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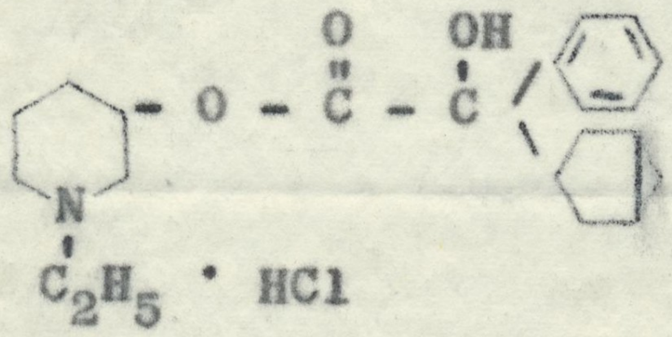
SOME EFFECTS OF A NEW PSYCHOTOGEN IN DEPRESSIVE STATES

L. G. Abood and L. J. Meduna
University of Illinois College of Medicine

A group of 3-N-substituted piperidyl benzilates have been recently demonstrated to possess psychotomimetic properties(1,2). The N-methyl-3-piperidyl benzilate, in dosages of 5-10 mg orally, produced distinct auditory and visual hallucinations in every normal individual tested. The hallucinations lasted for many hours, and were accompanied by gross distortion of visual perception and by a confusional state corresponding to delirium. A number of subjects exhibited paranoid ideation and ideas of grandeur, while others suffered a complete loss of contact with the environment, and frequently reacted to their hallucinations. When the toxic symptoms disappeared, the subjects experienced a marked physical weakness for 10-24 hours, after which period they regained their pre-experimental status.

It was noticed, however, that some of the normal volunteer subjects developed a change in their basic mood and drive. This change usually appeared 24 to 48 hours after the physical weakness disappeared. The newly emerging modulation of mood can be characterized as slightly hypomanic and of increased drive. This last observation indicated that the drug might be useful in the treatment of psychiatric states in which the outstanding symptom is a depressed mood.

In the course of examining the structure-activity relationships of various congeners of the piperidyl benzilates (3), it was found that substitution of a cyclopentyl for one of the phenyl groups in benzilic acid considerably enhanced psychotogenic potency and greatly prolonged the duration of action. The compound, designated JB-329*, has the following structure:



N-ethyl-3-piperidyl cyclopentylphenyl glycolate hydrochloride

This derivative also seemed to produce considerably more hyperactivity and central stimulation than did its benzilate congener. The present communication concerns the use of JB-329 on psychiatric patients.

Case No. 1: The first patient, DH, was a 60-year-old man, a former bricklayer, who had been hospitalized for the last ten years. Examination revealed his case to be one of severe depression with suicidal tendencies, caused apparently by the neurotic

reaction of his burned-out body to the insoluble problem of his wife's psychotic illness. The patient was given 12 mg of JB-329, and within an hour showed signs of confusion, drowsiness, ataxia, and hypereflexia. A few hours later he began having hallucinations, was disoriented, extremely restless, and beginning to lose contact with the environment. Autonomic symptoms were present throughout, such as mydriasis, tachycardia, dryness of the mouth, and muscular weakness. At the end of 24 hours, he seemed considerably less depressed, smiled, laughed, and was much more talkative, although he professed to be just as depressed as he was before the treatment. Psychological re-examination with the Edwards and Rorschach tests indicated a definite improvement in mood and general outlook, and although the depression still existed, it seemed realistically based, and was considerably less overwhelming. The patient, however, refused to go back to his psychotic wife, and was returned to a state hospital.

Case No. 2: EP, a 33-year-old unmarried white man, complained of depression, extreme apathy, and a chronic spastic colitis. He had quit his job over a year ago because of an increasing depression, accompanied by feelings of inadequacy and lack of desire to work. Psychological tests revealed him to be immature, with little or no affect, no signs of anxiety, and no insight into his condition. He reacted to 10 mg of JB-329 in much the same manner as the previous patient, covering a time-span of 18 hours. At the end of this period, he appeared very cheerful, and all of the depressed, haunted features of his face had disappeared. He gave the impression of a man well on the way to recovery after a long illness. That same day he indulged in a rather vigorous game of baseball, mixed, and talked freely with the other patients. He admitted feeling more aggressive and exuberant, and expressed a desire to go back to work as soon as he was discharged. Psychological re-examination showed him to be more responsive, less inhibited, and his outlook less limited. The patient was discharged two days after receiving the drug, and two days later he procured a position, which he still retains after three months.

Case No. 3: C McC, a 47-year-old married man, had a history of intermittent depressions since 1953. He had been unable to work during the past year because of the depression. At the time of his admission, he showed symptoms of restlessness and extreme agitation; he was harassed by self-accusations and feelings of guilt. Pre-therapy tests revealed an inadequate personality with an extremely passive dependence on other people. The existent anxiety and depressive features were overlaid upon a long-standing character disorder. The patient's response to 12 mg of JB-329 differed from the previous patients only insofar as the hallucinatory episodes were far more vivid and of longer duration. After 36 hours, the patient exhibited marked increase in motor activity and a dramatic improvement in mood. Psychological re-examination revealed that he was now able to express hopeful and resolute attitudes toward the future, although he still had little confidence in his ability to achieve the goals he envisioned.

Two weeks after being discharged, he spontaneously wrote a letter from which were taken the following statements: "For your information, my progress has been good. I am working about full time ...I have gained about ten pounds. My appetite is very good now. ...I am extremely grateful to you for what you have done."

Case No. 4: LCCT was a 54-year-old white married woman who appeared very much older, and had been in a very severe depression for the last ten years. She had phobic paranoid reactions, suicidal ideas, and hysterical attacks accompanied by screaming, excessive crying, and other indications of desire for attention. Psychological examination indicated an unsound personality structure which seems to have been infantile even before the onset of the present illness. The effects produced by 12 mg of JB-329 were similar to those in the other patients, and lasted for 24 hours. The following day, she appeared more vivacious and most of the outward signs of her illness had disappeared. On the succeeding day, she socialized for the first time with other patients, and participated in occupational therapy activities. She seemed surprisingly cheerful, enjoyed her food, and appeared outgoing. After three days, when her husband came to take her home, she reacted violently and relapsed into her previous condition. Her condition was apparently developing into a full-blown psychosis. Electroshock therapy was administered during the next week, and although the patient showed improvement at first, she again relapsed into the previous agitated depressive condition.

Case No. 5: KB, a 46-year-old white unmarried female with paranoid delusions, was depressed and apathetic. She was extremely tense and anxious, and her grasp on reality was tenuous. Her reaction to 10 mg of JB-329 was similar to that of the other patients, except that the hallucinations and disorientation lasted up to 36 hours. Two days later, she appeared definitely animated, cheerful, and composed. When questioned about her past condition, she replied, "I feel much more alert and don't feel depressed. Strangely enough, this was one of the first things I noticed. I feel now as if before the treatment I had been living in a flat two-dimensional world and I had sort of retreated into myself, and now, after this treatment, I feel I am out in the normal three-dimensional world. I feel much more alive...I have more energy and enthusiasm." The patient resumed her work on the day following her discharge. She continued to show improvement during the next few weeks, although after one month she appears to be relapsing into her former state. She reported, however, that a symptoms, which she referred to as a "catatonic nightmare," a condition during which sheeseemed to be conscious but was unable to move and which had existed for many years before the treatment, had completely disappeared and had not yet returned.

DISCUSSION

Five cases have been presented which serve as pilot experiments in the application of the piperidyl benzilates to patients manifesting psychopathology. Of the five cases, the first and

the fourth can be considered as experimental successes but therapeutic failures. These two particular cases have never responded well to any other form of therapy, including electre-shock and drugs.

In three cases (Nos. 2, 3, and 5) the single application of the experimental drug proved to be of therapeutic value. Cases No. 2 and 3, who were unable to work for over a year before the experiment, were able to do so. Case No. 5, which is the most interesting of our small experimental group, was working prior to the experiment; but that patient's statements and our objective observation are both indicative of the therapeutic effectiveness of the drug. Case No. 4 proved to be a therapeutic failure with respect to the drug, but the patient also failed to recover after electric convulsive treatments.

All five cases treated had only one symptom in common--some degree of depression. The other most remarkable common feature of cases No. 2, 3, 4, and 5 was an extreme infantile personality which could not be expected to change after a single treatment of whatever sort. If it were not for the fifth case, where the most remarkable changes were produced, this drug, JB-329 and its congeners could be earmarked for the treatment of depressive states only. In the fifth case, however, beneath the light depression were deeper disturbances of thinking and perception eluding superficial observation. In effect, she was psychotic. Whether her particular paranoid state should be diagnosed as latent schizophrenia, affective psychosis, or schizophreniform is beside the point. The importance of this case is that it indicates some usefulness of the piperidyl benzilates in a patient with marked perceptual and cognitive disturbances.

There are a great number of questions unanswered by this preliminary experiment. Both the extent and duration of improvement have not been fully assessed. It remains to be determined 1) whether repeated administration of the drug in hallucinogenic doses would have produced a greater degree of improvement in the successful cases and total or partial improvement in the unsuccessful fourth case; or 2) whether the production of the psychotogenic state is necessary at all to produce improvement; or 3) if daily repeated small doses of the drug for an extended time would have produced the same but slower improvement. Both the effect and proper dosage schedule of a maintenance amount of JB-329 have yet to be determined. Finally, the proper field of application of this drug in psychiatry is in doubt. As far as the experimental results on normal and pathologic subjects permit any conclusion, the drug would be applicable to depressive states. Our fifth case, however, raises some slight hope that JB-329 or related derivatives might be useful in treating the grave personality disorders commonly diagnosed as szhizophrenia.

The use of anticholinergic agents in the treatment of schizophrenia is not new. Forrer and co-workers (4) administered very large

doses (up to 200 mg) of atropine intramuscularly to schizophrenics manifesting some degree of anxiety. Such doses of atropine produced coma; but most of the psychotogenic and stimulating actions achieved with JB-329 were absent. It remains to be seen whether the basic mechanism of these two modes of therapy is similar, although our findings suggest that atropine is devoid of the excessive stimulating properties of JB-329. LSD-25, another hallucinogen, has been used therapeutically in treating psychotics, largely as an adjunct to psychotherapy or electroshock convulsions (5, 6).

With regard to the mode of action hardly more can be said than that the substance has definite anticholinergic properties, but evidence that the central effect itself involved cholinergic blockade is lacking (1, 3). The piperidyl benzilates in smaller doses produce facilitation of motor neurons (Renshaw cells) in the lumbar region of the cat's spinal cord, while larger doses produced complete inhibition (7). Acetylcholine is presumed to be a mediator in Renshaw cells which are believed to exercise a generalized suppression in motor neurons innervating skeletal muscle. Himwich (8) has demonstrated an inhibition of electrical activity in the reticular bulbar formation of the rabbit with 2.5 mg/kg of JB-329, in contradistinction to LSD, which is excitatory. Such neurophysiological studies are merely preliminary and, although they may explain certain effects of the drug, such as hyperreflexia, considerably more work of this sort remains to be done.

The clinical results with the drug are even more obscure, particularly since the therapeutic effects become apparent long after the hallucinations and autonomic symptoms have disappeared. Furthermore, studies on animals indicate that the drug is readily hydrolyzed in the body, and is completely eliminated in 24-48 hours. One can only conclude, therefore, that therapeutic effects are related to the drug in a secondary manner. The piperidyl benzilates probably serve as a trigger mechanism for a long series of neurophysiological effects resulting in the improvement in the patient's psychopathological status. Subsequent clinical work is aimed at working out proper dosage schedules, as well as the indications for the use of this and other related drugs.

SUMMARY

A new anticholinergic psychotomimetic agent, N-ethyl-3-piperidyl cyclopentylphenyl glycolate (JB-329), has been used in the treatment of a small number of depressed patients. The drug induces a drive of activity accompanied by some mood elevation. This seemingly desirable effect from a therapist's viewpoint occurs after a period in which there are psychopathological effects of a definitely psychotic nature. The post-psychotic effects which seem desirable are of a prolonged duration (days to weeks possibly). There is at least slight evidence in two cases of a continuing state of improvement in integration of the mental functioning and behavior.

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FOOTNOTES

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DEPARTMENT OF EXPERIMENTAL PSYCHIATRY HILLSIDE HOSPITAL GLEN OAKS, N. Y. OCT 1958

Institute of Human Nutrition, Praha,
(J. Mašek)

A PSYCHOSIS CAUSED BY BENACTYZIN INTOXICATION

Miloš Vojtěchovský

The dimethylaminoethyl ester of benzylic acid is known in the literature by the following names: Benactyzin, Suavitil, Parasan. It was synthesized in 1936 in the CIBA Laboratories in Switzerland as a spasmolytic agent, but it was not until 1955 that it first came to be used in psychiatry by *Munkvad & Jacobsen*, where it proved to be a useful tool for decreasing anxiety and psychic tension, without having any hypnotic side effect. During the following two years it was roughly investigated for both its clinical and pharmacological qualities and was applied to many patients in various institutions. The specific action of this drug upon the central nervous system placed it, together with the tranquilizers, on the level of the leading modern psychopharmacological agents. For its composition and central nervous action it was called an "antiphobic" agent, while its chemical structure ranged it among the diphenylmethanes having a central nervous effect (together with e.g. Meratran, Frenquel, or Atarax). Therapeutically it is used more commonly in cases of neurosis than in psychotic cases. Its pharmacological and clinical attributes have been described thoroughly in other publications. This substance was also synthesized in Czechoslovakia, in the Laboratories of the Institute for Research in Pharmacology and Biochemistry and has been tested since May 1956 in several clinical institutions (Dr. *Hanzlíček*, Dr. *Vinař*, Dr. *Vojtěchovský*). The results of these tests have been published elsewhere. At the clinical department of the Institute of Human Nutrition we administer Benactyzin in the therapy of some gastrointestinal diseases.

Thus we had an opportunity to observe the course of an acute intoxication, which we refer to in the following case history. It was the enormous size of the dose used, fifteen times greater than described in the literature (*Jacobsen* (1955)—90 mg), as well as the fact that to our knowledge it is the only case where psychotic symptoms appeared, which stimulated the communication.

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CASE HISTORY

L.B., a 29 year old married female, a physician by profession, with a sensitive personality, but without previous psychiatric symptoms, during a short period of emotional excitement following some misunderstanding with her husband, consumed almost a teaspoonful of pure Benactyzin. (During the reconstruction of the case it was ascertained by weighing approximately the same amount of the drug, that the patient had consumed about 1300–1400 mg of Benactyzin). It was used solely for its soothing effect without any intention of committing suicide. The course taken by the intoxication, as described by the patient herself and corroborated by her husband and the physician summoned to the case, was as follows: About ten to fifteen minutes after taking the drug the patient became confused, she felt as if she were looking at herself and her surroundings from a distance and as if everything was running away from her. She expected to faint, but remained seated quietly on the sofa. After about twenty minutes she became agitated and leaving her seat walked in a very unstable manner to the bathroom to take a shower. There she noticed in the semi-darkness a pile of laundry lying on the floor, and on top of it she suddenly saw her six months old son. Let us continue in the patient's own words. "I was unable to realize at the time that this could not be true since the baby was actually at home with his grandmother. As I kept looking the baby suddenly turned pale, then yellow, his eye-balls deviated to one side and he appeared to be on the verge of dying. Finally, before my very eyes, he started fading away and disappeared. In a wild attempt to find him I searched among the laundry and then, feeling completely desperate, I ran out to seek an injection for him. My husband prevented me from going out. I accused him of being the cause of our baby's possible death." According to the husband there followed a short struggle and the patient was compelled to remain in the room. What occurred in the next period is covered by amnesia (that is between the twentieth and the fiftieth minute), and it is the husband alone who continues the description of the case as follows. "She showed signs of anxiety and her face held a terrified expression. Her orientation in space was altered, when she tried to seize an object she would miss it by about 20 cm, she would also miss the chair when trying to sit down. She became more and more agitated and repeatedly tried to run into the corridor, even though she was only partly dressed, with the persistent idea of obtaining the injection for saving her child. A short time later, having managed to escape, she was found on another floor, in vain seeking an opening into a wardrobe and talking confusedly about the death of her baby. She was brought back into the room, where she became slightly calmer." The patient is able to continue the description of the events which followed (that is about an hour after the consumption of the drug), as the amnesia was lifted for this period. "I tried to understand that I could not really have seen the baby, since he was not there, but whenever I thought about him the whole situation appeared again very clearly before my eyes and I felt a terrible anxiety. At this time I partly realized that I had only suffered from a hallucination. I tried to focus my mind on my surroundings and the conversation, but my thinking was disrupted and I was unable to integrate individual notions into a logical whole, even though I did partly realize the inadequacy and incoordination of the words I used. I believe I even repeated certain phrases stereotypically."

At this time, that is between the first and second hour of the intoxication, the physician, who had been summoned, noted considerable psychomotor excitation, agitation, inadequate behaviour and inadequate answers to questions and diagnosed

a psychotic state. The patient confessed having taken a large dose of Benactyzin, but resolutely denied any suicidal intention. Her face was flushed and showed signs of crying, her pupils were dilated and she looked terrified, her pulse was 921 min., her blood pressure was not recorded. Caffeine and coramine were applied hypodermically. The patient violently protested against taking the injection saying, "Do not give it to me, but to my son, who is dying." Two hours later, when the physician saw the patient once more, there were still slight signs of psychomotor agitation and emotional instability, but the patient had just experienced a critical attitude towards the hallucination and psychotic state.

In her story the patient describes her feelings during the period between the second and fourth hour after consumption as follows: "After the injection I felt roughly normal. I realized the impossibility of what I had seen, but I still remembered it with a feeling of terror." Her husband observed that she became calmer after the injection, but her speech was still inadequate.

Four hours after taking the drug she became normal, but was very tired and sleeply. An hour later, that is five hours after taking Benactyzin, she was able to ride home on the bus. Then she spent a quiet night, and the following day she was without symptoms.

EPICRISIS

Ten to twenty minutes after consumption of 1300–1400 mg of pure Benactyzin a 29 year old married and mentally healthy female, a physician by profession, showed signs of indisposition, ataxia and derealisation, later there appeared psychomotor excitation and a temporary true optical hallucination showing the horrible image of the death of the patient's baby. This experience led to great anxiety and psychomotor excitation and the whole behaviour was centered on saving the baby. In the period between the twentieth and fiftieth minute of the intoxication the patient passed into a delirious state, wih confused consciousness and followed by amnesia. This stage was characterized by the appearance of a secondary delusion about the death of the child and accompanied by aggressive behaviour motivated by the wish to save him. Thinking was incoherent, there was a feeling of blocking of the thoughts with a strong accentuation on anxiety, agitation and ataxia. The physician who examined the patient some time between the first and second hour after the intoxication, noted a psychotic state with signs of agitation, inadequate answers to questions, and the delusion about the death of her baby. Upon physical examination a flushed face, dilated pupils, and tachycardia were observed. The psychomotor agitation decreased after the application of coramine and coffeine and there arose a critical attitude towards the hallucination and delusion experienced, but the emotional bond to their memory remained. Disorders in thinking stood out foremost (blocking of the thoughts). These were apparent in the form of incoherence and perseveration. Three or four hours later the psychotic state had definitely ceased and was re-

placed by tiredness and sleepiness. After this phase there were no further complications.

