		21			14	16				14 21 33			
B	6 7	6 7			9	9	14	9	35			33			
C	12	12		12		29		29				29	29	40	
D		21					39	21				21	40	40	
E	24	24	44				40	2				29 33	40	40	
F	49	49		15			40					29	29	40	
G	19			7	9	9	9	9							50
H	20														
I	28	28		28	9	9		9			9	9 33			
J	28				9	9		9		31		(11) 29 33			
K					9							11			
L					9				34			11			
M	28	28													36

TABLE IIb

References to Table IIa. The designations for the rows and columns are the same as in Table IIa. The numbers refer to the bibliography list at the end of this article.

ones seen in light sleep; in addition there may be continuous or episodic disturbances in the EEG, sometimes of a paroxysmal type, which do not occur in the normal waking or sleep EEG; and thirdly later on the basic waking activity again becomes more stable but at a slightly slower frequency than before the treatment. These changes are interpreted by Bente as an adaptive process which leads over dissolution and lability of brain function to reorganization at a less active level.

Anti-depressive drugs, like imipramine or amitriptyline, mostly do not produce a slowing effect but at times a mild acceleration. Mono amine oxidase inhibiting compounds appear to produce few EEG changes, though cortical slowing has been seen in animals. [21]

Bente interprets the changes observed with phenothiazines in terms of a reduction of activity to a lower level of *vigilance,* of a regression of the state of wakefulness to a more primitive level, which then makes a re-integration of cortical processes possible. [4]

Another hypothesis, though similar in some respects, is the one proposed by Wikler [53] and taken up by Fink; [18] it states that all those drugs which produce slowing of the EEG are associated with tranquilization, and that those producing a flat or fast EEG produce or increase anxiety and sometimes hallucinations. However, both mentioned hypotheses do not take into account the effect of the minor tranquilizers and of the barbiturates which also produce fast activity.

The effect of chlorpromazine upon the hypothalmus and the autonomic nervous system has been emphasized by Gellhorn. [22] More recently, Selbach [43] has offered a fairly elaborate theory which explains the drug effects in terms of a more general hypothesis about regulatory events in the autonomic nervous system. Psychotropic drugs are thought to facilitate either ergotropic or trophotropic reaction. (Selbach equates these terms with adrenergic and cholinergic respectively). Counter-regulations may interfere with this effect; thus the epileptic attacks occurring during treatment with phenothiazines are interpreted by Selbach as ergotropic counter-reactions during a drug-induced trophotropic state. The clinical electroencephalographic effects are interpreted in the same terms; thus, slow wave production indicates "tropotrophy". This approach has been criticized on the basis that autonomic drugs in the stricter sense, such as adrenalin or acetycholin, do not show principally psychotropic effects. [1]

The *minor tranquilizers,* namely meprobamate and the benzo-diazepines, are different from all other therapeutically used drugs, except barbiturates, in that they produce an excess of fast activity of medium voltage in the EEG. This finding, in adults without medication, would be considered abnormal, according to Gibbs and Gibbs. [24] These authors also draw attention to the fact that this type of fast activity has a functional significance quite different from the low voltage fast activity seen in arousal and similar situations; rather it resembles the one seen in young children during drowsiness; similar changes occur in adults after head injury, particularly when a tendency to convulsive seizures is present.

Hallucinogenic drugs, on the other hand, produce the arousal-like low-voltage fast record. [18, 53] The same is true for *stimulant drugs* such as amphetamine. [28] On the other hand, psychotogenic drugs which induce confusion rather than hallucinations, such as Sernyl, make the EEG background activity slower. [20]

A number of attempts have been made to determine the *correlations between clinical psychiatric findings and the electroencephalographic data,* as they are influenced by such drugs.

Bente [4] has drawn attention to the fact that the effect of drugs upon the EEG depends upon the features of the pre-treatment EEG, and that *changes in the state of the psychosis* can modify the drug effect upon the EEG. It can for instance be ob-

served that the appearance of manic symptoms goes together with a decrease of phenothiazine induced changes in the electrical activity. For such reasons, Bente [5] has recently started to investigate the natural history of the EEG during the course of the major psychoses.

Results of a similar nature were obtained by Shagass *et al.* [47] who studied the effect of some drugs upon evoked cerebral responses in man. They found that, in paranoid and depressed patients, imipramine changes the recovery function of the cortex, as well as the amplitude of the evoked responses, in direction toward the normal values. The normalization did, however, take place in correspondence with the clinical improvements, and not with the drug application itself.

