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Activation of Psychosis by a Combination of Scopolamine and Alpha-Chloralose

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The investigation of physiologic concomitants of disturbed behavior has been of interest for many years. In particular, the use of the EEG has been emphasized since the days of Hans Berger, and some meaningful correlations have been made in the case of "psychopathic" or aggressive behavior disorders. The value of the EEG in recognizing epilepsy and epileptic equivalents is common knowledge. However, in spite of much work on psychosis and a fairly widespread agreement that there is a "higher incidence" of EEG abnormalities in hospitalized psychotic patients than in the general population, little other meaningful correlation has been noted. For a good review, Ellingson[6] may be referred to. Interest in this subject has been renewed in recent years by the description of subcortical electrophysiologic abnormalities in psychotic patients by Heath, Sem-Jacobsen, Delgado, and others. These investigations have raised the question as to whether there is in some or all psychotic patients a coincident neurophysiologic dysfunction which can be consistently demonstrated. If such an abnormality could be demonstrated in at least a subgroup are psychotic patients, an important clue might be afforded the further investigation and more rational therapy of schizophrenia and other psychoses.

That there is correlation between disturbed cerebral function and behavioral abnormality has long been emphasized in the case of the psychomotor epileptics, whose complete seizures may well resemble psychotic states, as Hughlings Jackson clearly recognized. More recently, Ervin, Epstein, and King * have pointed out the high incidence of a personality disorder often similar to schizophrenia in patients in whom temporal spike abnormalities were present in the EEG, whether or not they had frank psychomotor seizures. Similar observations have been made by Hill[10] and others.

The possibility of electrophysiologic dysfunction in the schizophrenic (not ordinarily detectable on the EEG) raises the question of whether proper activation might make it detectable, as is often the case in epilepsy. Our attention was drawn to a report by Bercel[3] suggesting the use of a mixture of scopolamine and α-chloralose (SAC) for the activation of the EEG in epileptics. In his small group of patients, all three with psychomotor epilepsy became acutely psychotic under this drug combination. He states this was not a typical psychomotor seizure. The French literature had emphasized the value of this drug combination in activating epileptic records, particularly because it did not produce clinical seizures (Baruk[4]). A recent article by Verdeaux and associates[14] reported on a group of 124 patients with "doubtful spells, character disturbances, impulsive behavior, or psychasthenic symptoms," whom they compared with 121 patients with overt epilepsy.

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* References 7 and 8

In this group of patients he noted that hypersynchrony and/or the appearance of spikes was the characteristic effect on the electroencephalogram. In 73 psychiatric patients, hypersynchrony appeared 48 times and was described as the characteristic of this group. The epileptic group, on the other hand, commonly showed spikes (except in cases of petit mal, where definite spike-and-dome complexes appeared). This author did not note behavioral changes in detail, although he did mention "states of satyriasis, confusional states, and certain psychic manifestations that French psychiatrists call larval epilepsy of Morel."

An earlier paper by Monroe and associates[11] describes the effects on the EEG of the first 30 psychiatric cases in our group given this drug. The common effect on the EEG was slowing and slight build-up in amplitude of the record. The most frequent change in the patient group was the appearance of paroxysmal, high-amplitude, hypersynchronous discharges, usually of a slow-wave type, which were either focal or generalized. Some patients showed, in addition, focal or generalized spike discharges, and a few patients showed only isolated spikes in response to the activation.

The physiologic basis of the EEG effect of SAC is not clear. Choralose has long been used as a laboratory anesthetic, and one of its characteristics is its both depressing and stimulating action on the central nervous system. For example, on peripheral sensory stimulation in animals, the evoked secondary response is suppressed in the cortical sensory receiving area while the primary response becomes exaggerated. It has also been noted that in animals under chloralose anesthesia a light tap on a limb may precipitate a motor seizure, as in the strychninized animal. The general impression is that chloralose produces an extreme facilitation of cortical responses while inhibiting other, particularly brain stem, responses, and indeed producing anesthesia. Gestaut[3] has emphasized the double, apparently paradoxical effect of chloralose on cerebral excitability, demonstrating the lengthening of the cycle of excitability of the cortex seen with all anesthetics, including the barbiturates, but coincidentally the increase in the amplitude of the cycles, similar to that produced by convulsive substances (pentylenetetrazol [Metrazol]). That the excitatory effect is primarily in the cortex is suggested by some work of Moruzzi,[5] who has demonstrated that the excitatory effect is abolished by decerebration in mammals and does not appear in pigeons, who have little cortex (see also Rosenblueth and Cannon[13]). As both sleep and stimulants are used clinically for EEG activation, it is not surprising that a drug with the combined properties described above would be a potent activator.

Because of these interesting physiologic properties, it was felt that administration of scopolamine-α-chloralose with simultaneous behavioral and EEG observations might prove a fruitful research technique. The purpose of this project was to investigate (1) whether there was a specific group of psychotic patients in whom the administration of SAC would produce EEG abnormalities; (2) whether behavioral disturbances could be produced in a significant number of psychotic patients; (3) whether the behavioral disturbances induced correlated with specific EEG abnormalities, and to what extent the behavioral changes were similar to the patient's spontaneous symptoms, rather than a simple toxic effect of the drug, as seen in alcohol or bromide intoxication, or some new pattern of disturbance, such as that produced by lysergic acid diethylamide (LSD) or mescaline, and (4) whether there was a specific symptom complex characteristic of those patients activated which would allow their recognition as a clinical diagnostic group.