DISCUSSION

The toxic dose of Benactyzin has not been ascertained for man. Experiments on the human subject were made impossible by the marked effect of even small doses of the drug upon the central nervous system, as may be observed both clinically and on the electroencephalogram (*Coady & Jewesbury* 1956). After a dose of four to six mg of Benactyzin, the following unfavourable side effects were described: dizziness, apathy, relaxation of the muscles, a dull feeling of the extremities, as if they were not connected with the body, sluggish thinking and lowered attention, decreased reactivity to external stimuli, blocking of the thoughts, derealisation, ataxia. Among the symptoms of disturbance of the vegetative nervous system, it was especially dryness of the mouth and palpations which stood out. The side effects described above occur in about 40 per cent. of the patients treated, causing a marked decrease in the therapeutic value of Benactyzin. The dose used to date never surpassed 90 mg (per single dose) and were never accompanied by qualitative disturbances in thinking or hallucinations or confusion (*Jacobsen* 1955).

The Benactyzin intoxication described above (about 1300 mg) was characterized by a delirious psychotic episode with a brief optical hallucination, followed by a secondary delusion, confusion, and psychotic behaviour. Before and after the delirious state in our case, there were the other side effects commonly described in the literature, namely ataxia, derealisation, and blocking of the thoughts. The atropine-like visceral effects which could be expected after such a large dose of the drug were not felt by the patient herself even though they could be observed to a small extent (tachycardia, flushed face, dilated pupils). The psychotic course of the intoxication could be explained by the specific and quantitative action of Benactyzin upon the central nervous system. While the theme of the psychotic episode might well be understood psychodynamically: a sensitive mother whose main problem of life is the health of her six months old child, the optical hallucination may be the realisation of her fears.

The relatively benign course and short duration of this intoxication and the negligible visceral symptoms which accompanied it, even though the dose taken surpassed therapeutic dosages more than a thousandfold, denote a relatively low toxicity of Benactyzin. On the other hand this case only accentuates the predominative action of this drug on the central nervous system.

SUMMARY

The clinical course of an intoxication by about 1300 mg of Benactyzin characterized by a short benign delirious psychotic state is described.

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Miloš Vojtěchovský, M.D.,
Praha XIV, Budějoviká 800,
Czechoslovakia.

Reprinted from Psychotropic Drugs

THE COMPARISON OF THE PSYCHOTIC EFFECT OF TRYPTAMINE DERIVATIVES WITH THE EFFECTS OF MESCALINE AND LSD-25 IN SELF-EXPERIMENTS

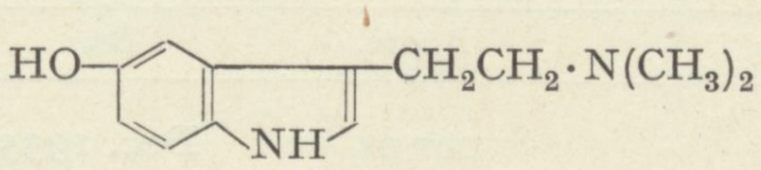
S. SZÁRA

Central State Institute for Nervous and Mental Diseases, Budapest (Hungary);
Forschungsabteilung, Psychiatrische und Nervenklinik der Freien Universität, Berlin (Germany)

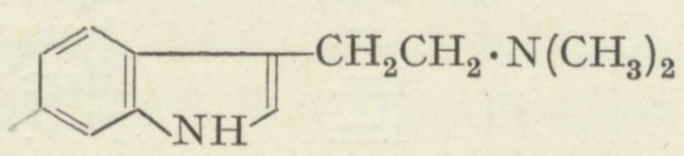
INTRODUCTION

Indolealkylamines have been considered for a long time as a group of active substances of rather slight pharmacological and almost no psychiatric interest. Renewed attention has been focused on them since the discovery of the presence of 5-hydroxytryptamine in blood, in the enterochromaffin cell system, spleen, kidney, and the central and peripheral nervous tissue. An excellent review on the pharmacology of indolealkylamines by ERSPAMER appeared in 1954, and many other reviews have appeared on 5-hydroxytryptamine or serotonin (AMIN *et al.*[1]; FREYBERGER *et al.*[11]; GADDUM *et al.*[12]; HIMWICH[13]; LANGEMANN[17]; PAGE[20]; ROTHLIN). The tryptamine derivatives have been of interest only in connection with their effect on blood pressure. Data on their effect on the central nervous system can be found only sporadically (NIEUWENHUIZEN[18]; SPEETER AND ANTHONY[24]). Our attention towards their possible psychotic action was attracted by the works of FISH, JOHNSON, AND HORNING[9] on *Piptadenia* alkaloids among which they found bufotenine, N,N-dimethyltryptamine, and their N-oxides. In experiments on animal they found these drugs to have psychotic effects, but experiments on humans were made only with bufotenin by FABING. We therefore decided to make self-experiments and experiments on normal volunteers with N,N-dimethyltryptamine and with the N,N-diethyl compound also (Fig. 1).

Bufotenine



DMT



T–9

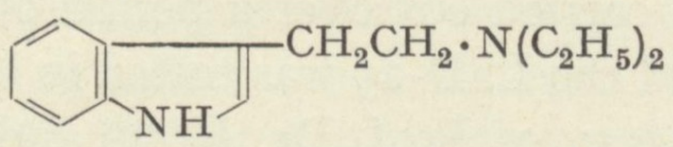


Fig. 1. The chemical constitution of bufotenine, DMT and T-9.

References p. 466.

METHODS AND MATERIALS

The N,N-dimethyltryptamine (DMT) and the N,N-diethyltryptamine (T-9) were obtained synthetically by the method of SPEETER AND ANTHONY.

For the purpose of purification the amines were distilled in high vacuum. For the experiments, sterile aqueous solutions of the hydrochloric salts were prepared and used in a concentration of 30 mg per ml. The lethal doses estimated in white mice by the usual method were 135 mg/kg in the case of DMT, and 120 mg/kg in the case of T-9.

Although the substances have been not very toxic in mice, we were very cautious in the self-experiments.

In the peroral experiments, starting from ¼ mg and increasing the dose up to 150 mg no observable psychic or vegetative effects were found. After the unsuccessful peroral experiments, intramuscular experiments were made. In this titration series other physicians of the Institute of Budapest took part. The doses administered were 10 mg, increasing to 150 mg (*i.e.* 2 mg/kg body weight). Psychotic effects were observed from 30 mg, *i.e.* 0.2 mg/kg body weight; they reached their optimum in doses about 0.7–1.0 mg/kg body weight. On further increasing the doses the psychotic symptoms were suppressed by the vegetative and organic symptoms. Therefore the further experiments on normal volunteers were made with the above-mentioned optimal dose. A detailed paper on the results obtained with normal volunteers, is to appear in *Psychiatria et Neurologica* (SAI-HALÁSZ *et al.*[22]).

THE SELF-EXPERIMENTS

The purpose of this report is to compare the psychotic effect of tryptamine derivatives with the well-known effect of mescaline and lysergic acid diethylamide in self-experiments. I believe that this method of experimentation is one of the best ways of obtaining direct information on subtle psychopathological phenomena, which are of great importance in understanding the schizophrenic syndrome.

TABLE I

THE DATA OF SELF-EXPERIMENTS

Substance	*Dose*	*Admin.*	*Date*	*Place*
I. Mescaline	0.35 g	per os	Dec. 1955	Budapest
II. LSD-25	100 μg	per os	Dec. 1956	Vienna
III. DMT	0.25 mg–150 mg	per os	March–April 1956	Budapest
DMT	75 mg	i.m.	April 1956	Budapest
DMT	60 mg	i.m.	June 1956	Debrecen
DMT	60 mg	i.m.	March 1957	Berlin
IV. T-9	60 mg	i.m.	Nov. 1956	Budapest

The experiments were carried out over a period of 16 months. I took mescaline at Christmas-time 1955, and the LSD-25 was tested in Vienna at the Psychiatric Clinic of the University, by courtesy of Prof. Dr. HOFF and Docent Dr. ARNOLD, in December 1956. The first intramuscular administration of DMT occurred at the end of April 1956, and was followed by the experiments on normal volunteers. We reported

References p. 466.

the results at the Annual Meeting of the Hungarian Physiological Society in Debrecen. During this meeting I made the second intramuscular experiment in order to get an electroencephalographic recording. A third DMT-experiment and some biochemical investigations were made in Berlin at the Research Department of the Psychiatric and Neurologic Clinic of the Free University, by the courtesy of Prof. Dr. SELBACH. The T-9-experiment was made intramuscularly in November 1956 in Budapest.

I shall not go into details about the effects of mescaline and LSD-25 because I am not able to add any new aspects to that well-known picture. Nevertheless, the chief features of these experiments will be mentioned later. At present I shall only describe in more detail the symptoms of DMT and T-9 model psychoses, in view of the lack of such reports in the literature up to now.

(a) The DMT-experiments

As mentioned above, DMT ingested *per os* has no observable effect. But an intramuscular injection of 30 mg could already produce some mydriasis and subjectively some perception disturbances. The larger the dose, the more striking are the symptoms. About the self-experiment made with 1.0 mg/kg, *i.e.* 75 mg DMT in total, I can report the following:

In the third or fourth minute after the injection vegetative symptoms appeared, such as tingling sensation, trembling, slight nausea, mydriasis, elevation of the blood pressure and increase of the pulse rate. At the same time eidetic phenomena, optical illusions, pseudo-hallucinations, and later real hallucinations, appeared. The hallucinations consisted of moving, brilliantly coloured oriental motifs, and later I saw wonderful scenes altering very rapidly. The faces of the people seemed to be masks. My emotional state was elevated sometimes up to euphoria. At the highest point I had compulsive athetoid movements in my left hand. My consciousness was completely filled by hallucinations, and my attention was firmly bound to them; therefore I could not give an account of the events happening around me. After ¾–1 hour the symptoms disappeared, and I was able to describe what had happened.

In the second intramuscular DMT-experiment, the duration in time and the symptoms were mainly the same.

At the third DMT-experiment, the dose was somewhat smaller (60 mg); the symptoms were thus milder, but qualitatively the same.

(b) The T-9-experiment

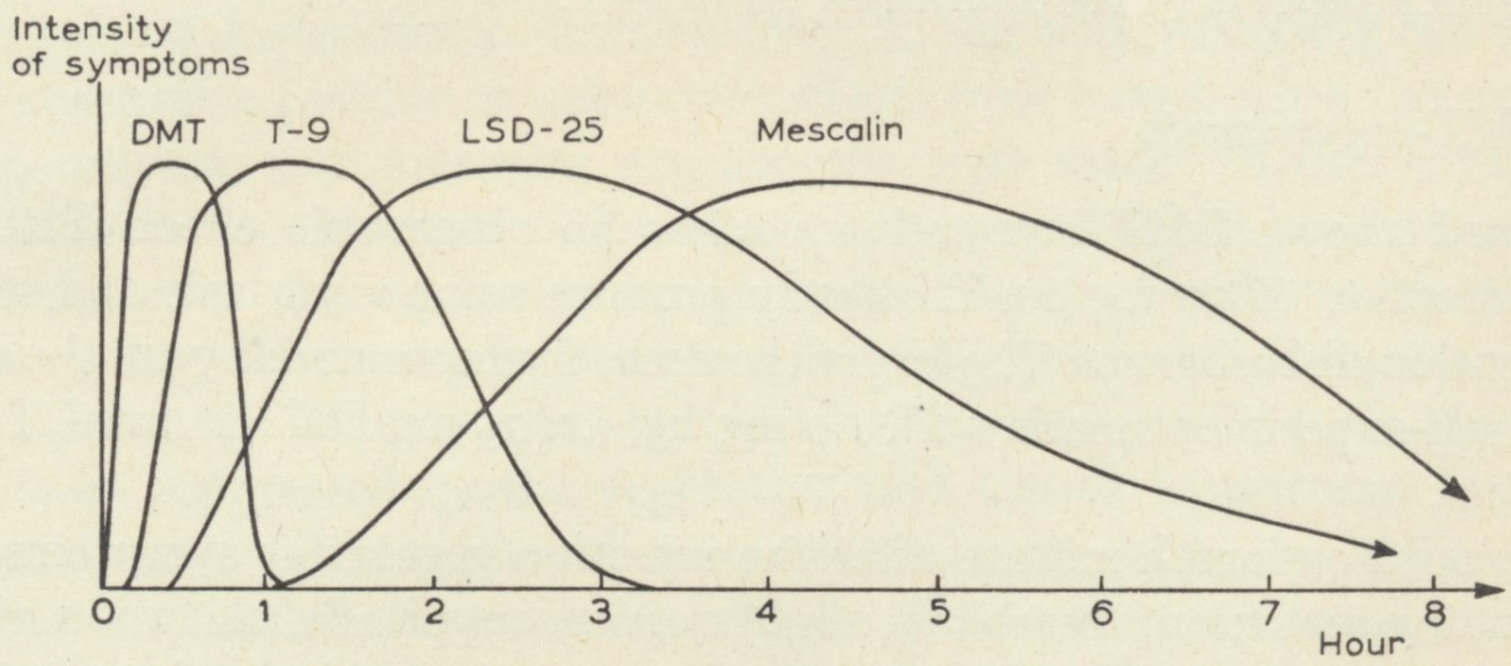
The symptoms of the T-9-experiment are briefly as follows. About 15 minutes after the injection of 60 mg of T-9 came the same vegetative symptoms as described for DMT. The illusions, hallucinations, and the athetoid compulsive movements in the left hand were the same as for DMT. But the alteration of the surrounding world and the emotional reaction to them were strong and impressive. The mask-like faces of the persons, the dream-like mysteriousness of the objects and the room gave me the feelnig that I had arrived in another world, entirely different and queer and full of secrecy and mystery. This wonderful but strange world attracted me at one moment, but the next moment I did not want to accept it. I became perplexed; I did not know what I ought to do. I began to walk anxiously up and down, and said: "I ought to do something, I must!" There was a peculiar double orientation in space

References p. 466.

and time: I knew where I was, but I was inclined to accept this strange world as a reality, too. The dusk of the room was lightened for some minutes, and again the light was switched off, and that seemed to me as if this period might be an entire epoch, filled with events and happenings, but at same time I knew that only several minutes had passed.

(c) *The comparison of the results*

I should like to compare the effects of the two tryptamine derivatives outlined above with the effect of mescaline and LSD-25. The most outstanding differences can be established in their time of duration.



Flg. 2. Schematic course of the self-experiments.

In Fig. 2 it can be seen that the duration of the DMT-induced model psychosis is about one hour, that of T-9 is about three hours, while the LSD- and mescaline symptoms lasted for 8–10 hours. The onset of the symptoms in the case of tryptamine derivatives is essentially quicker than the onset of the others. The elevation of the dose of DMT did not produce a longer state of intoxication, but the symptoms were more organic. It is remarkable that in all the four model psychoses the symptoms developed and passed away in wave form.

The special symptoms are demonstrated in Table II.

TABLE II

THE MAIN SYMPTOMS OBSERVED IN SELF-EXPERIMENTS

Symptoms	*Mescaline*	*LSD-25*	*DMT*	*T-9*
1. Vegetative symptoms	Preceded the other symptoms		Coincided with the other symptoms	
2. Athetoid movements	—	—	+	+
3. Illusions	++	++	+++	+++
4. Hallucinations	—	—	++	+
5. Disturbances of				
a. spatial perception	+++	+++	+++	+++
b. time perception	+	+	+	+++
6. Bodily sensations	+	+++	+	+
7. Depersonalisation	++	+ ++	+	+++
8. Emotional reaction				
a. euphory	+	—	++	+++
b. anxiety	—	++	—	+
9. Autism	—	—	—	+++
10. Language changes	—	+	+++	+

References p. 466.

As can be seen, the different symptoms were not equally apparent in every case.

(1) The vegetative symptoms in mescaline and LSD-25 preceded the other symptoms, while in the case of the tryptamine derivatives the sensory disturbances appeared as early as the vegetative symptoms began.

(2) An interesting phenomenon observed only in the tryptamine derivatives was the appearance of athetoid, choreiform compulsive movements. As far as I know, these symptoms have not yet been described in the case of other hallucinogenic substances.

(3) The perceptional disturbances are qualitatively the same for all the substances; only quantitative differences could be observed.

(4) The emotional reactions, however, were qualitatively different, *viz.* my reaction to mescaline and DMT was euphoric, to the LSD-25 anxious, but in the case of T-9 euphoria and anxiety alternated. These phenomena, together with the severe autism and the above-mentioned ambivalency were observed only in T-9. However, it is well-known from the literature that it can occur in the case of mescalnie and LSD-25 also (HUXLEY[14], SOLMS[23]).

The comparison shows that the structure of a model psychosis, which can be considered as a form of the acute exogen reaction type (BONHOEFFER), depends on the chemical structure of the causative agent, apart from the fact that absorption, metabolic and excretion processes may determine the course in time.

BIOCHEMICAL INVESTIGATIONS

The rapid onset and the short duration of the symptoms in the DMT-induced state is very interesting from a biochemical point of view, and it is probably connected with the rapid metabolism of DMT (FISH *et al.*).

We know from the investigation of ERSPAMER[6] that in rats the main breakdown product of DMT is 3-indolylacetic acid (3-IAA) which is excreted in the urine partly in free form, but largely bound to glycocol as indolaceturic acid. We investigated the excreted indole derivatives in the human volunteers chromatographically and photometrically, and obtained the same results as ERSPAMER (SZÁRA[25]). In addition, an interesting phenomenon was observed (Table III). We found in the urine after a larger dose of DMT more 5-hydroxyindolylacetic acid (5-HIAA) excreted than was normally present. Unchanged DMT was not estimated in the urine extracts. These data suggested

TABLE III

THE APPROXIMATE AMOUNT OF TOTAL 5-HIAA EXCRETED IN A 6 h PERIOD BEFORE AND AFTER THE DMT EXPERIMENT

No.	*Dose of DMT*	*Amount of 5-HIAA**	
		after expt.	*before expt.*
1	150 mg	1.0 mg	3.0 mg
2	150 mg	1.2 mg	3.0 mg
3**	75 mg	1.5 mg	1.2 mg
4**	60 mg	2.0 mg	1.5 mg

* Estimated by two-dimensional chromatography, developed with *p*-dimethylamino-benzaldehyde, and the eluted spots measured colorimetrically.

** Self-experiments.

References p. 466.

that the DMT is very rapidly metabolized, and perhaps displays its effects by means of serotonin. In order to obtain more information about the relationship in the blood, I made an experiment with 60 mg DMT. The extracts of 15 ml blood taken before, and 10, 30 and 90 minutes after the experiment, were chromatographically investigated, and I found qualitatively only two indol derivatives, namely tryptophan and 3-IAA, but no serotonin 5-HIAA or unchanged DMT could be demonstrated. The 3-IAA level of the blood was elevated in the 10th and 30th minute (Fig. 3).