The effects produced by intravenous injection of thiopental sodium were found by Goldman [26] to be different in schizophrenic patients from those in other persons. The schizophrenic subjects showed a more pronounced development of activity in the beta and theta frequency bands. These characteristics became less marked when the patients improved during phenothiazine treatment, and they reappeared when they relapsed. Similar results were reported by Mowrer et al. [37]

Drugs which produce slow activity in the EEG can potentiate the slow wave effect of *electroshock treatment*. Thus, very abnormal appearing tracings can sometimes be produced. This can be misleading if the treatment history is not available to the electroencephalographer. For barbiturates, this type of effect had been described by Roth *et al.* [38]

Another point of clinical importance is that the *changes* which the drugs produce in the EEG *may outlast the chemical action*. For instance, in schizophrenics who have well recovered, the drug-induced slowing may persist after a patient has discontinued the drug, and the EEG only resumes the pretreatment characteristics when the patient relapses. [4]

In earlier work, Shagass utilized quantitative aspects of the EEG effects produced by barbiturates for diagnostic purposes in the so-called *sedation threshold*. This again emphasizes the fact that the drug effect depends upon the clinical picture. Even affective changes of shorter duration are reflected in the test results. [46]

Epileptiform focal and paroxysmal EEG *disturbances* are usually seen in those patients who already show slight disturbances in a baseline EEG. [4, 51] With respect to the clinical diagnosis Bente found that focal or paroxysmal EEG disturbances during drug treatment are seen mainly in cases which are not clearcut schizophrenics or manic-depressives, and which he therefore labels "atypical psychoses"; these cases might, in his opinion, represent a disorder which is related to, but mostly not identical with, epileptic illness. [4]

So far as we know there are no clear statements in the literature whether any particular clinical or electroencephalographic group of epileptics is more liable than others to increase or decrease their seizure frequency, during treatment with psychotropic drugs, and whether a difference in that respect exists between the various antipsychotic drugs. Chlorpromazine and other fast acting phenothiazine compounds have successfully been used to activate mild epileptiform disturbances for diagnostic purposes. The minor tranquilizers are reported to have an anti-epileptic effect. This is particularly true for diazepam of which Feldman [15] states that it is 10 times stronger in this respect than chlordiazepoxide. Gibbs, [23] on the other hand, does not believe that chlordiazepoxide has a pronounced anti-epileptic effect.

From the table it can be seen that those drugs which have some anti-epileptic properties are also liable to cause epileptic seizures upon withdrawal; they are furthermore liable to produce fast activity in the EEG;

and finally some of them have in common that they are habit forming.

The question if a psychotropic drug produces *abnormality in the EEG* however goes beyond the appearance of epileptiform activity. The generalized slow or fast activity, which is much more frequently seen than epileptiform disturbances, quite often goes beyond the limits of normalcy as established for subjects who are not on drugs. On the other hand, there has been no clear evidence that *focal* disturbances can be produced in EEGs which previously were entirely within normal limits.

Bente [4] reports that a good *therapeutic effect* with phenothiazines can almost always be seen in those cases where a low voltage fast EEG shows a marked increase of alpha activity during the treatment. With those drugs which produce this alpha activation only after a longer latency period, the therapeutic effect also takes longer. Also, if the EEG does not change at all during treatment, there is usually no therapeutic success. Bente emphasizes that it is only the re-integrative stage of the EEG changes which matters, while the degree of the earlier occurring dissolution of the EEG is not correlated with the therapeutic success. The results of a discussion about this topic were recently summarized by Jasper [30] who stated that when the EEG is unreactive both to sensory stimulation and to drugs, the behavioral prognosis seemed poor and the likelihood of cerebral atrophy great.

Gibbs and Gibbs, [25] as well as Towler, [49] had the impression that with diazepam there exists a correlation between time and dose of administration on the one hand and EEG changes on the other, but not between EEG changes and clinical improvement.

II.

In *animal experiments,* it has been possible to gain some initial knowledge about changes of the electrical activity in various brain areas as they are produced by drugs. Though much of the reported work will need further elaboration and confirmation, and though the application of results in animals to the human organism is not always clearcut, the following survey may be justified in the attempt to gain some systematic knowledge about drug induced changes in subcortical electrical activity. It will also serve to illustrate the desirability of electrophysiological experiments in conjunction with clinical drug studies.

Some *general principles* will first be discussed. The hypothalamus and midbrain, in animals as well as in man, are particularly rich in serotonin and norepinephrin. The hippocampus, as well, has a fairly high content of serotonin (summary in Sourkes [48]). It can therefore be expected that any particular chemical process involving one of these substances will predominantly occur in a *circumscribed anatomical structure,* and that the resultant electrophysiological effect will likewise mainly concern the activity of one anatomical structure, in addition to possible effects upon all neurons and other body cells. Similar principles seem to be of importance with respect to other chemical interactions.