Method

The technique of chloralose activation in our studies was similar to that employed by Bercel.[1] All the patients had had a previous routine EEG. A 10- to 15-minute base-line EEG recording was made on the day of the experiment, including at least one 3-minute period of hyperventilation. Scopolamine a chloralose was dissolved in water

and given by mouth. EEG recordings were started with hyperventilation every 15 or 30 minutes. Records were followed for as long as two to three hours, or until maximal EEG abnormalities appeared. In some patients, follow-up studies were done during the next 24 hours. Also, pulse rates were taken as an additional method of following the effectiveness of the chloralose. Side-effects were essentially those reported in the original study.[11]

In all of the subjects, both volunteers and patients, a combination of 500 mg. of chloralose and 0.5 mg. of scopolamine hydrobromide was used. When the study was begun, this combination of drugs was the only available product that contained pure α-chloralose. Recently, however, α-chloralose has become available, and it is planned to use this preparation in the future, since comparative studies reveal that scopolamine has no potentiating effect as far as behavioral or EEG changes are concerned.

The experimental set-up included an EEG room with one-way mirrors so that the subject could be under constant observation. One of us or an EEG technician was always in attendance. The standard technique for electrode applications to the scalp and the EEG recordings was used. A brief mental-status examination was usually performed at the beginning of the test and again at the end. In addition to this, the patients were encouraged to be spontaneous in reporting of symptoms, feelings, thoughts, or sensations during the test period, but no direct questions were asked. At the end of the study, the subjects were carefully questioned about specific changes in affect or thought content, particularly regarding the appearance of symptoms spontaneously occurring in the past. If these were reported only on direct questioning, their validity was carefully weighed.

The control series consisted of 31 subjects. The first 15 were primarily laboratory workers, physicians, and other personnel connected with the project. Of these 15 subjects, 4 showed borderline EEG abnormalities during the base line which were intensified on activation through the administration of chloralose. The second group of volunteers consisted of 16 subjects, mostly nurses, medical students, secretaries, etc., and, of these, 3 showed borderline abnormalities in the base-line EEG. It is interesting to note that the second group of volunteers were primarily "solicited volunteers," who worked either in the medical school or at the hospital used in conjunction with the study. They showed a high incidence of emotional problems, many attending the outpatient psychiatric clinic; and there was a high incidence of previous head injury or neurologic disorder in this group. Many were obviously motivated to volunteer to "find out more about themselves." This group was a dramatic reminder of the importance of distinguishing between "controls" and "volunteers," particularly in psychological investigations.

Half of the neurology patients had a proved diagnosis of focal cortical disease on clinical, laboratory, or operative examination. In two cases only equivocal findings were present on neurologic examination. The other neurologic patients were a group of suspected epileptics for whom careful hospital work-up, including routine EEG's, had failed to clarify the diagnosis and for most of whom the EEG was normal or borderline.

The psychiatric patient group is not a cross section of a usual hospital population, since many of the early cases examined had marked impulsive or "episodic" behavior, although later cases were selected at random. Our hospital population also contained many patients diagnosed as schizophrenic, although no secondary symptoms of delusions or hallucinations had ever been present. This weighted patient sample probably accounts for the higher incidence of base-line EEG abnormality than is usually seen and may produce a higher per cent of activation with SAC than a chronic hospital population would show. No patients or volunteers over 50 or under 17 years of age were used. All of the psychiatric patients had neurologic work-ups and routine skull x-rays.

Results

Electroencephalographic Findings.—Figures 1 and 2 summarize the experimental findings; however, certain important details need elaboration. Of the 15 neurologic patients who have proved central nervous system lesions, 13 showed focal activation on the side of the lesion (if it was lateralized) after the administration of SAC. This occurred despite the fact that eight had either normal or borderline EEG's during routine electroencephalographic studies.† The two who did not show activation had minimal localizing signs and symptoms, with no x-ray or operative evidence of focal lesion. The 16 epileptics reported all had minimal symptoms and signs, and 13 of the 16 had normal or questionable electroencephalograms during the usual routine recording. It is to be noted that after SAC 15 of the 16 had defi-

† By borderline EEG we mean slight build-up on hyperventilation with immediate return to normal, questionable amplitude asymmetry, slightly slow or fast records, or questionable focal or random spikes.