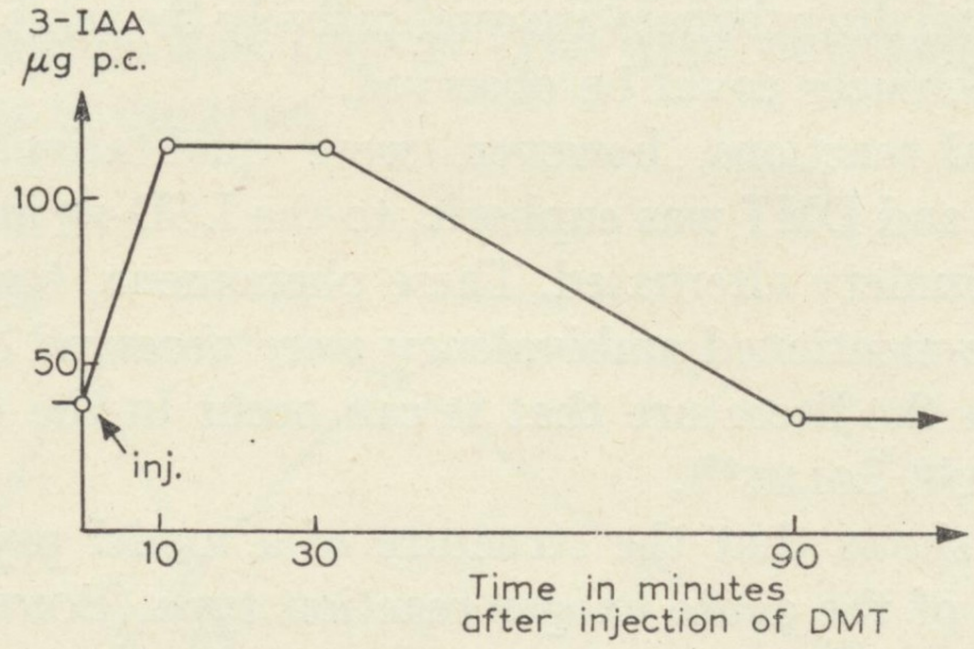


Fig. 3. The 3-IAA level of blood during the DMT experiment.

This finding did not support the presumption that serotonin plays a role in the psychotic effect of tryptamine derivatives. The evidence, however, is not sufficient to allow one to draw definite conclusions in this respect.

DISCUSSION

In discussing the mechanism of action of tryptamine derivatives, it must be admitted that at present there is no definite knowledge about the biochemical mechanism of action. The clinical picture, however, taking the other experiments on normal volunteers also into consideration, enables us to give some information concerning this mechanism.

The rapid onset of the psychotic symptoms makes it seem probable that DMT affects directly those brain structures that are affected indirectly by LSD and mescaline (BLOCK[2]). The appearance of choreiform athetoid movements is possibly due to an effect on structures other than those affected by LSD or mescaline. The tryptamine derivatives seem to be the first hallucinogenic substances to cause athetoid movements, and should therefore provide a new tool for investigating experimentally the exact mechanism of this phenomenon.

Unfortunately, I have not enough time to develop in detail the very interesting psychopathological symptoms of T-9, which reminded me of the conception of the "schizophrene Grundstimmung", described by WYRSCH[27].

It is, however, very remarkable that tryptamine derivatives without the OH-group in the 5-position are able to produce mental phenomena. As UDENFRIEND *et al.* demonstrated in animal tissues, there is no enzyme that could decarboxylate tryptophan to produce tryptamine; it is assumed therefore that only the enteral bacteria can produce this substance.

References p. 466.

There is a possibility that from this tryptamine the schizophrenic organism may produce hallucinogenic substances in the wrong way enzymically. It is noteworthy that Prof. BUSCAINO and his team[4] recently presented evidence of a disturbance in the indole metabolism in schizophrenia. Further work in this field would be desirable.

SUMMARY

The psychotic effects of N,N-dimethyltryptamine (DMT) and N,N-diethyltryptamine (T-9) have been compared with the effects of mescaline and LSD-25.

The most outstanding features of DMT model psychosis are the rapid onset and the short duration of the symptoms. This may indicate a different mechanism of action from that of LSD and mescaline.

New symptoms appearing with both tryptamine derivatives are the choreiform athetoid movements. This phenomon could be a new tool for investigating experimentally the mechanism of the extrapyramidal compulsive movements.

The psychotic effects of tryptamine derivatives supports the aminotoxic and indole theory of schizophrenia.

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DISCUSSION

A. SAI-HALÁSZ, *Istituto Centrale per le malattie Nervose e Mentali, Budapest (Ungheria)*

Il collega SZÁRA ha avuto occasione stamane di parlare in dettaglio sugli esperimenti fatti con me con la dimetiltriptamina in soggetti normali. Ora vorrei richiamare l'attenzione soltanto su un fenomeno, che mi sembra assai interessante dal punto di vista clinico. Su 30 persone esaminate 22, cioè il 73% avevano sintomi semilateralizzati: le illusioni e le allucinazioni, i disturbi dello schema corporeo e dello spazio, i movimenti atetosici ed anche i segni di lesioni piramidali prevalevano a

sinistra. Questa differenza era netta. Per esempio un soggetto sperimentale guardando la mano sinistra diceva che essa non gli apparteneva più, aveva cambiato forma ed era divenuta luminosa e bellissima; guardando invece la mano destra, diceva che non presentava nulla di straordinario. Abbiamo sperimentato su tre persone mancine, e in questa i fenomeni prevalevano alla parte destra. Si dovrebbe concludere che la dimetiltriptamina produce una lesione semilateralizzata dell'emisfero non dominante del cervello.

Questo fenomeno finora non segnalato dalla letteratura per gli altri farmaci psicotropi ci propone due questioni:

(1) La prima sarebbe la seguente: come si può immaginare, che una sostanza chimica abbia un effetto nocivo molto più forte sull'emisfero cerebrale non dominante? Sappiamo al contrario, che è appunto l'emisfero dominante il più sensibile, specialmente se danneggiato nel sistema vascolare.

(2) La seconda domanda è di carattere psicopatologico. Si tratta cioè di sapere se questa semilateralizzazione ci può dire qualcosa sugli aspetti delle psicosi sperimentali. HOFF e PÖTZL hanno già dimostrato collo "Zeitrafferphänomen", che lesioni organiche dell'emisfero non dominante possono produrre fenomeni psicopatologici molto strani. Lo "Zeitrafferphänomen" è stato descritto già da BERINGER nel corso di psicosi sperimentali mescaliniche. Secondo la nostra opinione sarebbe di grande interesse studiare ancora le psicosi sperimentali già conosciute, al fine di evidenziare se ci sono differenze fra le due parti del corpo. Ci pare probabile, che questo fenomeno non sia un effetto solo della dimetiltriptamina. Ad ogni modo, conoscendo i fatti suddetti, noi possediamo ora una nuova sostanza per aiutarci a conoscere meglio i problemi dell'emisfero cerebrale non dominante.

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Psychotropic Drugs

Effects of psychomimetic drugs on cerebral synapses

The psychomimetic drugs allow us to elicit at will a limited, reversible, mental derangement in man and a related distorted behavioral pattern in animals. They can therefore be highly potent tools equally for the physiologist, the behaviorist, and the experimental psychiatrist. The tremendous versatility of the brain is nonetheless the manifestation of activity in a finite number of structures and of mechanisms relating them. It follows, therefore, that the multiple patterns that add up to biological behavior must share in part the available mechanisms. It is by virtue of this probability, rather than because of any exact or fancied resemblance to the clinical conditions, that the study of chemical or so-called model psychoses and the agents producing them can be expected to be fruitful.

To the physiologist this suggests the need for identification of the underlying unitary processes involved; to the behaviorist, the identification of the combinations constituting known behavior patterns; and to the experimental psychiatrist, the comparison of natural and induced psychoses. All can profitably use drugs as tools for analysis. The clinician, furthermore, can convert these findings into tools for diagnosis and the means for therapy.

The high vulnerability of synapses to chemical influences makes them a natural focus of inquiry. We have utilized the synapses of the optic cortex of the cat (lightly anesthetized with sodium pentobarbital) activated by transcallosal impulses initiated in one cortex and evoking post-synaptic impulses recorded at the symmetrical point in the opposite cortex. This has proved a very convenient preparation and the data are representative of a variety of cerebral synapses, including cortical, subcortical and medullary synapses[1]. By intracarotid injection we achieve an active concentration of the drug or chemical in the ipsilateral hemisphere with sufficient dilution on entry into the systemic blood stream to obviate peripheral effects. The ipsilateral recording electrode simultaneously monitors the input and output of the terminal synapses in the system, which is submaximally activated every two seconds.

In this way we have established that synaptic transmission is under the control of a delicate chemical equilibrium between cholinergic excitation reciprocating with adrenergic inhibition. It is then evident that a disturbance of this equilibrium would lead to abnormal synaptic transmission, resulting in disturbed cerebral and mental function.

Among the synaptic inhibitors naturally found in the mammalian brain are adrenaline, noradrenaline, and serotonin. The last is by far the most powerful[3]. Substances with a chemical similarity to these become candidates for the role of psychomimetic drugs. Such is indeed the case with mescaline, adrenochrome, adrenolutin, lysergic acid diethylamide (LSD-25) and bufotenine. Mescaline is closely related chemically to adrenaline, which on oxidation is converted initially to the indole, adrenochrome. Adrenolutin is a minor modification of adrenochrome. Serotonin and dimethyl-serotonin, or bufotenine, are indoles, and LSD-25 can be regarded as built on an indole nucleus. It strengthens the argument, therefore, that we find all of these to be synaptic inhibitors[3 4]. Furthermore, their ranking as synaptic inhibitors parallels the ranking as to psychomimetic potency in man.

The agreement between data from the anesthetized cat and the human encouraged us to believe and test that tranquilizers, reported to be clinically effective in partially offsetting mental disturbance, would have a predictable action on synaptic inhibition by psychomimetic agents. If the synaptic inhibition so produced were truly instrumental in bringing about psychotic behavior, then the improvement of such behavior that is observed clinically might be due to antagonizing of an endogenous chemical corresponding to the exogenous psychomimetic drugs.

This, indeed, turns out to be the case. The prophylactic administration of chlorpromazine, promazine, reserpine, and azacyclonol, in doses having no effect *per se* on synaptic transmission, prevents or reduces the synaptic inhibitory action of the psychomimetic drugs[2].

Overdoses of tranquilizers clinically produce toxic phenomena, some of them taking the form of depression, and even psychosis. Likewise, large doses of the tranquilizers produce a depression of synaptic transmission indistinguishable from synaptic inhibition. Characteristically, the tranquilizers exercise their clinical effect without a corresponding degree of depression. This is reflected in the ratio of depressant to prophylactic dose, or "synaptic safety margin". This safety margin is nonexistent for phenobarbital, equals 2 for reserpine, 10 for promazine and 20 for chlorpromazine and

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EXPERIMENTAL PSYCHIATRY
HILLSIDE HOSPITAL
APR 30 959

azacyclonol. The above data suggest the hypothesis that synaptic inhibition is one of the mechanisms responsible for some forms of mental disturbance. A perversion of metabolism resulting either in an excess of endogenous inhibitory substance or an excess susceptibility of the neurons upon which it acts, would result in abnormal patterns of activity whose variety would be determined by varying thresholds and, in particular, by abnormal inhibition interrupting normal control, and thereby releasing more primitive and less adaptive —perhaps subcortical—patterns of activity.

Such conceptions emphasize the role of naturally occurring inhibitory indoles in mammalian brain. Of these, serotonin is highly active, dimethyl-serotonin or bufotenine is twice as active as serotonin, while adrenaline and adrenolutin are relatively weak inhibitors. Psychotic manifestations have been clearly described for all but serotonin, whose powerful peripheral disturbing actions seriously obscure the picture when it is introduced by the usual routes. For this reason we are testing the effects of intracarotid serotonin injections in man.

The importance of serotonin has caused us to extend our original observations of its cerebral synaptic inhibitory action with experiments designed to record the action of "*in situ* serotonin". This is accomplished by the use of iproniazid, the inhibitor of monoamine oxidase (MAO), the enzyme responsible for the destruction of serotonin. With intracarotid injections of iproniazid we can reproduce the cortical action of serotonin and show that, at the height of the synaptic inhibition, the MAO titer on the inhibited side is, in fact, lower than on the control side; as would be expected if iproniazid is exercising its action by inhibiting MAO and, consequently, accumulating natural serotonin at the synapses.

Following the reasoning already outlined, we again assessed the pertinence of the data to possible clinical significance by testing the action of tranquilizers against serotonin. We find that the tranquilizers exercise a prophylactic or preventive action against the inhibitory effects of serotonin in the same way that they antagonize psychomimetic drugs.

A comparison of the cerebral synaptic action of psychomimetic drugs with that of naturally occurring cerebral synaptic inhibitors and their modification by tranquilizers produces data consistent with the hypothesis that a disturbance of synaptic equilibrium—in this case, by a preponderance of inhibitory effectiveness—is a potential mechanism for some kinds of mental disturbance, and that therapeutic results could be anticipated by various means of preventing or annulling this effect. The opposite kind of disturbance or a preponderance of excitatory effectiveness seems also plausible. The prevention or annulling of this deviation in synaptic equilibrium would require different measures. The effectiveness of different tranquilizers and varying therapeutic measures might be expected to become diagnostic criteria.

Veterans Administration Research Laboratories in Neuropsychiatry, V. A. Hospital, Pittsburgh, Pa. U.S.A. AMEDEO S. MARRAZZI

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EXPERIMENTAL PSYCHIATRY
HILLSIDE HOSPITAL
GLEN OAKS, N. Y.

Chemical aspects of Psilocybin, a psychotropic principle from the Mexican fungus, Psilocybe mexicana HEIM.

by A.Hofmann, Basle

Summary

The psychotropic active principle of Psilocybe mexicana Heim has been isolated in crystalline form. This fungus is one of the so-called magic or sacred Mexican mushrooms used since precolumbian times by the indians of Mexico during religeous ceremonies and also by soothsayers to acquire clairvoyance.

Psilocybin forms white crystals which are fairly soluble in water, but practically unsoluble in most organic solvents. Analysis, spectra and colour reactions indicated that it is a substituted indole derivative containing phosphorus. Degradation studies showed that psilocybin is a phosphorylated derivative of tryptamine.

The special structural features of psilocybin are discussed and compared with the chemical constitution of other naturally occurring indole derivatives (serotonin, bufotenin, LSD, etc.).

Pharmacology of Psilocybin.

by A.Cerletti, Basle

The results of the pharmacological analysis of this new tryptamine derivative can be summarized in the following way: In the unanesthetized animal the drug produces central autonomic effects (mydriasis, slight hyperthermia etc.) without any motor excitation. On the contrary - by increasing the doses a reduction of spontaneous motor activity has been observed in mice, rabbits and monkeys. The EEG-pattern of curarized rabbits shows after Psilocybin a regular 4-5 rhythm with disappearence of spindle activity and slower waves. Both mono- and polysynaptic reflexes in the intact and spinal cat are enhanced by the smallest effective doses of Psilocybin. Similarly the reaction time of mice in the hot plate test is shortened by Psilocybin both in the normal as well as in the morphine pretreated animal. The circulatory reactions differ according to the species: Dogs show a moderate but prolonged fall of the blood pressure and tachycardia, whereas the cat reacts with a transitory pressure rise and bradycardia. Marked constriction of the nictitating membrane is a regular observation in the anesthetized cat. In contrast to the many effects observed in vivo, and which mostly can be attributed to central autonomic stimulation, the study of Psilocybin on a variety of isolated organs shows only little activity of the drug on peripheral structures.

Psychoses, Poorly Understood By

Mccaughan —

Dempf, GB

Horder, NE

Edreira, JG

Baltzan, A

Res. Sr.

Col. Graduate Med Hosp

NEJ Med 256 — 735-742

Age 57

Invesne

PSYCHOSIS AND TREMOR DUE TO MECAMYLAMINE

M. HARINGTON
M.B. Cantab., M.R.C.P.
SENIOR REGISTRAR AND MEDICAL TUTOR
PRISCILLA KINCAID-SMITH
M.B. W'srand, M.R.C.P., D.C.P.
REGISTRAR
DEPARTMENT OF MEDICINE, POSTGRADUATE MEDICAL SCHOOL OF LONDON

MECAMYLAMINE as a ganglion-blocking agent for treating hypertension was introduced two years ago (Freis 1955, Ford et al. 1955), and since then it has been widely used in clinical practice, its chief advantage being that it is fully and regularly absorbed when given by mouth. It produces the same side-effects, due to blockade of the parasympathetic system, as do other ganglion-blocking drugs, but in addition reports have been published in America indicating that mecamylamine may also have a toxic action on the central nervous system (Schneckloth et al, 1956, Deming et al. 1957).

We describe here four patients in whom tremor and mental disturbance, with confusion and hallucinations, developed while they were receiving mecamylamine, and we suggest that this may be a not uncommon complication of treatment with mecamylamine given in large dosage.

Case-reports

Case 1.—A man, aged 55, was first seen in July, 1955, complaining of headaches. He had two years' history of high blood-pressure and fifteen years' history of gout. Although intelligent, he was unstable and did not follow any regular occupation.

On examination his blood-pressure was 230/140 mm. Hg; he had numerous retinal hæmorrhages and exudates; his urine contained a trace of albumin and could be concentrated to 1·020; and his blood-urea level was 30 mg. per 100 ml.

Treatment.—Benign essential hypertension having been diagnosed, he was treated with subcutaneous pentolinium, to which reserpine 0·1 mg. thrice daily was later added. This regime reduced his blood-pressure, and his fundi considerably improved.

Mecamylamine therapy.—In July, 1956, mecamylamine was substituted for the pentolinium, 20 mg. thrice daily being necessary to keep the blood-pressure down to 140/80 mm. Hg, with the patient in the erect position, for the greater part of the day. This dosage, however, caused troublesome side-effects, at first principally constipation, but later difficulty in micturition associated with frequency.

Readmission.—In February, 1957, retention of urine developed and the patient was readmitted to hospital. His blood-urea level was now 60 mg. per 100 ml., rising after ten days to 72 mg. per 100 ml.; he had a urinary infection, which was treated with tetracycline. Soon after admission his requirement for mecamylamine fell: the dosage was reduced from 60 to 30 mg. daily, and his blood-pressure was maintained at 110/70 mm. Hg with the patient in the upright position.

Mental and nervous symptoms.—On Feb. 19, 1957, he had a tremor of the hands. All hypotensive treatment was stopped, but next day the tremor had increased and he became mentally confused. Two days later his condition had deteriorated further: he had a coarse generalised shaking affecting his whole body, present at rest, and accentuated on attempting any voluntary movement. His speech was slurred and jerky. There was a general increase in muscular tone and in the deep reflexes; the plantar responses remained flexor. He was completely disoriented in both space and time and had vivid frightening hallucinations. His extreme restlessness and picking at the bedclothes suggested alcoholic delirium tremens. From time to time he had lucid intervals during which he had considerable insight into his condition. Repeated large oral doses (10–15 ml.) of paraldehyde subdued the tremor and relieved the hallucinations for three to four hours at a time.

This striking clinical picture persisted for a week and then gradually subsided. By March, twelve days after the mecamylamine treatment had been stopped, the hallucinations had disappeared and the patient's mental state had returned to normal. He could now remember in detail what had happened during his delirium. Slight tremor persisted for a further two days before finally clearing. During this period he had been treated with subcutaneous pentolinium because his blood-pressure had risen after the cessation of hypotensive therapy; but it was difficult to keep his blood-pressure down, because he was confined to bed. He was discharged from hospital on March 14, 1957, taking two injections of pentolinium daily; his blood-urea level had fallen to 38 mg. per 100 ml.

Readmission.—Four months later he was readmitted with uræmia and left ventricular failure and died in five days.

Necropsy

There was atheroma of the blood-vessels at the base of the brain; the gyri were flattened, but no localised abnormality was found on section of the brain. The kidneys showed lesions of malignant nephrosclerosis.