There is thus frequently a question if changes in electrical activity in a particular area are caused by local chemical events, or rather by a change in the electrical input to that area, which may be caused by chemical influences elsewhere.

The experimental results concerning the *limbic system* are the most difficult ones to assess. This is of course in line with the fact that the function of these structures is not well understood. However, it appears fairly well accepted that important relations exist between the hippocampus and the reticular formation, mostly in the sense of antagonism. [27] In this connection it is of interest that the effect of drugs, and perhaps of E.C.T. (Pinelli, 1962; quoted from Arrigo *et al.* [2]) upon these structures often is in opposite directions. Amphetamine, which excites the reticular formation, is thought to

have a secondary depressive effect upon the hippocampus; [9] sometimes it seems that an electrophysiological effect is followed by a biochemical one: when pentobarbital suppresses the reticular formation, the hippocampus is released, but later on the hippocampus itself appears to be suppressed chemically. [29] Another relation of this type appears to exist between the septal area, which may normally "dampen" hypothalamic activity, [32] and thus emotional output; and the amygdala which on the contrary seems to be concerned with motivational reinforcement of behavior. [25] Imipramine has been seen by Schallek *et al.* [40] to depress the septal area; this could account for its mood-lifting effect (through release of the hypothalamus). The mono amine oxidase inhibitors iproniazid and isocarboxazid enhance the excitability of the amygdala and may, according to the same authors, thus produce a similar effect. Meprobamate and chlordiazepoxide, on the other hand, which have a tranquilizing effect, suppress both the septal area and the amygdala. A further complication arises from the relation of these structures to the hippocampus. For chlordiazepoxide, Himwich *et al.* [29] found that it suppresses rhinencephalic structures; on further investigation however it was found that only amygdalo-hippocampal responses were reduced whereas responses obtained in one hippocampus by stimulating the contralateral hippocampus were sometimes even facilitated. Differential effects upon amygdala and hippocampus seem also to be produced by mono amine oxidase inhibitors. [21, 40]

It is apparent from the table that drugs with similar therapeutic action in general produce similar subcortical effects. Furthermore, those drugs which increase the excitability of the hippocampus tend to aggravate clinical epilepsy and those which decrease it tend to have some anti-epileptic effects.

The following are *results concerning various chemical classes of dugs*. Bradley and coworkers have compared the effects of a number of drugs in cats, either with chronically implanted electrodes, sometimes unrestrained for studies of behavior; or in cerveau isolé or encéphale isolé preparations; stimulation of sense organs or of the brain stem reticular formation were carried out, and conduction within the brain stem and from the thalamus to the cortex was measured. [9, 10, 11] They compare *central depressants* and *central stimulants* on the one hand with drugs acting upon the cholinergic portion of the *autonomic* nervous system on the other hand. With barbiturates the arousal effect of peripheral as well as reticular stimuli was suppressed in the EEG as well as in behavior, with amphetamine it was similarly increased. However, with physostigmin only the EEG arousal was increased, and with atropin it was decreased, while the behavioral arousal was not changed. In the first type of drug it appeared that the primary site of action was the reticular formation; with the autonomic drugs, the site of action was less clear. Changes in the activity of the hippocampus were also seen which in the case of pentobarbitone and amphetamine were thought to be secondary to the changes in the reticular formation. Atropine and physostigmin, on the other hand, apparently produced changes in the hippocampus by direct chemical means.

Furthermore these authors compared *chlorpromazine* and *LSD 25* and found that the arousal produced by external stimulation was decreased with chlorpromazine and increased with lysergic acid, whereas the effect of direct stimulation of the reticular formation did not change much. The conclusion here was that the changes in both cases took place in the afferents to the reticular formation, chlorpromazine impairing and LSD facilitating this input. It has however been pointed out by Ursin [50] that the action of these two drugs is not entirely opposite because chlorpromazine blocks the input to the reticular formation also from telencephalic cortical areas and from the amygdala whereas LSD does not facilitate the same

type of input. Ursin instead suggests that the action of LSD might start at the sense organ and take place at every synapse, up to the cortex. According to Bradley, chlorpromazine lowers the significance of incoming stimuli, similarly to what happens in habituation, whereas LSD overcomes habituation which may have taken place.