Experimental Gp.		Baseline EEG			Activated EEG			Behavioral Responses					
	Sub-Group	Normal	Borderline	Abnormal	Normal	Borderline	Abnormal	Relaxation	Minimal change in behavior	Clouding of sensorium	Seizure	Recurrence of discrete symptoms	Psychotic behavior
Volunteers	Without personality disorder (19)	16	2	1	13		6	14	2	3			
	History of neuro complication (4)	2	2				4	2	2				
	With known personality disorder (8)	3	2	3	1		7	3	4				1
Total = 31		21	6	4	14		17	19	8	3			1
Neurologic Patients	Focal lesion (15)	2	7	6	2		13	11	3	1			
	Epilepsy (16)	11	2	3	1		15	8	3	1	2	1	1
Total = 31		13	9	9	3		28	19	6	2	2	1	1
Psychiatric Patients	No drugs (44)	23	8	13	10	1	33	12	10	2		2	18
	On drugs (21)	14	5	2	5	1	15		13	2			6
Total = 65		37	13	15	15	2	48	12	23	4		2	24

Fig. 1.—Summary of reactions to scopolamine-α-chloralose (SAC).

nite evidence of EEG abnormalities compatible with the clinical diagnosis. A detailed report of these patients is now in preparation, but they are mentioned here to support the concept that the paroxysmal hypersynchrony or spiking activity seen after administration of SAC is an augmentation of a real potential for this type of physiologic response. This concept is also supported by the consistent augmentation of any slight abnormality in the EEG in all groups studied. If this is true, it is striking that of the 65 psychiatric patients 48 should show definite paroxysmal electroencephalographic activity after the administration of SAC, although only 15 had any abnormalities during routine electroencephalograms. This group of 48 patients does not include those who showed mild generalized slowing in the record, which we feel is characteristic of the toxic effects of SAC. (This effect can be elicited in normals who have not shown activation with the usual dose of 500 mg. if the dose is raised to a toxic level.) To us this suggests that in a large group of severely disturbed patients, one of the physiologic abnormalities heretofore not conclusively demonstrated is this tendency toward cortical hypersynchrony (Hill [10]).

Our small group of volunteers, however, showed a high incidence of similar activity, with 17 of 31 demonstrating paroxysmal hypersynchrony after SAC. However, detailed reinvestigation of the group revealed that in eight volunteers detailed psychiatric and psychological studies in the departmental outpatient clinic done prior to this study showed evidence of severe personality disorder, with a diagnosis of probable psychosis. Four others had a good history of central nervous system complication; three, of severe head trauma; one, of migraine. In this particular group of 12 volunteers, 11 showed activation. Only 3 of the 19 in the group who did not have evidence of disturbed behavior or a borderline base-line EEG were similarly activated. It is obvious from the above that a carefully screened

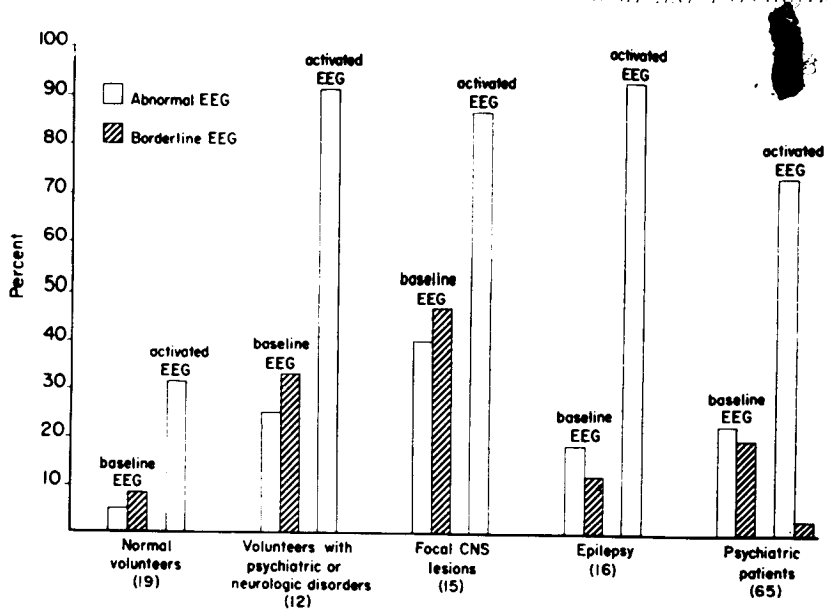

Fig. 2.—EEG responses to activation.

group of volunteers is needed to serve as "normal controls."

In agreement with Baruk,[4] we found that, despite this CNS activation, only 3 of the 127 subjects had actual seizures. Two had psychomotor seizures associated with automatic movements, bizarre behavior, clouding of sensorium, and amnesia; the other lost consciousness and had occasional myoclonic jerks in the upper extremities, which could be aggravated by passive movement, after the onset of psychotic behavior. She responded readily when 4 grains (0.25 gm.) of phenobarbital sodium was given intravenously, regaining consciousness immediately.

Behavioral Response.—The SAC used in this study is marketed in Europe as a sedative.‡ The usual clinical response is a sense of lassitude, even weakness, indifference, and light sleep. Other effects are minimal behavioral changes (Fig. 1), such as loss of inhibition, mild euphoria, expression of warm, dependent needs, sometimes slightly seductive behavior, and occasionally excessive gaiety or silliness. Accompanying this response there may be minor motor changes with myoclonic movements, particularly in the hands, aggravated by spontaneous or passive movement in the extremity. There may be a slight ataxia, and occasionally a positive Romberg sign, dizziness, and weakness.