Case 2.—A woman, aged 65, was admitted to hospital in July, 1956, with left ventricular failure. She had eight weeks' history of exertional dyspnœa. Her blood-pressure was 300/160 mm. Hg, and she had hæmorrhages and soft exudates in her fundi. Her blood-urea level was 30 mg. per 100 ml. She was treated with digitalis, mersalyl, and hypotensives—at first subcutaneous pentolinium and later oral mecamylamine. When first seen at Hammersmith Hospital in September, 1956, she was very much improved symptomatically, but her blood-pressure was 200/130 mm. Hg, and the dosage of mecamylamine was increased from 12·5 to 20 mg. twice daily. In October the dosage was further increased to 45 mg. daily; but, although this dosage did not control the hypertension, urinary retention developed and she was admitted to hospital on Oct. 29, 1956.

On admission she was cooperative and well oriented but somewhat apprehensive and overexcitable. Her blood-pressure was 290/140 mm. Hg, and soft exudates but no papillœdema were noted in her fundi. There was no sign of heart-failure. Her urine contained albumin, and her blood-urea level was 66 mg. per 100 ml. Mecamylamine therapy was continued, the dosage being slowly increased until on Nov. 6, 1956, she was having 65 mg. daily. Her systolic blood-pressure remained about 200 mm. Hg.

Mental and nervous symptoms.—In the early hours of Nov. 11, 1956, she became agitated and confused, having hallucinations of voices and complaining of noises in the head. Her blood-pressure was 170/90 mm. Hg. She had general hyperreflexia.

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During the succeeding days her confusion increased, and she was disoriented for most of the time but had intervals of insight and cooperation. Mecamylamine therapy was stopped on Nov. 13. On Nov. 17 she was grossly confused and hallucinated, with paranoid delusions. She also had a coarse tremor of arms and legs. Her blood-urea level had risen to 97 mg. per 100 ml. on Nov. 17 and to 140 mg. per 100 ml. on Nov. 20. She became more agitated and violent and was completely inaccessible. On Nov. 21 her condition made it necessary to transfer her to a mental observation ward. She went progressively downhill, her blood-urea level rose to 296 mg. per 100 ml., and she died on Nov. 30, 1956, without any improvement in her mental state.

Necropsy

The left kidney was small (55 g.) with generalised ischæmic atrophy suggesting occlusion of the renal artery. The right kidney weighed 110 g., and its histology was that of florid malignant nephrosclerosis. The brain showed a small area of softening in the right internal capsule, and the cerebral arteries were considerably affected by atheroma.

Case 3.—An electrical engineer, aged 53, was found in January, 1956, to have a blood-pressure of 240/140 mm. Hg, bilateral papillœdema, heavy albuminuria, and a blood-urea level of 40 mg. per 100 ml. Malignant essential hypertension was diagnosed, and he was treated with subcutaneous pentolinium and with rauwolfia alkaloids; but his blood-pressure was difficult to control, and during the next six months further deterioration in the fundi and increasing cardiac enlargement were noted.

On admission to Hammersmith Hospital in July, 1956, he had heart-failure, blood-pressure 260/140 mm. Hg, bilateral papillœdema, hæmorrhages and exudates in his fundi, and albuminuria. His blood-urea level was 139 mg. per 100 ml.

Treatment with subcutaneous pentolinium was continued, a dosage of 30–40 mg. twice daily being necessary to control his blood-pressure. Rauwolfia was not given. Chlorpromazine 50 mg. thrice daily was given because of vomiting. After a month the heart-failure had cleared and the blood-urea level fallen to 60 mg. per 100 ml.

Mecamylamine therapy.—On Sept. 10, 1956, mecamylamine therapy was started, and pentolinium was withdrawn gradually during the next few days. The blood-pressure was not satisfactorily controlled during the period of transfer, but by Sept. 17 it was down to 140/80 mm. Hg, with the patient in the erect position, for most of the day. This was achieved with a dosage of 20 mg. mecamylamine thrice daily. By now the blood-urea level had risen again to 100 mg. per 100 ml. The fundi still showed papillœdema, but there were no fresh exudates or hæmorrhages.

Mental and nervous symptoms.—On Sept. 24, 1956, shaking of the limbs and trunk was first noted. This tremor also affected the face and tongue; it was coarse and present at rest but exaggerated on voluntary movement. The speech was jerky and difficult to understand. There was a general increase in muscular tone; the tendon-reflexes were exaggerated, and knee and ankle clonus could be elicited; the plantar responses were flexor. Mecamylamine was withheld after it had been taken for fourteen days, and pentolinium therapy was restarted; but the tremor increased, and four days later the patient became drowsy and confused. He was now disoriented and hallucinated, speaking to imaginary people and seeing snakes and insects crawling across his bedclothes. His body shook so violently as to rock the whole bed. Paraldehyde reduced the tremor somewhat, but he remained confused and steadily deteriorated. His blood-urea level rose to 170 mg. per 100 ml., his urinary output fell, and he died, after repeated attacks of left ventricular failure, on Oct. 7, 1956.

Necropsy

The brain was overweight (1490 g.) and œdematous, with a small area of recent softening at the posterior end of the putamen on each side and a recent small hæmorrhage in the mid-pons. The kidneys were typical of malignant nephrosclerosis.

Case 4.—An electrician's mate, aged 46, presented in January, 1956, with four months' history of blurring of vision and dyspnœa. His blood-pressure was 250/150 mm. Hg and he had bilateral papillœdema with scattered retinal hæmorrhages. His urine contained albumin, granular casts, and occasional leucocytes; his blood-urea level was 155 mg. per 100 ml. There was no history to suggest previous renal disease. In view of his visual symptoms hypotensive therapy was considered advisable, in spite of the severe renal failure, and treatment was started with subcutaneous pentolinium. At the end of February his blood-urea level was 222 mg. per 100 ml.

Mecamylamine therapy.—At this stage he was given oral mecamylamine. He was not very sensitive to it, 60 mg. in divided doses daily being needed to keep his blood-pressure down to 160/100 mm. Hg. On April 14, 1956, six weeks after mecamylamine therapy had been started, he was readmitted to hospital with increasing trembling of his arms and legs for the previous three days. On admission his blood-pressure was 160/90 mm. Hg. He still had bilateral papillœdema. He was dyspnœic, and his jugular venous pressure was raised.

Mental and nervous symptoms.—He was drowsy and mentally confused. He had occasional spontaneous quivering of his lips and a coarse irregular tremor of his limbs. His muscular tone was increased; his lower limbs showed almost cogwheel rigidity. His tendon-reflexes were uniformly increased, and he had bilateral ankle clonus. His plantar responses were flexor. Hypotensive therapy was stopped, and he was treated only with digoxin, but the confusion and tremor persisted, and he died on April 16, 1956.

Necropsy

The kidneys showed the changes of malignant nephrosclerosis. The brain showed cerebral œdema, but no localised lesion or other abnormality.

Discussion

The clinical picture was similar in each of these four patients. In three the first neurological abnormality to be noted was a coarse tremor which affected the trunk and head as well as the limbs and caused difficulty with speech. It was variable in the early stages, perhaps hardly noticeable when a limb was at rest, but brought out when voluntary movement was attempted. The shaking of the trunk made it look as if the patient was shivering. The tremor was equally present on both sides of the body. At its height it was so violent in two patients as to shake the whole bed. Mental symptoms were observed before the tremor in one patient, but in the others a few days after the tremor. They consisted of a clouding of consciousness with confusion and disorientation, together, in three cases, with hallucinations which were usually visual but sometimes also of hearing or of touch. The mental state fluctuated, and there were lucid intervals, with some insight, between periods of extreme delirium. Both tremor and mental symptoms were alleviated temporarily by administration of paraldehyde, in case 1 strikingly so. In this patient, who recovered from the episode, the mental abnormalities disappeared first, the tremor persisting for a few days before finally clearing.

Examination of the nervous system in these patients revealed a general increase in muscle tone, symmetrically exaggerated tendon-reflexes with clonus, and flexor plantar responses. In no case were any lateralising signs found. Electroencephalography in three cases gave records which were difficult to interpret because of artefact due to muscle tremor; there was complete absence of alpha rhythm, but in no case was positive evidence found

either of a general metabolic disturbance or of a localised lesion.

The patients all had severe hypertension. In two this was frankly malignant, with papillœdema; in the other two the presence of active retinitis and progressive renal failure indicated that the hypertension was in a premalignant phase, and at necropsy lesions of malignant nephrosclerosis were found in the kidneys. Renal function was impaired in all. In three there was gross renal failure with a raised blood-urea level which continued to rise until death; in case 1, who already had some renal impairment, shown by a failure of concentrating power, but who had a normal blood-urea level, there was a further deterioration in renal function and a temporary rise in the blood-urea level coincident with a urinary infection. This patient's blood-urea level had returned to normal by the time that his neurological symptoms had cleared, but it rose again later, and uræmia was present at his death four months afterwards.

All four patients were receiving large dosages of mecamylamine (60–65 mg. daily) because smaller amounts had not reduced the blood-pressure. The duration of administration of mecamylamine before neurological symptoms developed varied from seven months in case 1 to fourteen days in case 3. Case 1 had the least impairment of renal function.

Since cerebral arterial disease is common in hypertensive patients, the question arises whether organic brain damage due to hæmorrhage or to infarction could have caused the symptoms observed. Evidence of local cerebral lesions was found at necropsy in two cases: in the right internal capsule in one case; and in both basal ganglia and the pons in the other. The whole clinical picture, however, was more like a toxic confusional reaction, bearing in its fully developed state a striking resemblance to alcoholic delirium tremens. The symmetry of the tremor, the absence of any lateralising signs in the central nervous system, and particularly the complete disappearance of symptoms in case 1 after mecamylamine had been withheld suggest strongly that this drug was to blame. In the patients who did not recover, uræmia and death supervened probably before sufficient time had elapsed to allow the mecamylamine to be cleared from the body.

Mecamylamine is a secondary amine and freely diffusible across cell membranes. There is evidence that this drug is concentrated within the cell (Milne et al. 1957). It is therefore likely that its mode of action differs from that of ganglion-blocking agents such as hexamethonium and pentolinium, which are quaternary ammonium compounds and are distributed only in the extracellular fluid. That mecamylamine has a different, and previously unrecognised, mode of action at the neuromuscular junction has been shown by Bennett et al. (1957). From this it might also be expected that mecamylamine, apart from producing the same side-effects due to parasympathetic blockade as other ganglion-blocking drugs, might also have toxic actions from which methonium compounds are strikingly free. There is some experimental evidence of a direct toxic action on the central nervous system. Rats given mecamylamine in large doses develop a tremor and have generalised convulsions before death (Milne et al. 1957).

The frequency of this complication of treatment is not certain. Doyle et al. (1956), Smirk and McQueen (1957) and Kitchin et al. (1957), in their accounts of clinical experience with mecamylamine, do not mention any neurological symptoms related to its administration. The four cases described here occurred among ninety patients treated with mecamylamine at this hospital (twenty of them with malignant hypertension). The average daily dosage of mecamylamine in the whole series, however, was only 35 mg., and only sixteen patients received more than 50 mg. daily. Moreover, this is a selected group of patients, including some with severe hypertension who were specially referred.

In addition to the cases described in detail above, three other patients treated with mecamylamine developed a tremor without mental symptoms: a woman, aged 31, with malignant hypertension and systemic lupus erythematosus and a woman, aged 51, with malignant hypertension and renal-vein thrombosis, both with moderate impairment of renal function (blood-urea level 40–70 mg. per 100 ml.); and a man, aged 51, with malignant essential hypertension and uræmia (blood-urea level 114 mg. per 100 ml.). The daily dosage of mecamylamine in these patients was 25, 50, and 30 mg. respectively. In the two women the tremor disappeared when the dosage of mecamylamine was reduced and pentolinium was partly or wholly substituted. It certainly seems that patients with severely impaired renal function are much more likely to develop symptoms of neurotoxicity while taking mecamylamine: of five patients in whom the blood-urea level was 100 mg. per 100 ml. or higher at the start of treatment four developed tremor and three of these mental symptoms. This complication is presumably related to the retention of mecamylamine in the body, its urinary excretion being reduced in renal failure (Milne et al. 1957).

Summary

Four cases are described in which a syndrome of tremor, mental confusion, and delirium developed under treatment with mecamylamine. Tremor developed in three other patients.

This complication of mecamylamine treatment occurred in patients receiving large dosages thereof (60–65 mg. daily); all these patients had or subsequently developed malignant hypertension and in all renal function was impaired.

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"How then does a good physician help a patient to face death and, accepting the ways of nature, to meet it? It is not done by all the busy paraphernalia of scientific medicine, keeping a vague shadow of life flickering when all hope is gone. . . . If man lives as a stranger in a lonely crowd, he dies utterly alone. Whereas his entry into the world is the first stage of the dissolution of an intimate partnership with his mother, his final departure is the ultimate in solitary procedures."—WILLIAM B. BEAN, *Arch. intern. Med.* 1958, **101,** 201.

ESSENTIAL FATTY ACIDS AND IDIOPATHIC HYPERCALCÆMIA OF INFANCY

A. T. JAMES
Ph.D. Lond.

J. WEBB
B.Sc. Lond.

THE NATIONAL INSTITUTE FOR MEDICAL RESEARCH, MILL HILL, LONDON

T. STAPLETON
D.M. Oxon., M.R.C.P.
ASSISTANT DIRECTOR

W. B. MACDONALD
M.D. Melb., M.R.A.C.P.
LECTURER

PÆDIATRIC UNIT, ST. MARY'S HOSPITAL MEDICAL SCHOOL, LONDON

ATTENTION has been drawn to the possible role of a deficiency of " essential " fatty acids (linoleic and arachidonic acids) in the genesis of idiopathic hypercalcæmia of infancy (*Lancet* 1957). It has been suggested (Sinclair 1956a) that in the preparation of evaporated milks there is some loss of essential fatty acids and an even greater loss in the production of National Dried Milk made by passage over hot rollers; thus infants fed on dried milk preparations might receive a diet deficient in essential fatty acids. This suggestion could have provided an additional explanation of the frequency with which hypercalcæmia of infancy has been recognised in the United Kingdom, where dried milks are widely used, although one established factor to explain this frequency has been the extent of fortification of infant foods with vitamin D (*British Medical Journal* 1956).

We have studied the fatty-acid composition of samples of human milk, cows' milk before and after drying by a variety of commercial techniques, stored dried milk, and evaporated milk. Similar analytical studies of whole blood from three healthy infants have been made, as well as from three infants with idiopathic hypercalcæmia; the latter were studied both before and after treatment with cotton-seed oil (a rich source of linoleic acid). The fatty-acid analyses were made with the gas-liquid chromatogram (James and Martin 1956).

Methods

Each sample of milk was extracted exhaustively with ether-ethanol overnight to remove the lipids. Samples of whole blood were similarly extracted. The lipid extracts were saponified with methanolic potassium hydroxide, and the non-saponifiable material was extracted with petroleum ether. The alkaline solution was acidified with 5*N* sulphuric acid, and the fatty acids were extracted with petroleum ether. The extract was dried over anhydrous sodium sulphate, and the acids were converted to methyl esters by refluxing with anhydrous methanolic hydrochloric acid. Samples were stored in high dilution in petroleum-ether solution at +2°C, and the solvent was removed by evaporation before applying the sample to the gas-liquid chromatogram.

Under the conditions used for the fatty-acid analyses the gas chromatogram does not differentiate between the cis-cis, cis-trans, and trans-trans forms of linoleic acid. In addition linoleic and linolenic acids (the C_{18} di- and tri-unsaturated acids) are not separated; so the figures reported refer to the sum of these two acids. However, the linolenic-acid content of all the fats studied is likely to be low.

Studies in collaboration with other laboratories have shown excellent agreement between the gas chromatographic and spectrophotometric techniques for determining (1) a combined value for linoleic and linolenic acids and (2) arachidonic acid. The linoleic acid isolated from cows' milk by the gas chromatogram has been shown to be 9 : 12-octadecadienoic acid by the micro degradation procedure described by James and Webb (1957).

Results

Changes in Fat-composition of Milk on Processing to Dried Milk and on Storage

In Table I are listed the linoleic-acid + linolenic-acid contents of fresh milk, the same milk after concentration, and then after roller drying of this concentrated milk. No loss of these two acids was found, although the same experiment was repeated several times.

Table I also shows the linoleic-acid + linolenic-acid contents of the same sample of milk after storage under various conditions. After three months at room temperature or at 37°C the " essential " fatty-acid content had fallen to two-thirds of the original value ; after six months' storage under similar conditions the " essential " fatty acids had dropped to less than half their previous value.

Comparative Analyses of Various Milk Preparations used in Infant Feeding

Table II shows comparisons of the fatty-acid composition (major components only) of two samples of human milk, fresh cows' milk, roller-dried milk, National Dried Milk, and 'Carnation' evaporated cows'-milk. The difference in the levels of linoleic + linolenic acids in human milk and cows' milk was less than has sometimes been supposed; but the effect of diet on these levels has yet to be determined.

TABLE I—LINOLEIC-ACID CONTENT OF COWS' MILK DURING PROCESSING AND STORAGE (AS PERCENTAGE OF ACIDS IN THE RANGE C_6-C_{20})

—	Fresh milk 12% total solids	Milk concentrated before drying (21% total solids)	After roller drying	Powder stored 3 mos. at room temperature	Powder stored 6 mos. at room temperature	Powder stored 3 mos. at 37°	Powder stored 6 mos. at 37°
Linoleic acid + linolenic acid	3·2	3·0	3·4	2·3	1·4	2·4	1·1

" Essential Fatty-acid " Levels in Blood of Infants with Hypercalcæmia

Case 1.—A male infant, born on Feb. 21, 1956, who had well-established hypercalcæmia, was studied at the age of 9 months. He was fed cotton-seed oil containing 50% w/w of linoleic acid for twenty days. During the first five days he received about 5 ml. of cotton-seed oil a day; during the next twelve days about 8 ml. a day; and during the last three days about 20 ml. a day. The serum-calcium (table III and fig. 1) had been high for so long that it seemed improbable that the fall from 15·8 mg. per 100 ml. to 9·9 mg. per 100 ml. in ten days was due to a chance variation in its level, although such variations are known to occur. Analyses were made of the fatty acids of whole blood taken from this child before, while, and after he was given cotton-seed oil. No significant change

TABLE II—MAJOR COMPONENTS OF MILK FATS FROM VARIOUS SOURCES EXPRESSED AS PERCENTAGE OF FATTY ACIDS IN RANGE C_6-C_{20}

Acid	Human milk		Cows' milk			
	Sample 1, ten days after start of lactation	Sample 2, three mos. after start of lactation	Fresh	'Ostermilk' roller-dried	National Dried Milk bought from a clinic	'Carnation' tinned milk
Myristic ..	5·7	9·0	..	10·7	10·6	9·4
Branched C_{15} ..	0·5	0·2	0·8	1·3	1·6	1·8
nC_{15}	0·8	0·4	1·0	1·3	1·2	1·4
Palmitoleic ..	3·9	2·6	2·2	2·2	2·0	2·4
Palmitic ..	26·5	20·0	26·4	29·7	16·6	21·8
Branched unsat. C_{17}	1·5	0·8	1·5	1·5	2·0	1·5
nC_{17}	0·7	Trace	0·7	1·1	0·6	0·8
Linoleic ..	5·1	4·4	3·2	3·5	4·1	4·4
Oleic	38·6	46·0	23·3	26·1	30·4	26·0
Isomers of oleic acid	Not measured		3·6	3·1	10·0	5·1
Stearic ..	12·1	7·7	10·3	12·0	10·5	13·8
Poly-unsat. C_{20} (not arachidonic)	1·8	Not measured	..	..	1·0	2·0

DEPARTMENT OF
EXPERIMENTAL PSYCHIATRY
HILLSIDE HOSPITAL
GLEN OAKS, N. Y.
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Effects of Pitressin Hydration on the Electroencephalogram

Paroxysmal Slow Activity in Nonepileptic Patients with Previous Drug Addiction

ABRAHAM WIKLER, M.D.
Surgeon (R), United States Public Health Service
LEXINGTON, KY.