Reserpin chemically appears to act mainly by depleting the stores of serotonin in brain cells. [14] In cats, the depletion of serotonin stores by the action of reserpin lasts for more than ten days and produces a sedation and also an increased limbic system excitability for the same period. Brodie sees the principal overall effect of reserpin in an increased parasympathetic output with sedation, reduced heart rate, lowered respiration, low muscle tone and so forth, in contrast to the action of chlorpromazine which he believes acts directly upon the energy expenditure by reducing it. [14] This latter effect seems to be due to the effect of chlorpromazine upon norepinephrine in the brain stem reticular formation.

Mono amine oxidase inhibitors appear to mainly raise the level of serotonin (but not of noradrenalin) in brain tissue. Schallek [39] reported that under chronic pretreatment with iproniazid the occurrence of electrographic sleep patterns was prevented in cats who underwent lesions in the pontine or mesencephalic reticular formation. This persistent activation pattern obviously originated in some area rostral to the mesencephalon. Pentobarbital however still induced sleep in these animals because it acts on the cortex and on the thalamus which had not been affected by iproniazid. Schallek *et al.*, [4] in unanaesthetized cats with chronically implanted electrodes, found a suppression of after-discharges in the hippocampus, after stimulation of that structure, during the effect of nialamid, another MAO-inhibitor. The threshold for direct responses was, however, not altered.

Anti-depressant drugs which are not mono amine oxidase inhibitors and which are chemically *related to phenothiazines* (imipramine and amytriptyline, and to some extent chlorprothixen) have been observed to also increase the excitability of hippocampus and amygdala. [29] We found no information if this increase is due to local chemical factors or to change in the electrical input. In addition, these drugs, like the phenothiazines, block the electroencephalographic alerting response caused by peripheral stimulation such as sound.

The *minor tranquilizers*, meprobamate and the benzodiazepines, depress the function of limbic system structures. [29, 40] Some of these results have already been mentioned.

REFERENCES

1. Achelis, T. D.: Discussion of the paper by Selbach. 43.
2. Arrigo, A., Savoldi, F., and Tartara, A.: Sympos. Internazionale sull' Haloperidol e Triperidol, Milano, Istituto Luso Farmaco d'Italia, 1962.
3. Ayd, F. T., Jr.: The Medical Clinics of North America, 45:1027-1040, 1961.
4. Bente, D.: *In:* Anthropologische und naturwissenschaftliche Grundlagen der Pharmako-Psychiatrie. Ed. by F.D. Achelis and H.v. Ditfurth. Thieme, Stuttgart, 1963.
5. Bente, D.: *Zbl. Neurol. Psychiat.,* 170:3, 1963.
6. Bente, D., and Itil, T.: *Arzneimittel-Forschung,* 7:611-615, 1957.
7. Bente, D., and Itil,, T.: *In:* Psychopharmacology Frontiers. Proceedings of the Psychopharmacology Symposium of the Second International Congress of Psychiatry, Zürich, September 1957. Little, Brown and Co., Boston, 1959.
8. Bente, D., Pfeiffer, W., and Müller, M. L.: Congr. of Psychiat. Neurol. of French Lang., 60th Session, Antwerp, July 1962.
9. Bradley, P. B.: *In:* Bewusstseinsstörungen, Symposium, H. Staub and H. Thölen, Eds., Thieme, Stuttgart, 1961.
10. Bradley, P.B., and Key, B.F.: *Electroenceph. clin. Neurophysiol.,* 10:97-110, 1958.
11. Bradley, P. B., and Nicholson, A. N.: *Electroenceph. clin. Neurophysiol.,* 14:824-834, 1962.
12. Borenstein, P., and Dabbah, M.: *Ann. med. psychol.,* 117:923-931, 1959.—Extract in *Zbl. Neurol. Psychiat.,* 154:235, 1960.
13. Borenstein, P., and Dabbah, M.: *Sem. Hôp.,* 37: 1589, 1961. Quoted from Bente, 1963a.
14. Brodie, B., and Costa, E.: *Psychopharmacology Service Center Bulletin,* 2:1-25, 1962.