Of the 127 patients who took medication, 9 showed a severe organic type of reaction. This was marked by clouding of sensorium with disorientation, memory loss, and perseveration, followed by amnesia. In many others of the experimental group, mild difficulties in finer intellectual performance, such as complicated calculations, awareness of the passage of time, or quick response to questions of orientation and recent memory, could be elicited, as well as slight vagueness in recalling the experience. However, as reported below, the clouding of sensorium was not in any way proportionate to the disturbed behavior shown in those that had a psychotic reaction.

‡ Kuhlmann, Paris.

Activation of Psychotic Behavior. Of the 48 psychiatric patients with EEG activation, 24 showed evidence of psychotic reactions, as described below (Fig. 3). In

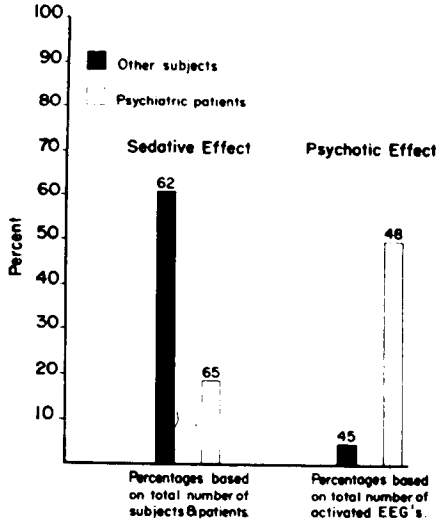

Fig. 3.—Behavioral responses to activation.

every instance this was accompanied by paroxysmal hypersynchrony, although not correlated with the degree of EEG change. Many patients showed the paroxysmal hypersynchrony without evidence of psychotic behavior. Of the 62 subjects, who included the volunteers and the neurologic patients, 45 showed EEG activation but only 2 demonstrated psychotic reactions. One became agitated, confused, depressed, and suicidal, had persistent vomiting, and showed hysterical acting out, requiring overnight hospitalization. A subsequent detailed medical history revealed that similar reactions had occurred on two occasions in the past when she had general anesthesia. The other, a neurologic patient with grand mal and psychomotor seizures, was actually hospitalized on the psychiatric service at the time because of the bizarreness of these seizures. He was of borderline intelligence but did not demonstrate psychotic behavior except during ictal states; he, therefore, was included in the neurologic group. Although he was oriented under the drug, he hallucinated a vision of his girl friend, talked with her, and tried to get up from the bed to hug her. The low incidence of psychotic behavior in those patients who have not in the past shown similar behavior spontaneously suggests that the phenomenon induced by SAC is not similar to the specific psychosis-inducing effect of LSD or mescaline. Moreover, normals who have shown no evidence of EEG activation or psychotic behavior under the drug, but who have taken high doses of SAC, show the toxic phenomenon of sleepiness, confusion, and disorientation, with amnesia, but no psychotic behavior. This supports the concept that SAC behavioral activation reflects an activation of true psychological potentiality for psychotic behavior. Figures 2 and 3 summarize in graphic form both the EEG activation and the behavioral activation of the experimental group under SAC.

In the group of 26 patients who showed psychotic behavior (Fig. 4) a predominant reaction was acting out of sexual, angry, or fearful impulses, which occurred in 14 cases; 12 complained of feelings of unreality or depersonalization; 9 had definite fear and rage reactions not accompanied by acting out; 9, depressions, while only 3 had overt hallucinations and 2 delusions; 6 showed extensive confusion, which was not just clouding of sensorium; only 2 had severe disorientation, and 3 had complete amnesia for the experience.

In view of the predominance of acting out and depersonalization manifest under the SAC and the fact that the overtly psychotic behavior was frequently similar to the spontaneous behavior shown by the patient (in 22 of the 26 patients), it was felt that this drug might differentiate a group of patients characterized by impulsive acting out of an episodic nature. Of the 26, 16 had definite evidence of impulsive behavior, and 19 showed episodic behavior disorders. Of the remaining experimental subjects who were psychiatric patients but who did not show psychotic behavior under the influence

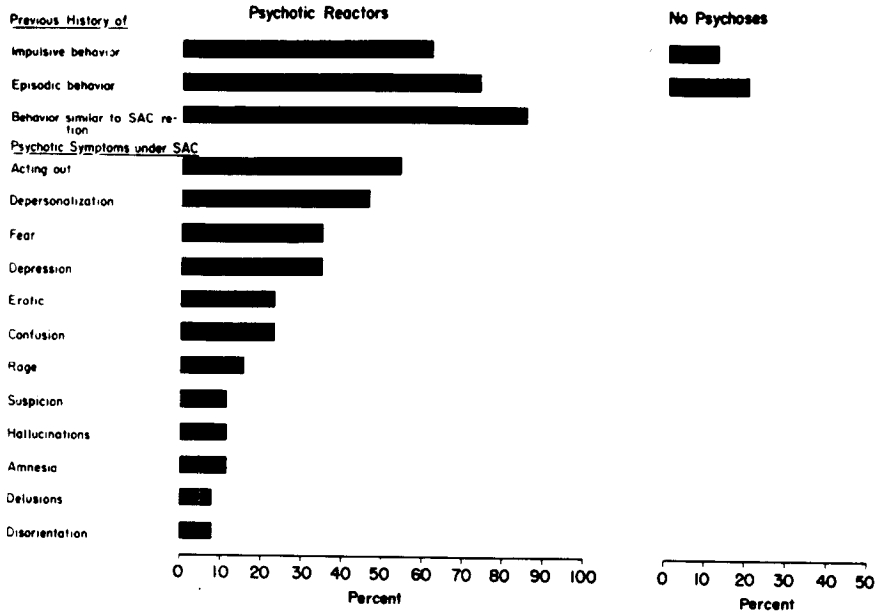

Fig. 4.—Summary of psychotic reactions to scopolamine-a-chloralose (SAC).