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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EFFECTS OF PITRESSIN HYDRATION ON THE ELECTROENCEPHALOGRAM

Paroxysmal Slow Activity in Nonepileptic Patients with Previous Drug Addiction

ABRAHAM WIKLER, M.D.
Surgeon (R), United States Public Health Service
LEXINGTON, KY.

ALTHOUGH hydration by forcing of fluids and the use of pitressin has long been employed to precipitate epileptic seizures for diagnostic purposes in persons suspected of having idiopathic epilepsy,[1] no study has been made of the electroencephalographic changes produced by this procedure, either in normal or in epileptic subjects. A single injection of pitressin has been reported to have no effect on the electroencephalogram,[2] but no data have been found on the effects of water intoxication except for the statement by Allen [3] that some experiments of this type on dogs had been attempted.

The present study was undertaken in an attempt to solve a clinical problem. A patient at the United States Public Health Service Hospital was referred for electroencephalographic study because he exhibited periodic episodes of antisocial behavior. A diagnosis of psychopathic personality had been made, but it was desired to rule out epilepsy. A routine electroencephalogram was essentially normal. A pitressin hydration test was then made with a view to provoking a fit, antisocial behavior or "epileptiform" changes in the electroencephalogram. Neither a fit nor antisocial behavior occurred during this procedure, but paroxysmal slow activity did appear in the electroencephalogram. This was difficult to interpret because of the lack of control data in the literature, and therefore further investigations were made.

MATERIALS AND METHODS

The subjects for these experiments were 14 male patients at the United States Public Health Service Hospital who were undergoing treatment for addiction

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From the United States Public Health Service Hospital.

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to opiates while serving sentences for violation of the Harrison Narcotic Act and who volunteered for this test. All these subjects had been in the institution six months or more and had not used opiates habitually for at least that length of time. Their ages varied from 32 to 46, with an average of 37.1. None gave a history of epilepsy, and in no case had a seizure been recorded since the patient's admission to the institution. All were in good health. For 7 patients a diagnosis of psychopathic personality was made on admission.

Electroencephalograms were made before and after pitressin hydration. Silver–silver chloride cup electrodes were applied to the scalp, and bipolar recordings were made from the frontal, precentral, parietal and occipital regions. The electroencephalograph was a four channel, capacity-coupled, amplifier and oscillographic apparatus with photographic recording on bromide paper. During the recording the patient lay quietly on a comfortable bed in an electrically shielded, soundproofed, air-cooled room. An observer was always present to note movement and to make sure the patient was not asleep. Records were taken before, during and after hyperventilation.

Each record was analyzed as follows: A representative thirty second sample was selected, and all waves over 5 microvolts in amplitude were measured and counted. Paroxysmal activity was not included in the strip. The mean alpha frequency was calculated by averaging all frequencies from 8 to 13 per second, and the percentage of alpha activity was determined by calculating the time occupied by such frequencies during a thirty second recording. A frequency spectrum was then plotted. The limits of individual variation from day to day were determined on several records, and, with this method of analysis, the variation in alpha frequency was found to be not more than 0.5 cycle per second, and that in percentage of alpha activity, 12 per cent.

The method of hydration varied to a considerable extent because of differences in the ability of the subjects to tolerate this procedure. In the first few experiments, pitressin was injected hypodermically every hour for seven hours (in doses of 0.3, 0.4, 0.5, 0.5, 0.5, 0.5, 0.5 cc.), and the patient drank 500 cc. of water every hour for eleven hours. Some patients were able to tolerate this, but others suffered from vomiting and abdominal cramps. The procedure was then altered by giving smaller doses of pitressin hourly for eight hours (0.2, 0.3, 0.3, 0.3, 0.3, 0.3, 0.3, 0.3 cc.) and administering 1,000 cc. of 5 per cent dextrose in distilled water intravenously every two hours until a total of 5,000 cc. had been given during the eight hour test period. Some minor modifications were made in the dosage in individual cases.

The patients were admitted to the research ward in the morning, and preliminary physical examinations and records of pulse, temperature, blood pressure, respiration and weight were made. An electroencephalogram was made in the afternoon. Pitressin hydration was begun early the next morning, and the patient was weighed at frequent intervals. Another electroencephalogram was made the same afternoon, after maximum hydration had been achieved. The patients were closely observed, and records of blood pressure, pulse, respiration and temperature were made every four hours during the period of hydration. A regular diet was prescribed, but coffee, tea and soup were excluded.

RESULTS

Clinical Observations.—Some of the patients were fairly comfortable during these procedures, but most of them had some degree of discomfort, chiefly nausea, abdominal cramps and occasional vomiting.

Considerable puffiness of the face appeared in a few patients. In none did alarming reactions of circulatory nature appear, and there were no significant changes in pulse rate or blood pressure. No epileptic seizures of any kind were precipitated. It was found that the smaller doses of pitressin (0.3 cc.) were just as effective in inhibiting diuresis as larger amounts and produced less discomfort. On the morning following pitressin hydration voluminous diuresis took place, and the patient's weight returned rapidly to or slightly below the control level.

Electroencephalographic Observations.—The data are summarized in the table. The average gain in weight at the end of hydration was

Effects of Pitressin Hydration on the Electroencephalogram

Subject No.	Total Pitressin, Cc.	Per Cent Gain in Body Weight	Alpha Frequency			Alpha Percentage			Comment
			Before	After	Difference	Before	After	Difference	
1	3.4	5.3	9.9	10.1	+0.2	71.0	73.7	+ 2.7	Shift to slow side and paroxysmal delta activity after hydration
2	3.4	5.0	10.2	9.8	—0.4	83.5	82.1	— 1.4	
3	3.2	4.5	11.1	10.6	—0.5	47.3	40.0	— 7.3	
4	3.2	2.7	10.7	10.5	—0.2	42.3	63.3	+21.0	Shift to slow side after hydration
5	3.0	2.6	11.5	10.9	—0.6	42.7	42.2	— 0.5	
6	3.0	5.1	11.6	11.4	—0.2	57.4	67.8	+10.4	Shift to slow side and paroxysmal delta activity after hydration
7	3.2	1.8	9.9	10.0	+0.1	87.1	90.8	+ 3.7	
8	2.6	3.2	10.3	10.0	—0.3	76.2	67.7	— 8.5	Shift to slow side after hydration
9	2.5	7.3	10.3	9.7	—0.6	74.3	58.9	—15.4	Shift to slow side and paroxysmal delta activity after hydration
10	1.3	4.3	11.5	11.5	0.0	22.6	22.9	+ 0.3	Paroxysmal delta activity after hydration
11	1.3	5.3	11.1	10.5	—0.6	42.9	63.9	+21.0	Shift to slow side and paroxysmal delta activity after hydration
12	1.3	4.4	10.9	10.7	—0.2	63.3	41.2	—22.1	Paroxysmal delta activity after hydration
13	1.7	5.3	10.4	10.4	0.0	67.0	61.2	— 5.8	
14	1.0	3.9	11.1	10.6	—0.5	60.8	46.9	—13.9	Shift to slow side and paroxysmal delta activity after hydration

3 Kg., or 4.1 per cent of body weight. In 3 of the subjects the mean alpha frequency was lowered 0.6 cycle per second, but in the remainder the changes in alpha frequency, although mostly in the direction of slowing, were within the range of daily variation. In half the patients the frequency spectrum showed a definite shift toward the slow side (fig. 1). In the remainder no definite shift could be observed. In no case was there an unequivocal shift toward the fast side of the spectrum.

The most striking change, however, was the appearance of bursts of slow activity (6 cycles per second) of moderately high amplitude in 7 of the 14 records after hydration (fig. 2). All but 1 of the control records were essentially normal and contained no paroxysmal slow activity, either before or after hyperventilation. In the one record

a scant amount of paroxysmal 6 per second rhythm was present, and this activity was greatly increased after hydration. In those records which showed paroxysmal 6 per second rhythms, such activity appeared in short bursts of 8 to 15 waves two to six times during the entire run, which was usually about three or four minutes. The incidence of paroxysmal slow activity was not entirely the same as that of shift in the frequency spectrum to the slow side. In 2 records there was a shift but no paroxysmal slow activity, and in 2 the latter was present but there was no shift in the spectrum. There was no correlation between the incidence of paroxysmal slow activity and the degree of hydration or the total amount of pitressin injected. Nor was there a correlation between the admission diagnosis of psychopathic personality and shift in frequency spectrum or incidence of slow activity. Such changes in the electroencephalogram after pitressin hydration were present in 50 per cent of patients with diagnoses of psychopathic personality and in 50 per cent of the others. Consciousness was not grossly disturbed

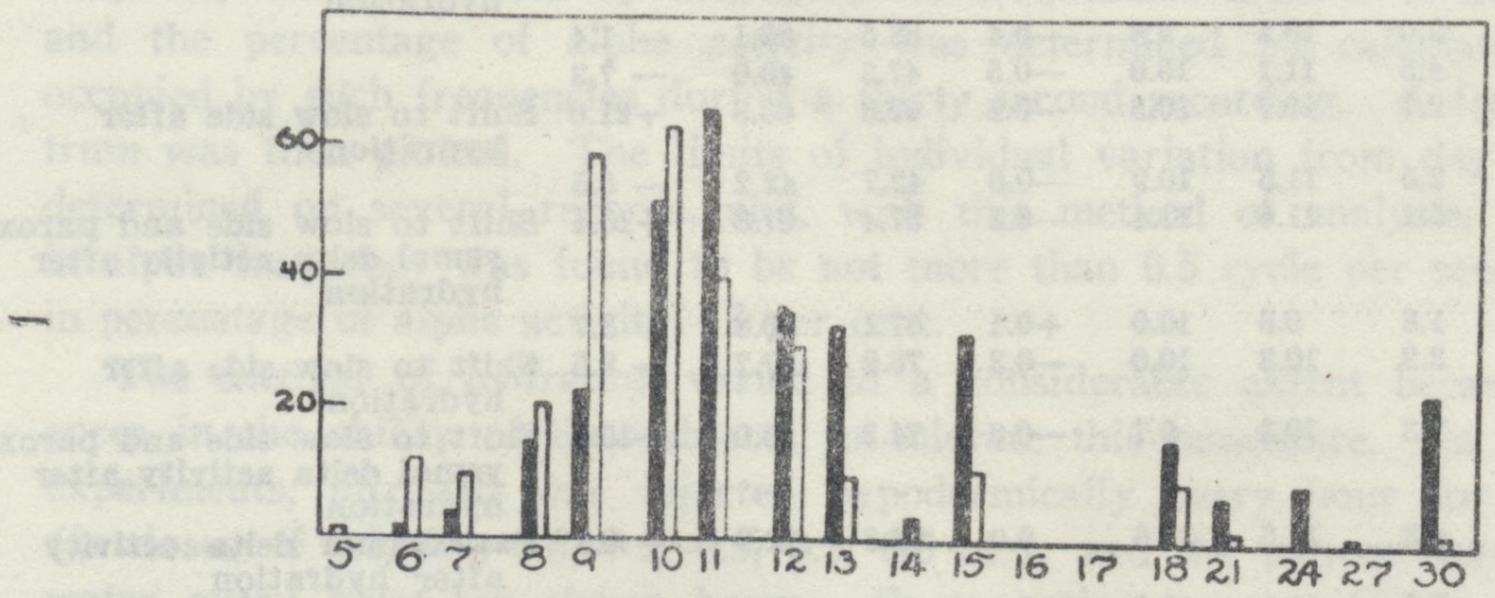


Fig. 1 (case 1).—Effects of pitressin hydration on the frequency spectrum of the electroencephalogram. The solid bars indicate values before, and the outline bars values after, pitressin hydration. On the abscissa are plotted frequencies in terms of cycles per second; on the ordinate, the number of such frequencies in a thirty second record. Note the shift to the slow side after hydration.

during the electroencephalographic recording so far as could be determined by the observer in the electroencephalographic chamber.

COMMENT

Although none of the patients gave a history or showed clinical evidence of epilepsy, the electroencephalograms obtained on half the subjects after pitressin hydration could be termed "epileptoid" because of the presence of paroxysmal slow activity. Furthermore, it is noted that this change occurred in only half the subjects and was independent of the degree of hydration. This suggests that the appearance of "epileptoid" changes in the electroencephalogram depends on individual susceptibility. It should be emphasized here that the persons subjected to this test were not truly representative of a "normal" group, since all

had previously been drug addicts and recent studies at this institution have shown that the great majority of the drug addicts fall into either the psychopathic or the psychoneurotic group.[4]

The findings provide a partial answer to the clinical problem which gave rise to this study. It is evident that the appearance of paroxysmal slow activity in the electroencephalogram after pitressin hydration cannot be considered indicative of epilepsy in the clinical sense of the

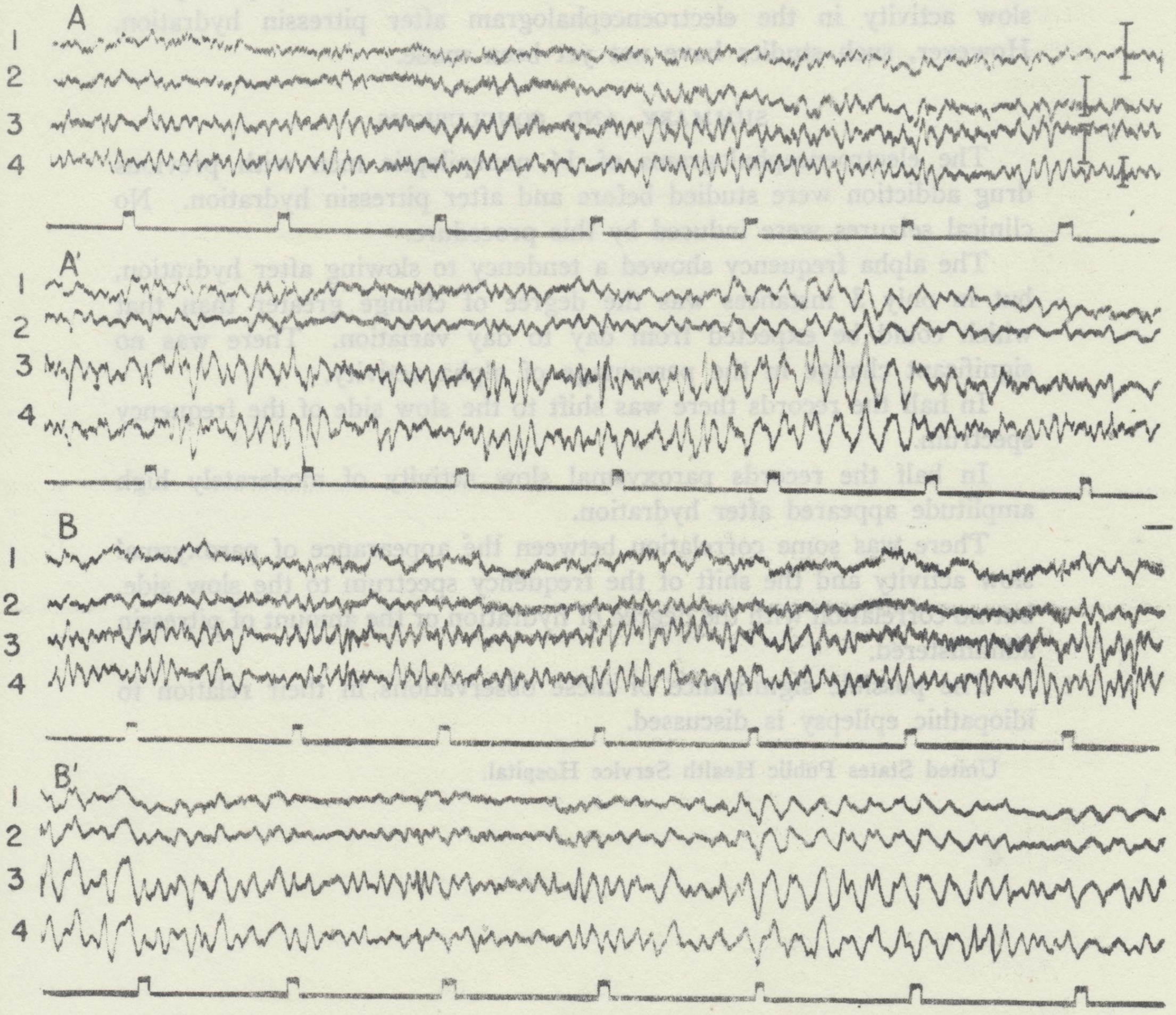


Fig. 2 (case 6).—Effects of pitressin hydration on the electroencephalogram (bipolar recording from the frontal (*1*), precentral (*2*), parietal (*3*) and occipital (*4*) leads; calibration 50 microvolts; time in seconds). *A* and *B* are control records made before and after hyperventilation, respectively; *A'* and *B'*, records obtained before and after hyperventilation after pitressin hydration. Note the paroxysmal 6 per second activity after hydration.

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4. Aldrich, C. K., and Ruble, D. C.: Studies on the Personalities of Drug Addicts, to be published.

term. However, it does suggest the possibility that the physiologic mechanism which underlies the production of clinical seizures by this method is also operant in certain susceptible nonepileptic persons and that, essentially, quantitative threshold differences determine whether or not, in any given case, clinical seizures will be precipitated. It would be illuminating, in this connection, to compare the group observed in this investigation with "normal" subjects and with persons known to have epilepsy with special reference to the incidence of paroxysmal slow activity in the electroencephalogram after pitressin hydration. However, such studies have not yet been made.

SUMMARY AND CONCLUSIONS

The electroencephalograms of 14 nonepileptic men with previous drug addiction were studied before and after pitressin hydration. No clinical seizures were induced by this procedure.

The alpha frequency showed a tendency to slowing after hydration, but in only 3 instances was the degree of change greater than that which could be expected from day to day variation. There was no significant change in the percentage of alpha activity.

In half the records there was shift to the slow side of the frequency spectrum.

In half the records paroxysmal slow activity of moderately high amplitude appeared after hydration.

There was some correlation between the appearance of paroxysmal slow activity and the shift of the frequency spectrum to the slow side, but no correlation with the degree of hydration or the amount of pitressin administered.

The possible significance of these observations in their relation to idiopathic epilepsy is discussed.

United States Public Health Service Hospital.

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EFFECTS OF METHADONE AND MORPHINE ON THE ELECTROENCEPHALOGRAM OF THE DOG

ABRAHAM WIKLER AND SOL ALTSCHUL[1]

U. S. Public Health Service Hospital, Lexington, Kentucky

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The present study was made as part of a comprehensive investigation of the comparative actions of methadone and morphine on the central nervous system (1, 2). The dog has been utilized in these studies because the effects of small doses of methadone and morphine on this species are analogous to those in man (3–5). In particular, however, we wished to compare the effects of large doses of methadone and morphine on the electroencephalogram since such studies cannot be made with safety in man. Some of the observations made in the course of these investigations are also of interest with reference to the pharmaco-physiologic aspects of convulsive seizures.