15. Feldman, P. E.: *J. of Neuropsych.,* 3, Suppl. 1, S 62 - S 67, 1962.
16. Fields, W. S.: (Ed.), Brain Mechanisms and Drug Action. C. C. Thomas, Springfield, 1957. — Extract in: *Electroenceph. Clin. Neuro-physiol.,* 10:385, 1958.
17. Fink, M.: *Electroenceph. Clin. Neurophysiol.,* 12:359-369, 1960.
18. Fink, M.: *in:* Symposium on EEG and Human Psychopharmacology, Montreal, 1961. *Electroenceph. Clin. Neurophysiol.,* 15:133-137, 1963.
19. Fink, M.: *In:* EEG and Behavior, ed. by G. H. Glaser. Basic Books, New York and London, 1963.
20. Flügel, F., and Itil, T.: *Psychopharmacologia,* 3:79-98, 1962.
21. Funderburk, W. H., Finger, K.H., Drakontides, A. B., and Schneider, J. A.: *Ann. N.Y. Acad. Sci.,* 96 Art. 1:289-302, 1962.
22. Gellhorn, E., Autonomic imbalance and the hypothalamus. University of Minnesota Press, Minneapolis, 1957.
23. Gibbs, F. A.: *In:* Discussion of Gibbs and Gibbs, 24.
24. Gibbs, F. A., and Gibbs, E. L.: *J. of Neuropsych.,* 3, Suppl. 1:S 73-S 78, 1962.
25. Gloor, P., Amygdala. *In:* Handbook of Physiology, Section I: Neurophysiology, Volume II. Amer. Physiological Society, Washington, 1960.
26. Goldman, D.: *EEG Clin. Neurophysiol.,* 11:657-667, 1959.
27. Green, John D.: The hippocampus. *In:* Handbook of Physiology, Section I: Neurophysiology, Volume II. Amer. Physiological Society, Washington, 1960.
28. Greville, G. D., and Heppenstall, M. E.: "Pharmacology," *in:* Electroencephalography, a symposium on its various aspects. Ed. by D. Hill and G. Parr, London and N. Y., 1950/52.
29. Himwich, H. E., Morillo, A., and Steiner, W. G.: *J. of Neuropsych.,* 3, Suppl. 1:S 15-S 26, 1962.
30. Jasper, H.: *Electroenceph. Clin. Neurophysiol.,* 15:133-137, 1963.
31. King, E. E., Naquet, R., and Magoun, H. W.: quoted from Schwartz et al., 42.
32. King, F. A., and Meyer, P. M.: 1958. Quoted from Schallek et al., 40.
33. Kletzkin, M.: *Ann. N. Y. Acad. Sc.,* 96 Art. 1: 263-278, 1962.
34. Longo: 1956. Quoted from Arrigo et al., 1962.
35. Longo and Silvestrini: quoted from Arrigo et al., 1962.
36. McKenzie, J. S. and Beechy, N. R.: *EEG Clin. Neurophysiol.,* 14:501-519, 1962.
37. Mowrer, M., Sila, B., Ulett, G. and Johnson, M.: Central Assn. of Electroencephalographers, 1960. *EEG Clin. Neurophysiol.,* 13:145, 1961.
38. Roth, M., Kay, D., Shaw, F., and Green, F.: *EEG Clin. Neurophysiol.,* 9:225-237, 1957.
39. Schallek, W.: *Dis. Nerv. Syst.,* 21, Suppl., 64-66, 1960.
40. Schallek, W., Kuehn, A., and Jew, N.: *Ann. N. Y. Acad. Sci.,* 96, Art. 1:303-314, 1962.
41. Schwartz, M., and Shagass, C.: *Electroenceph. Clin. Neurophysiol.,* 15:265-271, 1963.
42. Schwartz, M., Shagass, C., Bittle, R., and Flapan, M.: *Electroenceph. Clin. Neurophysiol.,* 14:898-903, 1962.
43. Selbach, H., *In:* Anthropologische und naturwissenschaftliche Grundlagen der Pharmako-Psychiatrie. Ed. by T.D. Achelis and H. v. Ditfurth. Thieme, Stuttgart, 1963.
44. Shagass, C., Azima, H., and Sangowicz, J.: *Electroenceph. Clin. Neurophysiol.,* 11:275, 1959.
45. Shagass, C., and Jones, A. L.: *Amer. J. of Psychiatry,* 114:1002, 1958.
46. Shagass, C., Müller, A. K., and Blanco Acosta, H.: *J. of Psychosomatic Research,* 3:253-270, 1959.
47. Shagass, C., Schwartz, M., and Amadeo, M.: *J. of Neuropsych.* 3, Suppl. 1:S 49-S 58. 1962.
48. Sourkes, T. L.: Biochemistry of Mental Disease. Hoeber Medical Division, Harper & Row, New York, 1962.
49. Towler, M. L.: *J. of Neuropsych.,* 3, Suppl. 1: S 68-S 72, 1962.
50. Ursin, H.: *Psychopharmacologia,* 3:317-330, 1962.
51. Ulett, G. A., Heusler, A. F., Word, T. J.: *Electroenceph. Clin. Neurophysiol.,* 15:135, 1963.
52. Ulett, G. A., and Johnson, M. W.: *Electroenceph. Clin. Neurophysiol.,* 9:217-224, 1957.
53. Wikler, A.: *J. Nerv. Ment. Dis.,* 120:157-175, 1954.