of this drug, only 5 out of 41 had histories of impulsive behavior, while 8 out of 41 had a history of episodic disturbances. It is interesting to note that approximately half of the psychiatric patient group was routinely taking one or another "ataractic" drug at the time of the test. There was no apparent effect on EEG changes, and probably no reduction in the psychosis-inducing potential of this procedure. It would seem from the above that the SAC activation of psychotic behavior does occur in those who are predisposed to this type of behavior. This observation has certain implications in terms of the mechanism of episodic psychotic episodes and possible choices for treatment.

Correlation of Behavioral and EEG Activation.—In this extended series, the correlation noted by Monroe[11] in the original study was not as precise. As would be expected, when the patient reported drowsiness or sleep, there were typical drowsy or sleep recordings on the EEG. High-amplitude generalized slow activity was often associated with markedly confused behavior, but other patients would show slowing to a similar degree without the confusion. Of the 26 subjects who manifested psychotic behavior under the influence of this drug, 9 had both paroxysmal or high-amplitude theta-delta and spiking activity, which might be generalized or localized. Only three in this group had moderate generalized slowing alone. The remainder presented high-amplitude, paroxysmal theta or delta activity, which might be focal, show a shifting focus, or ultimately become generalized and continuous. Thus, at the moment, we can make no specific correlation between scalp recordings and the various types of behavioral changes. As reported in the previous study,[11] nine patients with subcortical electrodes in at least the septal, hypothalamic, and hippocampal region, as well as on the cortex, have not helped in making correlations between behavior and electroencephalograms.

Report of Case

To clarify the type of patient most likely to show both the electroencephalographic and

the behavioral activation under SAC, we would like to present in detail one case history, accompanied by a discussion of the similarities and differences in those patients who showed no electroencephalographic activation after the administration of SAC.

A 27-year-old housewife, a mother of two mentally retarded children, was admitted to the hospital in February, 1945, for evaluation and treatment of episodic psychotic reactions, lasting from a few hours to a few weeks, and severe enough on six occasions to require hospitalization or incarceration in jail. These episodes, described as "spells" by her husband, were preceded by mounting irritability, hypochondriasis, and severe occipital headaches. As the attack progressed, there would be withdrawal and lack of emotional response, accompanied by a staring, vacant look in the eyes; this would be followed by outbursts of rage and destructiveness, at which time the patient would be physically abusive toward her husband or children, or self mutilative, and, in fact, on two occasions suicidal. These "spells" would be accompanied by visual hallucinations, particularly of her children cringing in fear, or at other times of her mother, husband, and children calling her names and admonishing her. She would break up furniture, tear off her clothes, and try to tear her hair "to get the snakes out of it." These attacks would be accompanied by varying degrees of confusion and disorientation. Although she claimed complete amnesia for the episodes, detailed questioning revealed that there was generally some hazy recollection. Following the attack, there would be a period of depression and remorse. Amobarbital (Amytal) sodium intravenously would often control the behavior and sometimes abort the attacks. At other times hospitalization was required for as long as two months, with the patient receiving EST and subcoma insulin. During the intervals between these attacks, the patient was hostile and irritable, constantly taunting her husband about past mistakes and suspiciously accusing him of extramarital affairs, whereas she herself was occasionally promiscuous. She had constant hypochondriacal complaints, which led to frequent visits to her doctor and several hospitalizations with two laparotomies.

The patient is the oldest of five children, the others being boys, born into a family of low economic and social status. The emotional climate of the home was unstable. The father, who apparently was affectionate toward the patient and gave her some emotional security, was described, nevertheless, as an alcoholic who was irresponsible and frequently away from home philandering. On the other hand, the mother, who was reliable and supported the family, was described as having a personality much like the patient's, being particularly hostile and restrictive toward the patient, while favoring the boys. The mother never allowed the patient to socialize freely, and during adolescence restricted her social activities, while accusing her unjustly of sexual promiscuity. She conveyed to the patient her own suspiciousness and sense that the world was a hostile place.

The patient says of herself, "I was always different and confused." She was shy and isolated, while quick-tempered and belligerent, rebelling against authority and fearful of school. She had numerous phobias, particularly concerning darkness and fire. The latter had some realistic basis, since, at the age of 3 years, she sustained severe third-degree burns over her body and face, requiring repeated plastic surgical operations, which had left her face considerably scarred and distorted. She was attached to her father but furious about his philandering, with her anger directed toward the girl friends more than toward the father himself. However, after her father's divorce and subsequent marriage, she accepted both her father and his wife, often expressing a desire to go and live with them. Her childhood and adolescence were characterized by isolation, and only superficial emotional relationships with peers or family. She met her husband in the hospital while undergoing a plastic operation, married him shortly thereafter, and had difficulties in adjusting to the marriage from the start. Sexual adjustment was always poor, with the patient failing to attain orgasm until the last year or so. Attempts at coitus, as well as her pregnancy and delivery, were accompanied by much acting out of the aggressive behavior described above.