METHODS. Electroencephalographic studies were made on eleven dogs. In eight of these animals the effects of methadone and morphine were observed without previous anaesthesia or curare. This was accomplished by the insertion of wire or "mercury cup" electrodes which made contact with the dura over the desired cortical area. The mercury cup electrode (figure 1) was inserted under aseptic conditions and permitted the recording of electroencephalograms without muscle artifacts in the same dog as often as desired over a period of several months. In one experiment a bipolar wire electrode insulated except for the tip (interelectrode distance about 1.0 mm.) was inserted into the left anterior lateral hypothalamic area and fixed in place by cementing its upper end to a metal cylinder which was screwed into the calvarium along with other screw leads which served as cortical electrodes. In these eight dogs the electrodes were inserted under sodium pentobarbital (Nembutal) anaesthesia but experiments were not made until one or more days later after full recovery from the anaesthetic. In the three remaining dogs screw electrodes were inserted into the calvarium and in the midline plane of the sphenoid bone (via the oropharynx to a depth of 1.0 to 2.0 mm. below the floor of the sella turcica). This was done under ether anaesthesia and the animal was then curarized ("Intocostrin" 1.5 cc. I.V. initially and 0.5 cc. I.V. at about 40-minute intervals thereafter) and artificial respiration was maintained through a tracheal cannula. Experiments were not begun until the ether effects had worn off as indicated by a return of the electroencephalogram to a normal pattern. In all dogs, silver disc electrodes were also fixed on the ears to serve as reference leads. In most experiments, a 3-channel Grass resistance-capacity coupled inkwriting electroencephalograph was used; in some, a four channel resistance-capacity coupled amplifier-oscillograph was used with photographic recording. Shielding of the animal was accomplished by a wire screen grounded cage.

The motor patterns of convulsive seizures produced by large doses of methadone or morphine were studied in six other dogs. After one or more seizures they were terminated by intravenous injection of Nembutal. Moving picture records were made for subsequent analysis of the convulsive patterns.

The dose range for methadone was 2.0 to 75.0 mgm./kgm. and that for morphine, 5.0 to

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[1] Now Resident Psychiatrist, Illinois Neuropsychiatric Institute, Chicago, Ill.

350.0 mgm./kgm. In all experiments initial doses were given subcutaneously while subsequent doses were given subcutaneously or intravenously.

RESULTS. The pre-medication resting electroencephalograms of the dogs varied considerably from dog to dog and on different days in the same dog (figure 2, control records). However, the changes produced by methadone or morphine were quite different from spontaneous variations in electroencephalographic pattern. After small doses of methadone (2.0 mgm./kgm.) or morphine (5.0 to 10.0 mgm./kgm.) irregular high voltage random slow waves appeared in cortical tracings although fast activity present in the control records persisted (figure 2). After larger doses of methadone (about 75.0 mgm./kgm.) or morphine (about

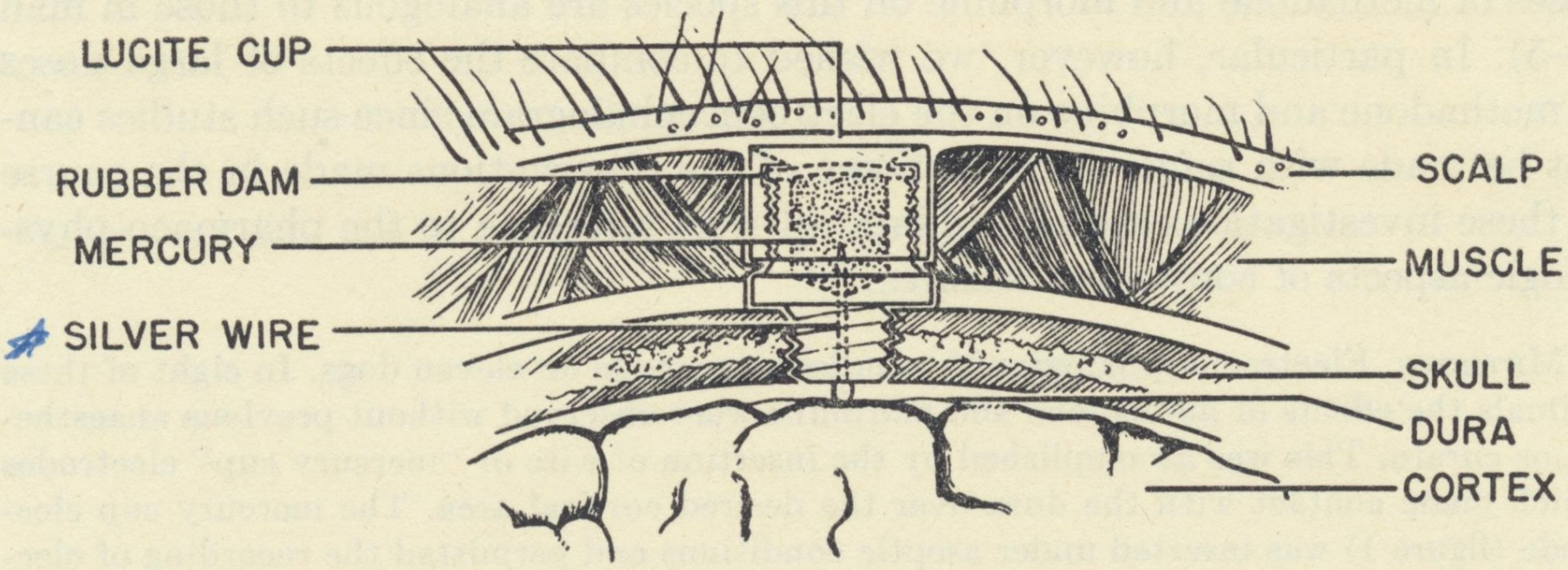


FIG. 1. Mercury cup electrode for recording E.E.G. from dura in unanesthetized and uncurarized animals. Under Nembutal anesthesia, the scalp and muscles are incised and a threaded trephine opening is made in the skull. The mercury cup is screwed in place and the scalp sutured over it. After recovery from anesthesia and healing of scalp wound, recording of E.E.G. is made by inserting a sharp-pointed, fine but rigid needle, insulated except for the tip, through the scalp and rubber dam cap into the mercury. The latter is connected by the stout silver wire to the underlying dura. After completion of record, the needle is removed. Mercury is resealed in cup by rubber dam. Procedure may be repeated indefinitely over a period of several months.

200.0 mgm./kgm.) the earliest change (about one to three minutes after subcutaneous injection) was the appearance of bursts of high voltage moderately fast activity (figures 3B and 4B) in the cortical tracings. Later, high voltage slow waves appeared in the cortical tracings (figures 3C and 4C). In several experiments another striking change was the appearance of bursts of high voltage "petit mal"-like spike and dome sequences after morphine (figure 4D) and less frequently and less typically after methadone (figure 3D). These complexes appeared in cortical tracings from one or both hemispheres but were not associated with any significant change in tracings from sphenoid leads (figures 3D, 4D, and 4F). In some experiments bilaterally synchronous spike and dome activity in the cortical tracings could be induced by sudden loud noises (clapping hands—figure 4D). Relatively early (twenty to thirty minutes) after methadone or later (two to four hours) after morphine high voltage spike seizure discharges appeared synchronously in the cortical tracings (figures 3E and 4G). In one of

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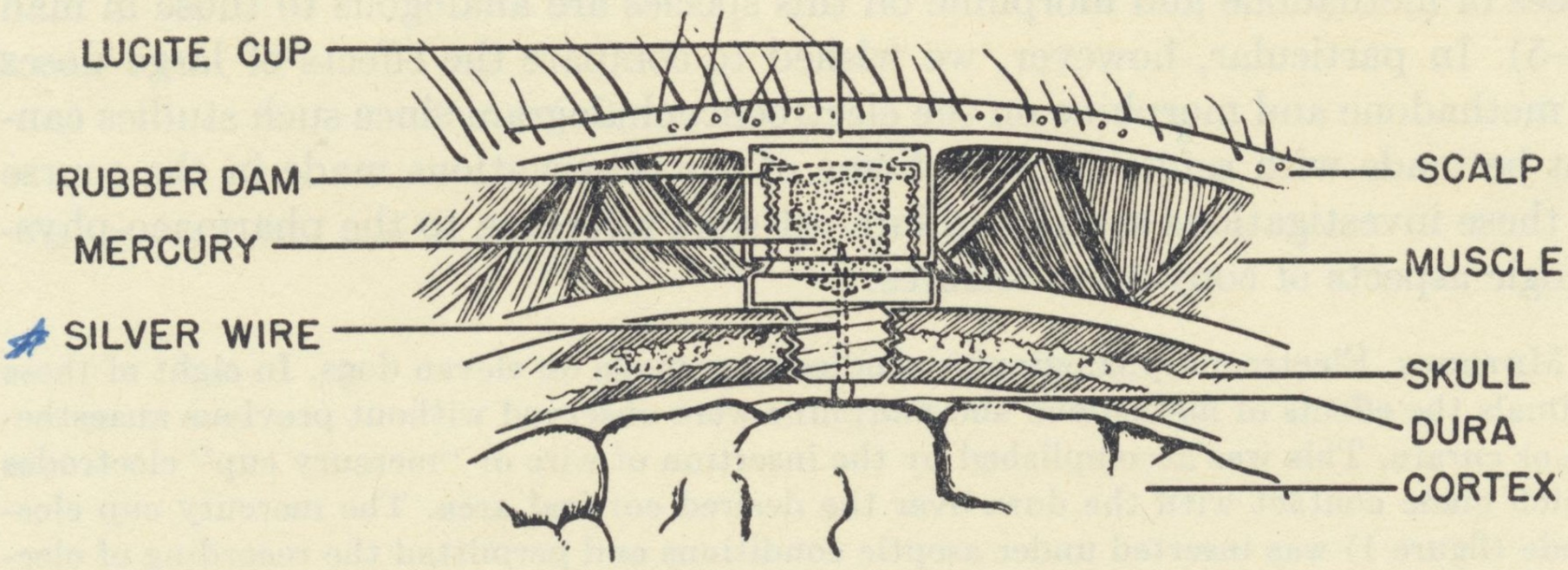


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*Since the publication of this paper we have substituted platinum wire for silver wire, since the latter forms an amalgam with mercury after a period of time and permits mercury to leak through.

three experiments with sphenoid leads, such spike seizure discharges appeared in the basal lead as well (figure 3E) and were followed by a steady 25 per second rhythm in the latter while the cortical tracings were isoelectric or showed only

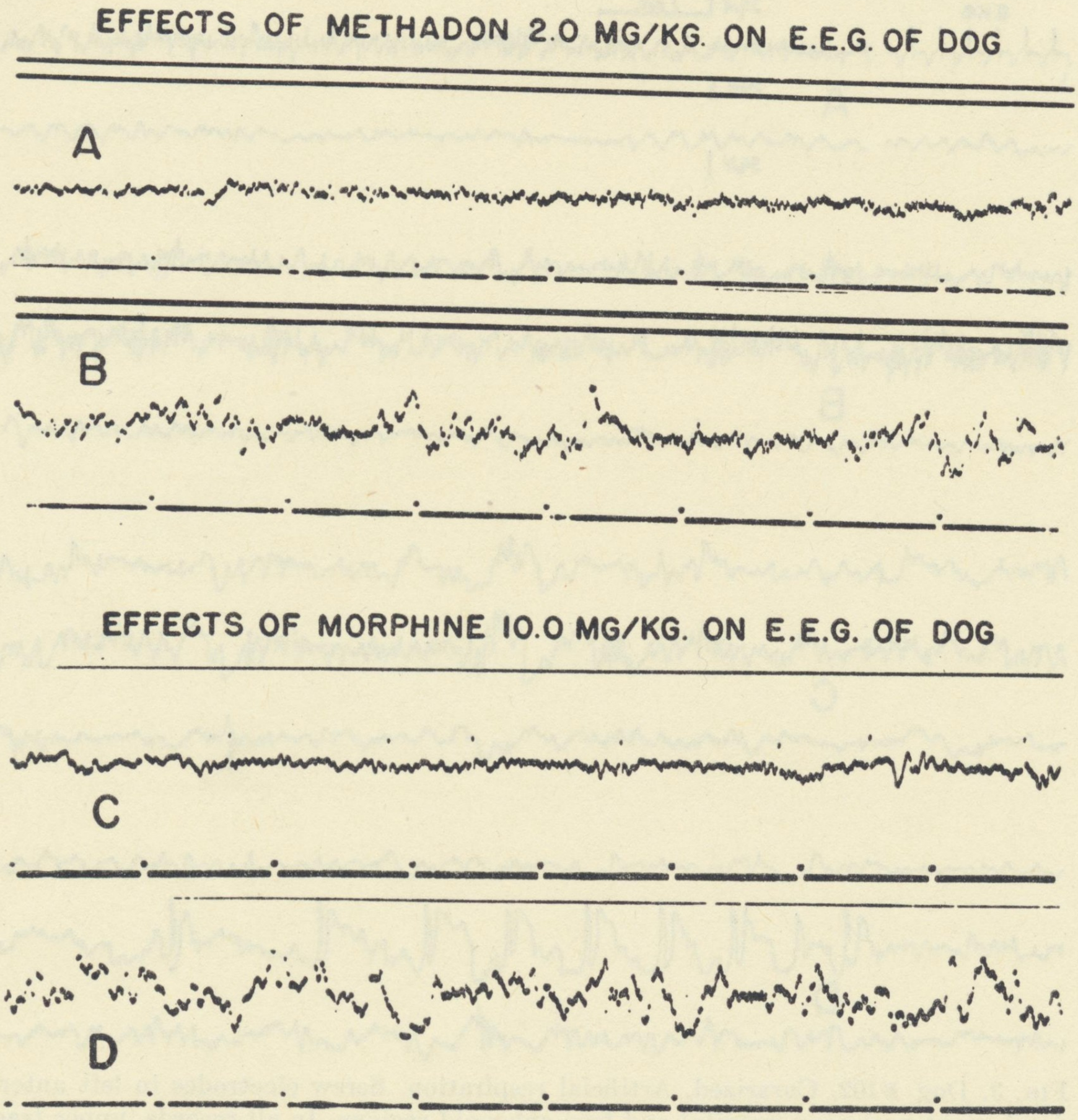


FIG. 2. Dog #70. Mercury cup electrodes in left fronto-parietal and right parieto-occipital regions. No anesthesia or curare. All tracings bipolar transcortical. Time in seconds. Gain same throughout. A—control. Note predominantly fast activity. B—two and one-half hours after methadone 2.0 mgm./kgm. subcutaneously. Note general increase in voltage and admixture of irregular slow waves. C—control, two days later. Note irregular rhythms, varying from 10–30 per second (large "spikes" are probably EKG artifacts). D—two and one-half hours after morphine 10 mgm./kgm. subcutaneously. Note changes similar to those in B.

slow activity (figures 3G and 3H). In another experiment the spike seizure discharge from the cortex followed immediately after a typical spike and dome paroxysm (figure 3G). In the single experiment with hypothalamic bipolar leads, typical spike and dome discharges after morphine 20.0 mgm./kgm. (subcutane-

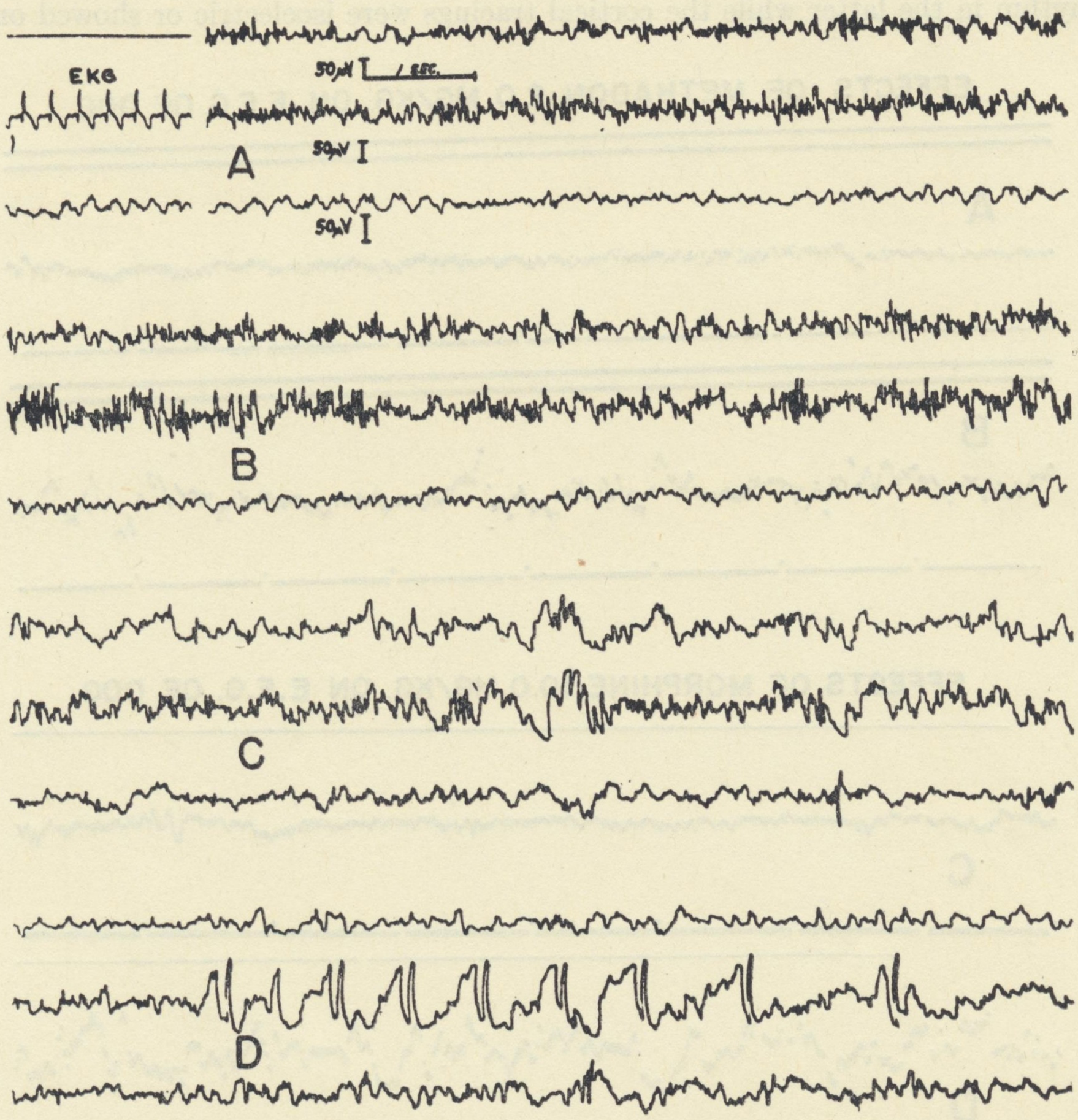


FIG. 3. Dog #102. Curarized. Artificial respiration. Screw electrodes in left anterior-parietal, right posterior-occipital and basi-sphenoid regions. In all records, upper tracing is right occipital to right ear, middle tracing is left parietal to left ear and lower tracing is sphenoid to left ear. Calibrations on "A" apply to all records except "F" where gain was reduced as indicated. A—control. Note mixture of fast and slow frequencies of moderate voltage in cortical tracings and periodic 4 per sec. waves of moderate voltage on a background of low voltage fast activity in basal tracing. EKG is shown to point out slow activity in basal tracing is of approximately the same frequency as heart rate. B—three minutes after methadone 75 mgm./kgm. subcutaneously. Note bursts of high voltage spikes in cortical tracings and little change in basal tracing. C—fifteen minutes after methadone. Note admixture of high voltage slow waves in cortical tracing; occasional random spike in basal tracing. D—nineteen minutes after methadone. Note burst of 2 per sec. dome

ously) appeared in the cortical tracing from one hemisphere; later the spike components increased progressively in voltage and the pattern assumed

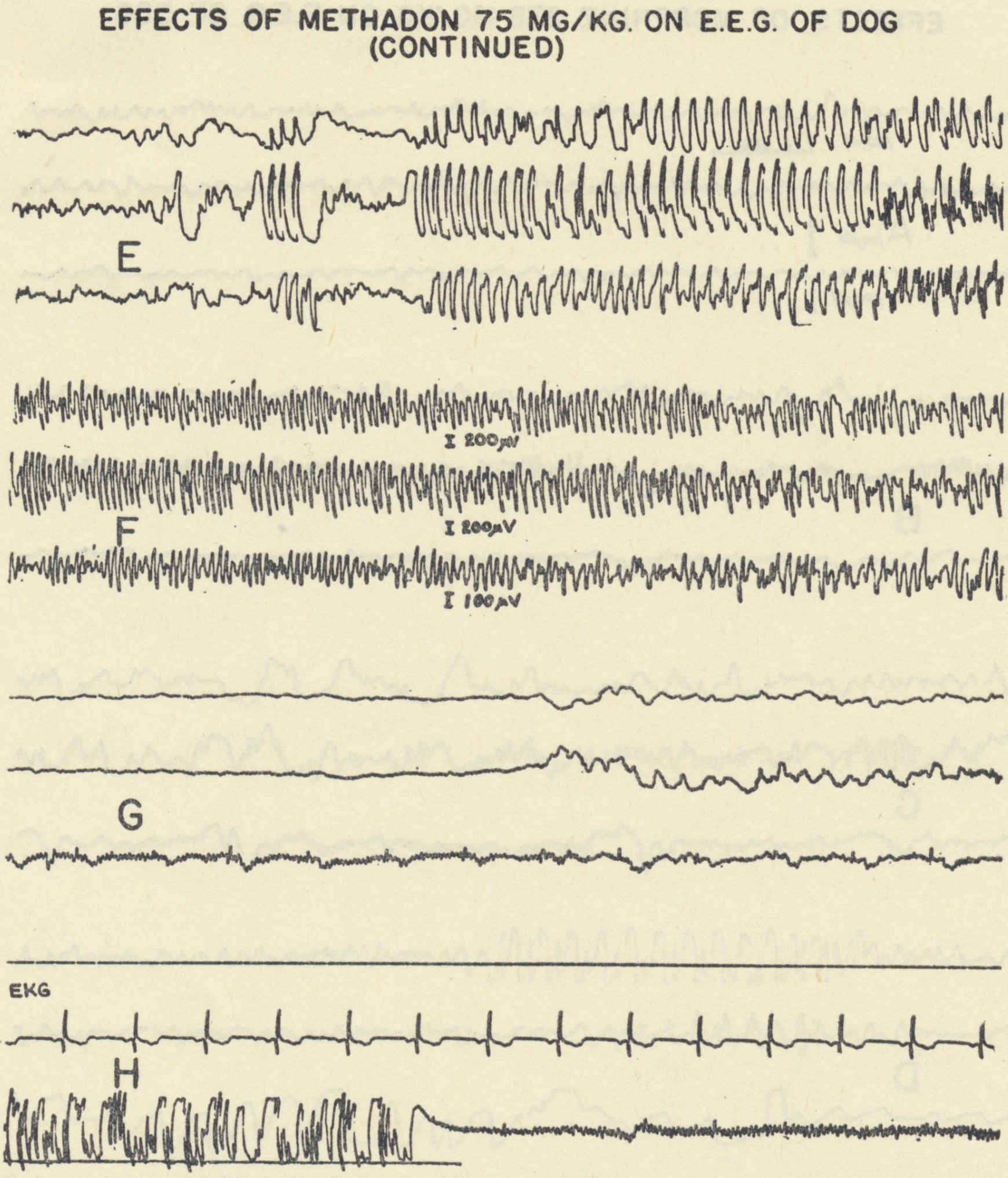


FIG. 3 (Continued)

and spike discharges from left-parietal region alone. E—twenty-two minutes after methadone. Note very high voltage seizure discharges synchronous in all tracings, consisting of repetitive spikes of about 8 per sec. frequency, gradually becoming faster. F—twenty-eight minutes after methadone during a second seizure discharge, shown at reduced gain. Frequency 15 per sec. G—end of seizure. Note steady low voltage 25 per sec. terminal discharge in basal tracing while cortical tracings are practically isoelectric at first, then show only irregular slow activity. H—thirty-seven minutes after methadone. EKG and basal tracings showing cardiac slowing and abrupt end of another seizure discharge followed by steady 25 per sec. low voltage activity.

that of a sustained high voltage spike discharge. The tracings from the contralateral cortex and from the hypothalamus showed no significant changes during this period. In all instances, after subsidence of the seizure discharges the cor-

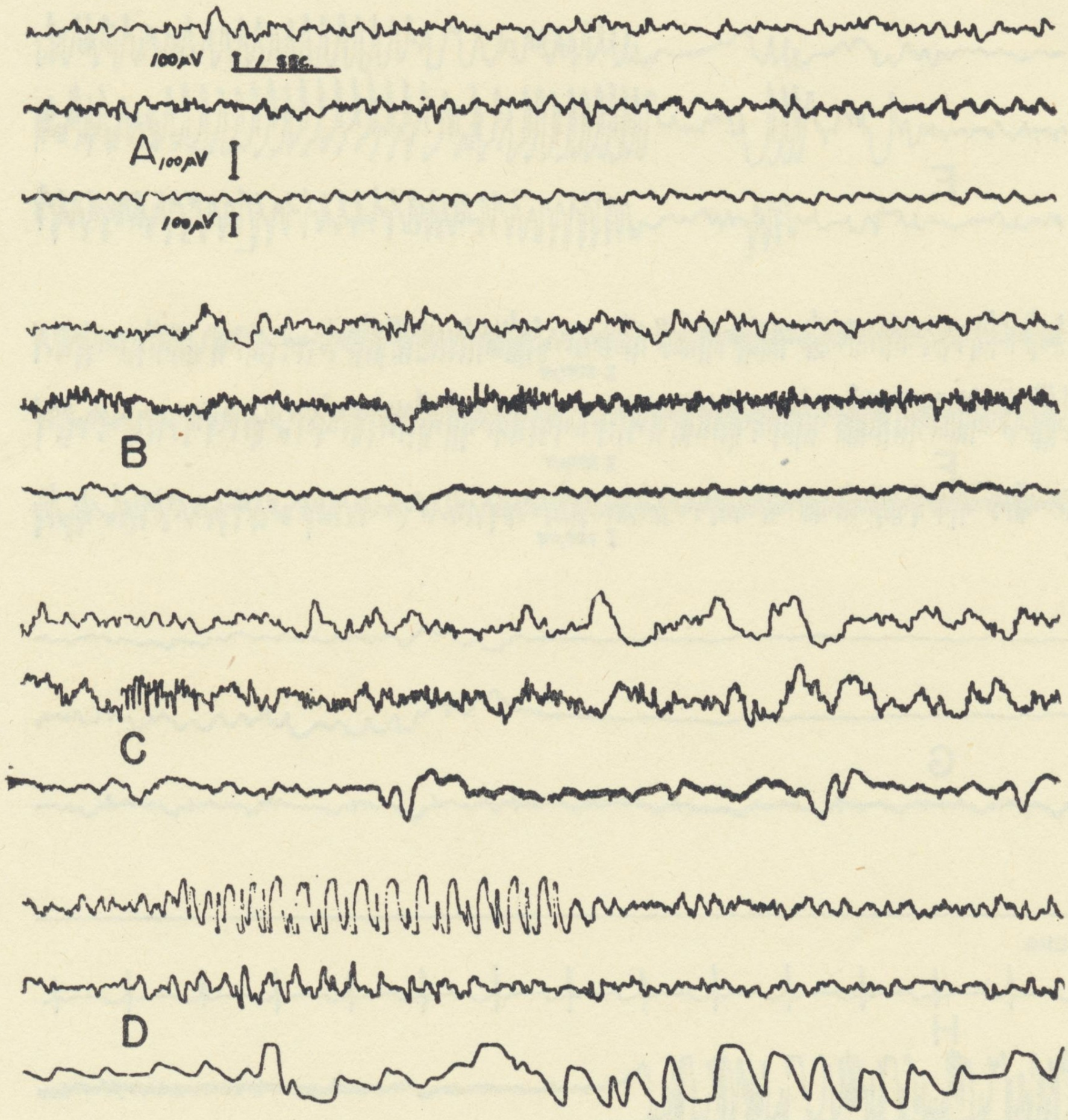


FIG. 4. Dog #93. Curarized. Artificial respiration. Screw leads in right parieto-occipital, left fronto-parietal and basi-sphenoid regions. In all records, upper tracing is right parieto-occipital to right ear, middle tracing is left fronto-parietal to left ear and lower tracing is sphenoid to left ear. Calibrations on "A" refer to all records. Note gain on middle record is almost twice that on the others. A—control. Note mixture of moderately high voltage slow and low voltage fast activity. B—one minute after morphine 200 mgm./kgm. subcutaneously. Note increase in moderately high voltage fast activity in cortical tracings; there is little change in basal tracing. C—twenty-seven minutes after morphine. Note admixture of high voltage slow waves in all tracings. D—one-half hour after total of 238 mgm./kgm.

tical tracings were isoelectric for a few seconds and then high voltage slow activity appeared. In most experiments this sequence of events was repeated several times after the last injection of either methadone or morphine.

The motor patterns of the seizures were similar after either drug except that

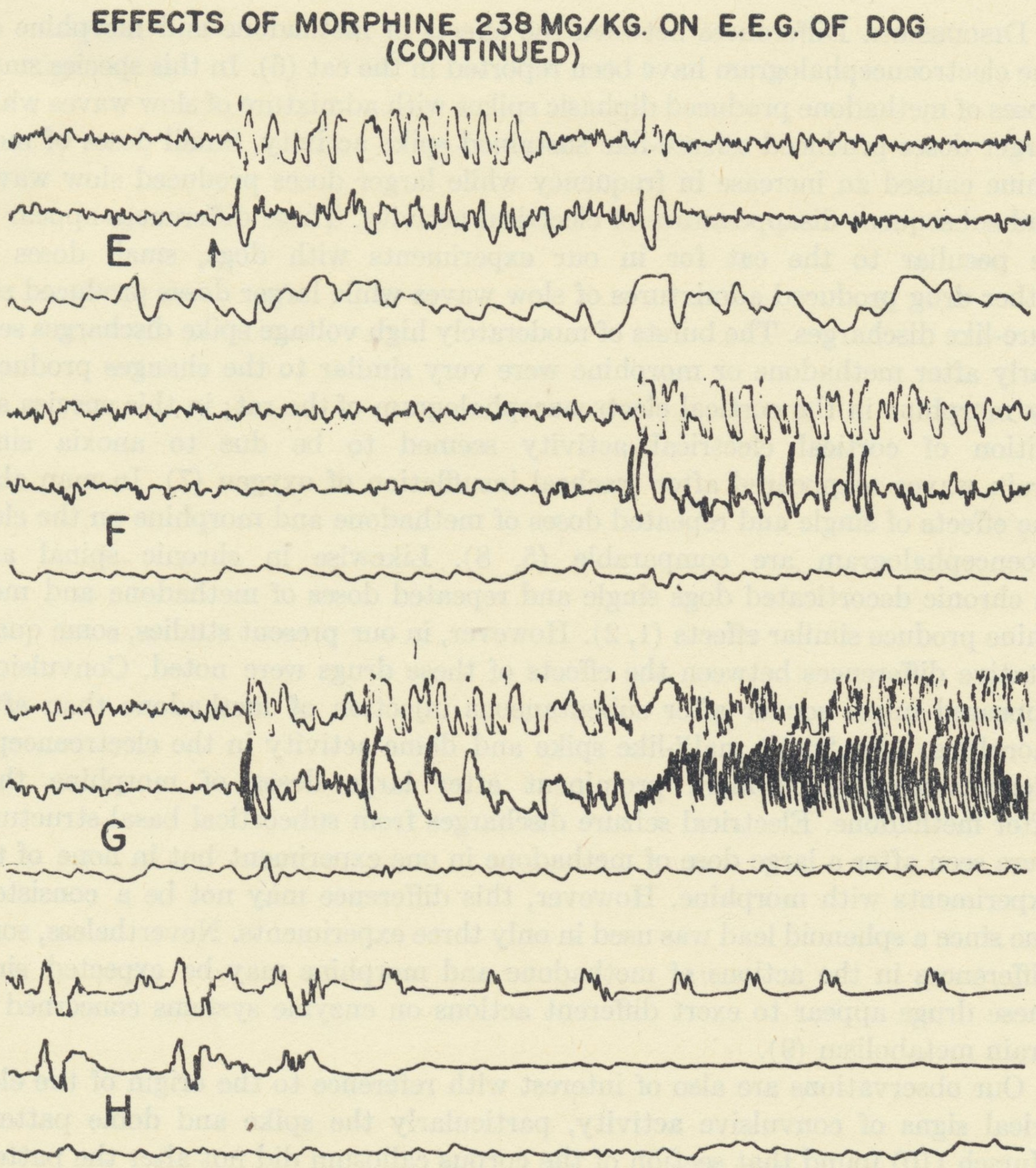


FIG. 4 (Continued)

of morphine (24 mgm./kgm. I.V. 3½ hours, and 14 mgm./kgm. I.V. 4 hours after first dose). Note burst of high voltage spike and dome complexes from right parieto-occipital region alone; irregular high voltage slow activity in basal tracing. E—seven minutes after D. Burst of spike and dome complexes from right parieto-occipital region with synchronous activity in left fronto-parietal tracing, elicited by clapping hands loudly. F—eight minutes after E. Similar synchronous cortical discharges occurring spontaneously. G—continued from F. Note burst of spike and dome complexes from cortical leads followed immediately by seizure discharge of very high voltage spikes. No change in basal tracing. H—end of seizure. No change in basal tracing.

they appeared sooner after large doses of methadone (ten to thirty minutes) than after large doses of morphine (two to four hours). Clonic movements were more prominent in the seizures produced by methadone. The morphine seizures were predominantly tonic.

Discussion. Differences between the effects of methadone and morphine on the electroencephalogram have been reported in the cat (6). In this species small doses of methadone produced diphasic spikes with admixture of slow waves while larger doses produced seizure-like sustained spike activity. Small doses of morphine caused an increase in frequency while larger doses produced slow waves and subsequent disappearance of electrical activity. These differences appear to be peculiar to the cat for in our experiments with dogs, small doses of either drug produced admixtures of slow waves while larger doses produced seizure-like discharges. The bursts of moderately high voltage spike discharges seen early after methadone or morphine were very similar to the changes produced by morphine in the cortical electroencephalogram of the rat; in this species abolition of cortical electrical activity seemed to be due to anoxia since brain waves reappeared after tracheal insufflation of oxygen (7). In man also, the effects of single and repeated doses of methadone and morphine on the electroencephalogram are comparable (5, 8). Likewise in chronic spinal and in chronic decorticated dogs single and repeated doses of methadone and morphine produce similar effects (1, 2). However, in our present studies, some quantitative differences between the effects of these drugs were noted. Convulsions appeared much sooner after subcutaneous injection of methadone than after morphine. Also "petit mal"-like spike and dome activity in the electroencephalogram were much more prominent after large doses of morphine than after methadone. Electrical seizure discharges from subcortical basal structures were seen after a large dose of methadone in one experiment but in none of the experiments with morphine. However, this difference may not be a consistent one since a sphenoid lead was used in only three experiments. Nevertheless, some differences in the actions of methadone and morphine may be expected since these drugs appear to exert different actions on enzyme systems concerned in brain metabolism (9).

Our observations are also of interest with reference to the origin of the electrical signs of convulsive activity, particularly the spike and dome pattern. Hursch (10) found that section of the corpus callosum did not alter the pattern of bilaterally synchronous "petit-mal" discharges in the cortex. Jasper and Drooglever-Fortuyn (11) and Hunter and Jasper (12) were able to produce spike and dome and sustained spike activity in both cortex and thalamus by electrical stimulation of medial thalamic structures. These observations suggest a subcortical origin of "petit-mal" complexes. On the other hand, Hayne, Belinson and Gibbs (13) as a result of studies in man, concluded that ". . . The present findings do not suggest a subcortical but a cortical origin for the three per second wave and spike of petit mal, because (a) the spike registers on the cortex as negative when referred to a relatively inactive area, (b) it can appear as an isolated and purely focal discharge in one cortical area and (c) no evidence was found that it is causatively related to thalamic or other subcortical activity." Our findings are strikingly analogous to those of the latter group since after large doses of morphine electrical seizure patterns could, and most often did appear in cortical tracings without concomitant significant changes in trac-

ings from sphenoid or hypothalamic leads, and spike and dome discharges were frequently observed in cortical tracings from one hemisphere only. However, while suggestive, our evidence is not conclusive with regard to the origin of spike and dome activity since in our experiments the two cortical electrodes were not in strictly homologous areas and our basal electrodes (sphenoid lead and bipolar hypothalamic leads) could not be relied on to pick up electrical activity in the dorsal thalamus. Our records also indicate that the spike and dome discharge and sustained spike activity are closely related since in several instances after large doses of morphine a spike and dome pattern was followed by prolonged sustained spike activity without interruption. Except for the question of the thalamic origin of these seizure discharges, these observations are analagous to those of Hunter and Jasper (12).

It is also of interest to note that when a seizure discharge was recorded from the sphenoid lead, this was followed by a sustained low amplitude 25 per second discharge apparently originating in subcortical basal structures. This resembled strongly the "after seizure" discharge seen in chronic decorticated cats following electroshock (14). In the latter study, morphine appeared to alter the electroshock seizure pattern so that fast and slow sequences resembling "petit mal" discharges were seen in some records. In our present investigation, this 25 per second discharge appeared in the sphenoid lead tracings while cortical activity was absent or of a different character. Such independent activity of subcortical structures and cerebral cortex has also been noted after fluoroacetate (15).

SUMMARY

1. The effects of small and large doses of methadone and morphine on the electroencephalogram were studied in unanesthetized and uncurarized dogs and in curarized dogs. The motor pattern of the convulsive seizures induced by large doses of these drugs was also observed in different dogs.

2. A "mercury cup" electrode is described which facilitates the repeated recording of electroencephalograms from the dura over the cerebral cortex in unanesthetized and uncurarized animals, without interference due to artifacts from the scalp and temporal muscles.

3. Small doses of methadone or morphine produce an admixture of fast and high voltage slow activity in cortical tracings. Large doses of either drug produce seizure discharges which may appear synchronously in cortical and basal tracings or in cortical tracings alone. The seizure discharges from cortical tracings were both of the spike and dome and sustained spike patterns. At times the former passed over into the latter without interruption. An "after-seizure" 25 per second low voltage discharge in the tracings from the sphenoid lead was not associated with activity in the cortical leads.

4. The motor pattern of seizures induced in dogs by large doses of methadone or morphine were essentially the same, although clonic movements were more prominent in the methadone convulsions. These seizures appeared much sooner after subcutaneous injection of methadone than after morphine.

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DEPART
EXPERIMENTAL PSYCHIATRY
HILLSIDE HOSPITAL
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EXPERIMENTAL SCHIZOPHRENIA-LIKE SYMPTOMS

NEUROPHYSIOLOGY LABORATORY
HILLSIDE HOSPITAL
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MAX RINKEL, M. D., H. JACKSON DeSHON, M. D., ROBERT W. HYDE, M. D.,
AND
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EXPERIMENTAL SCHIZOPHRENIA-LIKE SYMPTOMS [1]

MAX RINKEL, M. D., H. JACKSON DeSHON, M. D., ROBERT W. HYDE, M. D.,
AND
HARRY C. SOLOMON, M. D.
Boston, Mass.