Aside from the scarring on the face, hands, and trunk, physical and neurologic examinations were noncontributory. Laboratory findings were all negative except for the electroencephalogram, which showed some short runs of 6, 7, and 7½ per second activity and a small build-up on hyperventilation, with immediate return to normal. The record was read as a generalized slightly slow record, consistent with, but not indicative of, epilepsy.

At the time of admission to the hospital, the patient was somewhat irritable and suspicious but otherwise cooperative, showing no evidence of the episodic behavior described above. Intellectual testing and a routine mental status examination revealed no abnormality. However, during the course of her hospital stay, she would show the typical "spells," which would generally last for 24 hours, but might persist for weeks. Attempts to control the behavior with anticonvulsants, such as diphenylhydantoin (Dilantin), phenobarbital, and trimethadione (Tridione), were unsuccessful, as were reserpine and chlorpromazine. The behavior could

ject be aborted by amobarbital sodium 7½ grains (0.5 gm.) intravenously, followed by maintenance doses of 3½ grains (0.25 gm.) by mouth or intramuscularly three times a day.

This type of patient presents a real diagnostic problem, not fitting descriptively into any of the usual diagnostic categories. This is the type of history one often obtains from patients with temporal lobe spikes, as has been described in detail in two previous papers by Ervin and Epstein.§ In fact, one of the patients in our series was written up in detail by Epstein and Ervin [8] (Patient M. G.). If one would emphasize in the history the episodic nature of her symptoms, as well as the clouding of sensorium, the diagnosis would be psychomotor epilepsy with a rather prolonged ictal response. If one would emphasize the schizoid and paranoid features in her personality, as well as the prolonged agitation and homicidal-suicidal behavior accompanied by visual and auditory hallucinations, the tendency would be to consider this person a catatonic schizophrenic. On the other hand, the impulsive behavior extending far back into childhood would suggest childhood behavioral disorders characteristically described as the impulsive hysterical acting out in adulthood. This type of diagnostic dilemma was typical of almost all the patients in this series who showed the psychotic response to activation with SAC.

The episodic impulsive behavior was most frequently an expression of rage, varying from childish temper tantrums, in which the patient would lie down on the floor, kick, and scream, through impulsive and sudden outbursts of physically abusive behavior toward those closest to him, to, rarely, the more organized acted-out dissocial behavior, such as stealing and forging checks. Quite often this rage was turned on the self, with bizarre suicidal attempts or self-mutilation. At other times, the episodic behavior was more typical of seizural states with loss of consciousness, but rarely typical grand mal attacks; more frequently there were diffuse automatic movements characteristic of psychomotor epilepsy. These episodic attacks were frequently accompanied by disorientation and amnesia, but not invariably so. The amnesia often seemed more a conscious malingering to deny responsibility for the hostile acts committed, as, for instance, was dramatically represented in one patient who was hospitalized because her behavior was accompanied by amnesia. Immediately after hospitalization, to gain her release, she proved the amnesia was a fabrication by relating in minute detail the events of the preceding 24 hours for which she had previously claimed complete amnesia. At times the episodic behavior was more typical of catatonic mutism, and at other times it was just episodic depersonalization or seductive and self-destructive acting out.

The behavior between the episodic outbursts would be characterized by poor interpersonal relationships and social adjustment, usually accompanied by narcissistic, self-centered preoccupation, irritability, paranoid trends, and lack of close emotional attachments.

Contrariwise, in many instances, those patients who had definite evidence of psychosis but whose symptoms were well structuralized, with organized delusions and adequate, if bizarre, control, and who were characterized previously by obsessive-compulsive rigid personalities, generally did not show electroencephalographic activation or marked behavioral changes under chloralose.

We seldom had the opportunity to run EEG records at the time of a spontaneous attack. In several instances when we did, the seizure was associated with spontaneous high-amplitude slow waves, similar to those induced by SAC. However, in the case here described, during the spontaneous attack there was no change in the scalp recordings from the base-line record, which showed a slight abnormality with 6 and 7½ per second generalized slow waves.

Comparison with Other Drugs

Fourteen of the subjects in this study had intravenous amobarbital sodium given slowly while they were interviewed: Five

§ References 7 and 8

were given *d*-LSD-25; 3, mescaline; 5, pentylenetetrazol, and 2, intravenous alcohol. Although some of the patients demonstrated episodic behavior as an obvious release phenomenon (under the influence of alcohol, for instance), we did not find that the patients who showed psychotic behavior under SAC responded in a similar manner when given amobarbital sodium intravenously to the point of slurring of speech without inducing sleep. If anything, they tended to normalize under amobarbital sodium, whereas those patients who showed a release phenomenon, with more psychotic behavior, under amobarbital did not respond in a similar manner with SAC. The reactions of the patient described above will be reported in some detail, with any deviations in the response of the other patients mentioned.

March 29, 1955: Chloralose. During the baseline recording the patient was pleasant and friendly, cooperative, and oriented in all spheres. Forty minutes after the drug she was crying and depressed. At one hour she complained of numbness in her right hand and arm. She described an "odd feeling," similar to that when her attacks come on, which, on questioning, suggested depersonalization. At 70 minutes she was expressing diffuse rage and tearing up the bedclothes. She admitted concern about her children and her inability to take care of them. Eighty-five minutes after the drug she complained of shakiness and showed occasional myoclonic jerks in the arm. Ninety minutes after the drug she began hallucinating, with her children and husband appearing before her and admonishing her for being bad. She verbally responded to these hallucinations. At that time, though somewhat confused, she was still perfectly oriented. At 100 minutes she began screaming, "Where am I?" and now appeared disoriented, thinking that she was in a different town and different hospital, although, on repeated questioning, she remembered vaguely where she was. More depression was seen now and less rage. At this time she revealed some significant dynamic material which had been inferred from the clinical history, namely, that she was overwhelmed with the responsibility of raising her children, felt guilty that she had been abusive and tried to kill them, and admitted that she expected retribution from her mother, who would not allow her to grow up and be a mother in her own right; therefore, the children must belong to her mother and are really her father's children. She expressed guilt over these incestuous fantasies, as well as fear of retaliation from her mother. Often, during an acute attack, she discussed leaving the children with her mother and moving to a distant city to live with her father. Except for the hallucinations, which occurred in only three instances, this is a rather typical activation of psychotic behavior by SAC.

May 23, 1955: Pentylenetetrazol, 700 mg., injected slowly intravenously. Except for mild subjective sensations of anxiety, there were no changes in behavior. During the next 24 hours, she participated in all ward activities, went on passes with her husband, and had no difficulty in sleeping and no somatic complaints. Most of the other patients who received Metrazol had some somatic side-effects; otherwise, this response was a fairly typical one.

May 27: Chloralose repeated. Interestingly, at this time, the patient showed no hallucinations and no bizarre acting out of rage or marked fear and depression. She had the same feeling of depersonalization and showed more clouding of sensorium, with organic confusion and perseveration.

May 30: *d*-LSD-25, 100γ. Forty minutes after the drug was given, the patient complained of feeling tense and "paralyzed," stating that she couldn't talk, although there was no obvious impairment in her speech. At 45 minutes she became nauseated and complained of blurred vision. One hour after administration of the drug, eye pressure revealed red lights, "maybe Indians." At 90 minutes she stated that she had to get up and go home to her children; she was crying and struggling. There was some difficulty in remembering the doctor's name, as she seemed to be in a "trance-like state." When her attention was secured, she was oriented and in contact with her surroundings. Two hours after the drug was given, a blocking agent was administered, which modified the subsequent response. At one time, she briefly hallucinated her children, but there was no conceptual elaboration on the basis of dynamic material, as described under the first chloralose reaction.

June 1: Mescaline sulfate, 500 mg. I.V. The immediate response was a sensation of being cold. "My skin is burning." She also complained of difficulty in breathing; she vomited, and described sensations in her legs as if they were "drawing up." She expressed anger at the doctor, as well as her husband, but would laugh while talking about it. She did mathematical problems quickly and was oriented in all spheres. One and one-half hours later, she complained of aches and pains in her back and neck; she saw lights flashing, saying it was as if "you look sparkly." There were no marked emotional changes, nor did she hallucinate at this time. In comparison with SAC, LSD and mescaline seem to induce more somatic complaints.

less acting out, more perceptual distortions, but less conceptual ones.

June 3: Repeated chloralose plus amobarbital sodium, 7½ grains. At this time, the patient responded to the chloralose as she did in the first experiment, again becoming agitated, rageful, tearing up things, and hallucinating her children and husband, the children being frightened, and the husband admonishing for her rageful behavior. After amobarbital was given the patient quieted down, no longer expressed anger and resentment, but, rather, showed expiatory behavior: "Do you like me?" and "Nobody's going to kill me, are they?" She said she was no longer angry at her husband or the doctor, and stated that, although she occasionally saw her children, "they are now smiling." In several other instances when amobarbital sodium was given, after a psychotic reaction with chloralose, a similar type of response would ensue, wherein the psychotic material, particularly the frightening and rageful affect, was reduced.

June 6: Spontaneous attack. On the ward she was restless, paced the floor, was no longer cooperative, and refused her medicine, stating, "I feel one of my moods coming on, and I am going to tear up everything." She tried to run away from the hospital and expressed a desire never to see her doctors again. She threatened the personnel, threw about the belongings in her room, and by evening was depressed and crying. She began tearing up her clothes and had to be forceably restrained. Twelve hours after the start of the spontaneous seizure, she was quieter, less agitated, and expressing some guilty feelings about her previous behavior, which she remembered clearly. This illustrates that the episodic psychotic behavior was not always accompanied by amnesia.

Comment

There has been an increasing awareness among psychiatrists and neurologists of a borderline group of severe behavior disorders, variously diagnosed as psychomotor epilepsy, hysterical acting out, or schizophrenia. The diagnostic category in which these patients are placed depends not only on the orientation of the physician, that is, whether he is a neurologist, a psychoanalyst, or a psychiatrist, but also on the acuteness of onset, the duration of disturbed behavior, and the degree of sensorial changes and subsequent amnesia. Therapeutic trial, either on anticonvulsive medication or on the usual somatic therapies for schizophrenia, particularly EST and insulin, has not aided in the proper diagnostic categorization of these patients because of their poor response to all somatic therapies, although it has been our experience that they often show marked improvement with intensive psychotherapy. Base-line EEG's are usually normal or equivocal, and electroencephalograms are usually impossible to obtain during acute attacks, so that laboratory procedures offer little diagnostic clarification. The complicated conceptually organized patterns of behavior manifest during these spells, and often concomitantly expressed in dreams usually reveal dynamically significant material, particularly expressions of rage and destructiveness toward Oedipal figures or sibling rivals, have reinforced the psychological importance of such episodic behavior, and perhaps oftentimes tended to minimize adequate neurologic and laboratory workups. As mentioned in the paper originally, many of our patients were selected for this study on the basis of being in this borderline group, although subsequently we made a conscious attempt to select them at random. To us it was not surprising, then, that many of the patients in this group, like the epileptic or focal neurologic patient, showed an activation of cerebral hypersynchrony under SAC. Without postulating a common etiologic relationship between epilepsy and these episodic psychotic states, we now believe that it can be demonstrated that both have this common potential for cerebral hypersynchrony. It seems to us that the historic observation of incompatibility between epilepsy and schizophrenia is best reformulated as follows: The massive cerebral discharges involving the motor areas and resulting in typical grand mal seizures do seem to protest against or alleviate the psychotic manifestations that otherwise might be present. However, we would like to suggest the idea that there may be a closer relationship mechanistically among these episodically disturbed patients, in categories now variously diagnosed as hysteria, psychomotor epilepsy, catatonic schizophrenia, episodic alcoholism,

and impulsive dissocial behavior, than there is with those patients in the same diagnostic category who show sustained, nonepisodic, disturbed behavior.

Interestingly, Karl Menninger,[12] in his revision of psychiatric nosology, based on modified psychoanalytic concepts, has come to similar conclusions, grouping together a number of episodic clinical syndromes under the heading of "Regulatory Devices of the Third Order: Episodic Discontrol." In describing this group, he states:

> The uncontrollable emergence of dangerous instinctual impulses is always something of a catastrophy. . . . Clinically and empirically we know these catastrophies in two forms; as continuous phenomena over a considerable period of time, and as a relatively brief episodic discontinuous phenomenon from which there is prompt recovery with a continued tendency for them to recur. It would seem that these episodic explosions serve to relieve enough tension to prevent the development of the continuous form.

Recent neurophysiologic studies have revealed that in both man and animals electrical stimulation of certain subcortical structures, particularly the septal and hippocampal-amygdaloid regions, can induce dramatic changes in behavior with or without changes in sensorium. In a recent article, French and associates[9] demonstrate that it is precisely these subcortical areas which would show seizural activity when the cortex is stimulated with parameters of currents that would elicit local "seizural-type" after-discharges. If there was subsequent spread of this local response, it would occur most frequently in the septal-amygdaloid region. Thus, it is not hard to conceive that the spontaneously induced hypersynchronous activity might result in rather complicated behavioral changes, and that these do not necessarily have to be accompanied by loss or impairment of consciousness or dramatic clouding of sensorium. We must admit, however, that our present study thus far has not revealed any precise correlation of central nervous system, electrophysiologic activity, and behavior. In view of the crudeness of our clinical technique, particularly the use of scalp recordings of the electrophysiologic activity of the cortex, this not surprising. However, the present da do give impetus to more intensive study the electroencephalogram in psychotic pa tients using activators, and also sugge renewed efforts in developing the "anticon vulsant" group of drugs, which may hol some hope for at least a pharmacologic adjunct to our present psychotherapeut efforts in those patients with episodic be havior disorders.

Summary

Electroencephalographic and behavior activation with chloralose and scopolamin was done on a group of volunteers, neuro logic patients, and psychiatric inpatient: There was a low incidence of EEG activa tion in volunteers without psychologic dis orders or neurologic complications. In th neurologic patients with evidence of foca central nervous system lesions, there wa almost always EEG activation compatibl with the diagnosis, even though previou EEG's had been normal or equivocal. I patients with a good history of epilepsy bu normal or equivocal EEG's, there was again almost inevitably, electroencephalographi activation compatible with the clinical diag nosis.

Surprisingly, 48 of 65 psychiatric inpa tients also showed electroencephalographic activation, with the appearance of high amplitude paroxysmal delta-theta activity and/or focal or generalized spikes.

Of the 48 activated psychotic patients, 2- demonstrated an exacerbation of psychotic behavior while under the influence of chlora lose and scopolamine, as compared with only 2 of the 45 volunteers or neurologic pa tients who showed electroencephalographic activation. The psychotic behavior was usu ally characterized by rageful acting out depersonalization, and confusion, and, rare ly, by hallucinations and delusions. The reaction to the drug was usually similar to the spontaneous psychotic behavior previously shown by the patient. Activation of the psychosis by scopolamine-α-chloralose

seemed to occur predominantly in a group of patients who had shown clinically the impulsive acting out demonstrated under the drug.

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