The nature and cause of the major psychoses are still unknown. Repeated attempts have been made to reproduce experimentally psychotic symptoms in the hope to uncover their psycho-physiological relationship. In 1886, Schmiedeberg succeeded in producing cataleptic phenomena in rabbits by the use of ethyl-urethan. In 1904, Peters(11) discovered the cataleptic action of bulbocapnine; Baruk and de Jong(1, 9, 10) investigated this, as well as many related chemicals, more extensively and demonstrated the catatonic effect upon man and animals. With the discovery of new chemicals and chemical compounds, new tools are made available to the psychiatrist to investigate psychoses experimentally, and a new branch, experimental psychiatry, is emerging. The experimental psychiatrist has the advantage of knowing the one factor, in the causation of psychotic symptoms, the chemical that was administered to the patient and started the chain of reactions. The psychopathological genesis, however, of the psychotic phenomena will best be investigated by methods of the interpretative analytical branch of psychiatry. Of the chemicals used experimentally at present 2 are outstanding: mescaline, an alkaloid known in its crude form as peyote for hundreds of years, though only in the past few years chemically synthetized, and d-lysergic acid diethylamide tartrate (L.S.D.), a member of the ergot group. Although these chemicals are quite different in their chemical structure, in their effect upon normal subjects and psychotic patients they show great similarities with regard to the production of psychotic symptoms. The schizogenic effect of mescaline has been reported in a number of articles, most recently in a brilliant experimental and psychopathological publication by Paul H. Hoch(8). Our paper is concerned essentially with the description of the effect of d-lysergic acid diethylamide tartrate (L.S.D.) upon male and female individuals who, subsequent to the administration of this chemical, responded with the production of psychotic-schizophrenic-like phenomena.

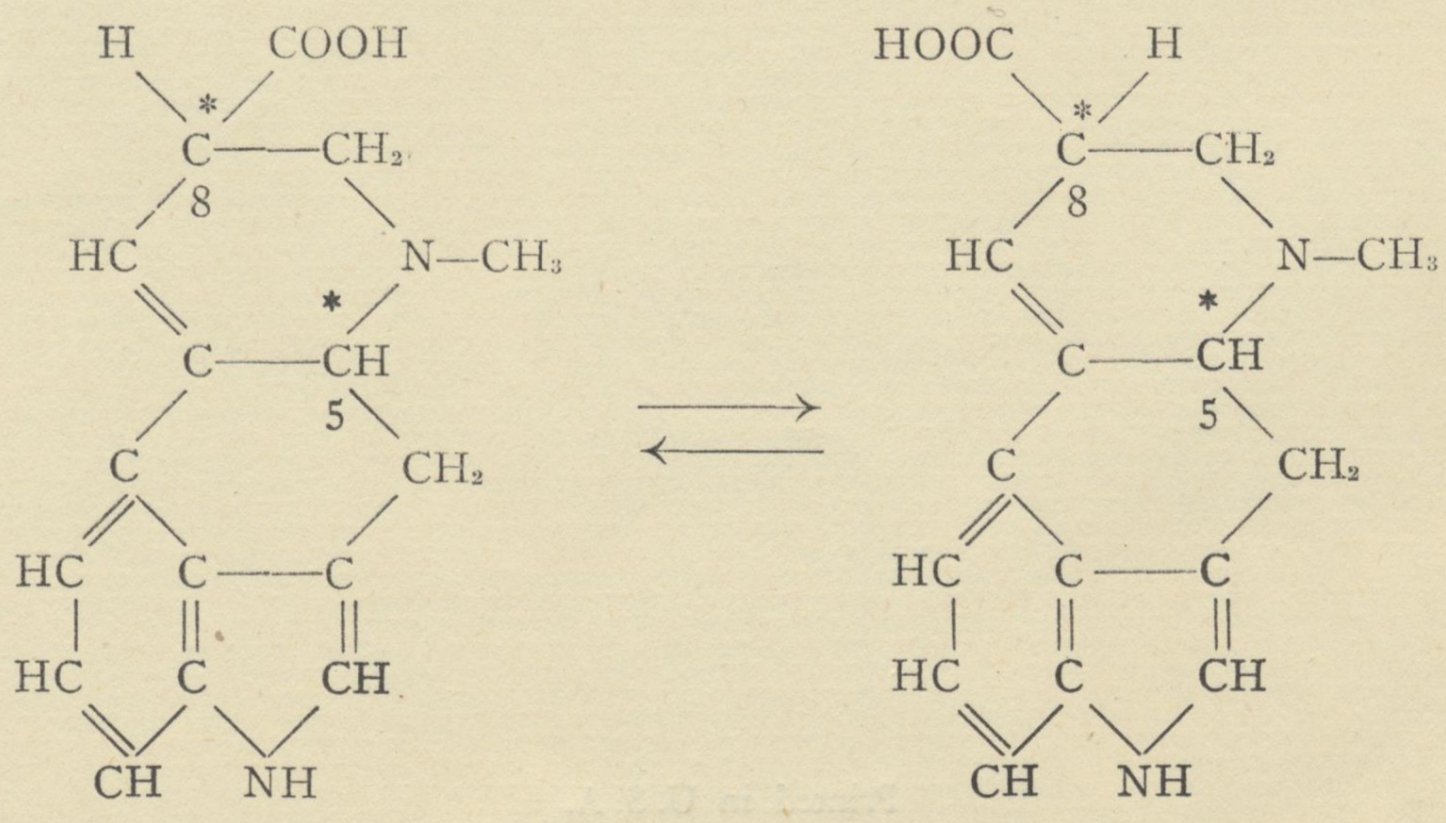
[1] Read at the 107th annual meeting of The American Psychiatric Association, Cincinnati, Ohio, May 7-11, 1951.

From the Department of Psychiatry, Harvard Medical School, and the Boston Psychopathic Hospital; Dr. Harry C. Solomon, Director.

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Chemistry and Pharmacology

L.S.D., which stands for the German *Lysergsäure Diäthylamid,* is the abbreviation used for the diethylamid tartrate of lysergic acid which, according to A. Stoll, A. Hofmann, and F. Troxler(17), is diastereomer but not structurally isomeric with isolysergic acid as seen in the accompanying formula.



It is water soluble and administered orally. Pharmacologically L.S.D. belongs in the group of the ergonovine substances. It has a definite effect upon the *in situ* uterus of the rabbit, and causes peculiar states of motor rigidity similar to the catatonic phenomena in the dog and cat as seen with bulbocapnine (19). In our own experiments we noted an especially strong physiological reaction in a 29-year-old very sensitive white girl who was menstruating at the time. She complained of most violent abdominal constrictions, which may have been caused by vehement uterine contractions. The peculiar psychological effect, seen as excitation in experimental animals, was first observed and described by the chemist, A. Hofmann. In his laboratory notes of April 4, 1943, he remarked that, while working with L.S.D., he noticed in himself a peculiar restlessness associated with slight dizziness. He had to interrupt his work and went home to rest. While at home, he felt as if intoxicated, a condition characterized by an extremely stimulated phantasy. After darkening his room, for the daylight bothered him very much, he had a most wonderful experience. Phantastic images of most extraordinary plasticity and intensive kaleidoscopic coloring passed before him. This state of intoxication lasted about 2 hours.

Literature

Following this discovery a number of authors investigated the effect of L.S.D. in self-experiments, on normal subjects, and on psychotics. W. A. Stoll(18), who first systematically investigated the psychological phenomena of L.S.D., confirmed Hofmann's experiences and reported as the most striking psychological findings disturbances in perception that led to hallucinations, acceleration of thinking, slight dimming of consciousness, but maintenance of judgment. He regarded the psychotic condition as an acute exogenous reaction type and pathologically as diencephalosis. Condreau(4) confirmed most of Stoll's findings, but reported that in his experiments the subjects' consciousness was not disturbed aside from the feeling of intoxication. He added that the subjects maintained their capacity of self-criticism, but showed increased distractibility and were less able to concentrate. The basic theme of thought remained unchanged, and the changes in feeling tone he felt to be merely an intensification of the previous underlying mood. He added as a new observation forced laughing and one instance of athetoid movements as suggestive of involvement of the diencephalon, thus contributing to W. A. Stoll's original conception. A. M. Becker(2) essentially confirmed the observations of Stoll and Hofmann and emphasized the astounding production of psychosis-like syndromes following the administration of mere "traces" of a chemical substance. He believes the psychological manifestations are the result of two different basic disturbances: affectivity and impulsivity on the one hand, and intentionality on the other. The most striking contrasts among his observations were manic-hyperkinetic and inhibited depersonalized manifestations. In contrast to Stoll, who termed L.S.D. a *"Phantasticum,"* Becker suggested the designation of *"Psychoticum"* for L.S.D. Umberto de Giacomo(6, 7), of Italy, in his experiments with rather large amounts of L.S.D. (300 to 500 gamma) observed in his patients catatonic-like phenomena, which were similar to those produced by bulbocapnine. M. Rinkel(12) and Victor H. Vogel(18) reported their experiences with diethylamide of lysergic acid, adding as new observations paranoic trends and, in contrast to previous publications, slowing of thinking and poverty of thought. Bush and Johnson(3) used L.S.D. as an aid in psychotherapy, and reported that their psychotic patients responded with an increase in activity and greater verbalization of psychopathology. They noted occasional short periods of confusion and disorientation, and occasional transitory visual hallucinations. Most of their patients showed some degree of euphoria.

Method and Procedure

In our own experiments, L.S.D. was given 17 times to 15 normal adult volunteers, students, nurses, and doctors, in the 19-48 age range, and, as freshly prepared solution, to some psychotics: dementia præcox and manic-depressive, depressive type. The observations on the psychotic patients are still in progress and will be published later. The

normal subjects, who were kept without breakfast, received L.S.D. in doses ranging from 20 to 90 gamma p. o., in most cases one gamma per kilogram body weight, while the psychotics were given 3 gamma per kilogram body weight. This increased dosage for psychotics was chosen on the basis of the unanimous reports in the literature that psychotic patients were particularly resistant to the effect of L.S.D. The subjects were kept under continuous observation by at least one of the authors for the first 5 hours and, on occasions, tape recordings of the subject's productions were made. The subjects remained under observation the same day at the hospital, and were seen again the following day. The main emphasis in our observations was on the clinical psychiatric picture. Routine neurological and circulatory system examinations were not done, but signs occurring in these areas were noted, if observed. In 9 of the experiments, electroencephalograms at or near 2 hours after L.S.D. were taken, and Rorschach tests were given to 5 normal subjects and concrete-abstract thinking tests to 2 subjects during the height of the L.S.D. reaction. Controls of EEGs and psychological tests were done while the subjects were in their normal mental state.

Results

I. *Disturbances of Thought and Speech.*—The most prominent psychological changes observed were those in thinking and speech. They were present in all our experiments. There was no cloudiness of consciousness, no intellectual weakness, but most frequently we observed difficulty in the power of expression. The subjects became more and more slowed down, poverty of thought became apparent, and the flow of speech became increasingly diminished and blocked. One subject, a middle-aged depressed patient, went into a complete stupor. In another instance occurred unwillingness to speak, a symptom similar to the negativism of the schizophrenic. Hesitancy, indecision, and impairment of abstract thinking were frequently present; also looseness of thought and actual disconnection with increased distractibility were common observations. As in schizophrenic patients, some of the subjects exhibited such phenomena as lack of spontaneity, irrelevance, pedantic imitation, and subjectively automatic speech. In one instance, we had the impression of the formation of a neologism. Acceleration of thought with flight of ideas associated with rhyming and punning; garrulity and loquacity of the hypomanic type were seen in a cyclothymic medical student within 45 minutes after the administration of L.S.D. In general, the effects appeared within 30-45 minutes after the oral administration of L.S.D., and disappeared gradually after 3-4 hours.

II. *Affect and Mood.*—Clear-cut blunting of affect and suspiciousness, as often seen in schizophrenic patients, were outstanding. These symptoms frequently led to feelings of indifference and unreality with disturbances in body image. The subjects experienced hostility and resentment, and on rare occasions ambivalence. The phenomena occurred about 15 minutes after the administration of L.S.D.; feelings of indifference and blunting tended to be protracted; suspiciousness, hostility, and resentment were always more transient. Changes in mood were twofold: euphoria and depression, which occurred in about equal number. Euphoria was either of the shallow elation type with silliness, as seen in the hebephrenic, or, in a cyclothymic subject, of the jovial and infectious type, as found in hypomanic and manic states. Depression was combined with dependency, indecision, insecurity, passivity, and feelings of being "lost." In no instance did we observe the happy and dreamy feeling of ecstasy as it has been described by other authors who experimented with L.S.D., mescaline, and other similar chemicals.

III. *Perception.*—Usually within 40 minutes after the intake of L.S.D. disturbances of perception were observed. Those of visual perception were most common and mainly of the illusional type. The subjects would see rippling or wavy lines on the wall that might evolve into geometrical pattern, or be associated with color such as yellow, orange, or pink. In some instances, subjects saw a thermostat on the wall as a crucifix but fully realized that the experience was an illusion. None of the subjects, however, had the feeling of seeing something of extraordinary beauty, as it was stated in early re-

ports on L.S.D., or as it may occur under the influence of mescaline.

Gustatory disturbances occurred frequently; the subjects experiencing a metallic or "funny" taste or heavy tongue.

Auditory perception was changed only in a few instances. The subject would hear a sound that was either near or distant, and in one instance of a depressed patient, the noise of a typewriter in an adjoining room was perceived as music, seemingly beautiful music.

The sense of time was disturbed in 11 out of 17 experiments. It was characterized by the feeling of time accelerated or retarded.

IV. *Hallucinations and Delusions.*—Disturbances in perception, in a complex way, often lead to hallucinations and delusions. A vivid phantasy, a pseudohallucination or illusion, in the process of mental dissociation, may ultimately appear as a real object outside the subject and thus constitute a real hallucination. By a similar process, changes in auditory perception, combined with existing suspiciousness, may lead to ideas of reference and delusions of persecution. It may be stated that hallucinations, predominant under the influence of most *phantastica,* subsequent to the injection of L.S.D. were rather meager and never showed the quality of an extraordinarily beautiful or threatening experience. The occasional visual hallucinations consisted mainly of formed images, which occasionally were preceded by crude flashes of light. Perhaps the above-mentioned disturbances of taste perception should be mentioned here as gustatory hallucinations. In only one instance we noticed an auditory hallucination, which consisted in hearing bells, although there were none anywhere around. Haptic hallucinations were experienced by two subjects. One male subject had the rather vivid feeling of his trousers being wet from urine, and one female schizoid patient was convinced that she lost urine and wet her slacks and the bed. She actually, later on, did wet the bed, and it may be possible that her hallucination was stimulated by autonomic excitation of the bladder mechanism. Morbid ideas were common; they included ideas of reference and ideas of influence. One female volunteer became quite paranoic and was still disturbed the following day. Major delusions, ideas of grandeur or persecution, as seen in the delusional states of the paranoic or paraphrenic, were not observed. That may be due, perhaps, to the fact that in our experiments on normal volunteers we used only relatively small amounts of L.S.D.

V. *Depersonalization.*—Alteration of personality occurred rather frequently. Those changes consisted mainly in the subject's feeling that his legs were either extraordinarily long or heavy; in one psychotic patient the feeling was that the leg between ankle and hip had disappeared entirely. Most common was the feeling of unreality as regard to the subject, himself, and the outer world. Though these phenomena were of minor magnitude, they, too, indicate symptoms particularly observed in the schizophrenic patient. In no instance were we able to elicit experiences of synæsthesias, as frequently seen in mescaline intoxications.

VI. *Behavior.*—The most and striking change consisted in underactivity, associated with lack of spontaneity and initiative. One schizoid-depressed patient went into a state of catatonia; another one became stuporous. A female schizophrenic patient, who had received 3 gamma/kg. body weight of L.S.D., became agitated; after an initial state of inertia, she suddenly stood up and went through many and various motions. She knelt down, kissing the wall, the floor, the examining table, and progressively became more and more excited. She tore off her clothes and became noisy to such an extent that the experiment had to be terminated by the intravenous injection of 0.5 g. of sodium amytal. In our normal subjects, overactivity or inappropriate behavior was rarely noted, but psychomotor manifestations, such as smiling, giggling, and laughing, more often appropriate than inappropriate, were frequently observed. This was particularly so in a student of cyclothymic personality make-up.

VII. *Intellect.*—In our normal subjects, intellectual functions were never disturbed. The subjects were aware of what they were doing at every moment of the experiment. Their memory also never became disturbed; each one was able to give, in a written report, a description of all the experiences he went through. Also, the psychotic patients did not show any particular memory defect.

Patients whose verbal expression became slowed down and finally completely ceased, as in the case of stupor or catatonia, were able the following morning, under sodium amytal or d-desoxy-ephedrine, to recall their thoughts or personal experiences of the day before under the influence of L.S.D.

VIII. *Autonomic Nervous System.*—All normal subjects and also the psychotic patients had numerous subjective complaints and symptoms. Since they mostly belong in the group of disturbances of the autonomic nervous system, they are best described here. The most common symptom was change in appetite, which more often was decreased, and associated with nausea, than increased. Complaints of headiness, giddiness, faintness, tremulousness, and shaking were frequently expressed. The subjects complained of chilliness and coolness of whole or part of the body, lump and "funny" feelings in abdomen, constriction with oppression in chest and precordial discomfort, violent cramps and constriction in the abdomen in a patient who just happened to menstruate. Objectively observed were flushing, sweating, shivering, and shivering with goosepimples. Tachypnœa, salivation, pallor, sighing, and urgency of micturation were scattered observations. Changes in pulse rate and blood pressure were of minor magnitude and observed only occasionally. Involuntary smiling, giggling, or laughing were considered in the nature of "risus sardonicus" where the subject described these phenomena as occurring without or against his will. One subject stated that in a smile he felt as if his facial muscles were like plastic wax being moved by some inexorable force. Pupils were often maximally dilated.

Gross disturbances of the cerebrospinal nervous system were not observed, except in some instances "dysarthria," which consisted of a transient stumbling over words and was never marked.

IX. *Electroencephalogram.*—EEGs were taken in 9 experiments at about the height of L.S.D. reaction, and compared with the EEG of the same subject in his normal state. In general, the EEG changes were only slight. Principal changes occurred in the alpha rhythm, which was characteristically increased in rate from 1-3 cycles per second. In one case, an individual who was very relaxed, a slowing of about 2 cycles per second was observed. Hyperventilation showed a diminished responsiveness and may be due to the subject's reduced cooperation.

X. *Psychological Tests.*

A. *Rorschach.*—Controlled Rorschach tests were given to 5 subjects at the height of L.S.D. reaction. All tests given during L.S.D. reaction showed abnormalities principally of the schizophrenic or paranoic type. There was noticed autistic thinking with decreased organization, contamination responses, and lack of logical thinking, also negativism and diminished emotional inhibition indicating anxiety, depression, and aggression. One Rorschach test revealed a moderately schizophrenic picture with autistic thinking and withdrawal.

B. *Concrete-Abstract Thinking.*—The tests consisted in employing proverbs and aphorisms and recording the subject's reaction. On the whole, the results, especially the wide range of responses in abstraction and overgeneralized and tangential thinking, were similar to those obtained in schizophrenic patients.

DISCUSSION

The common denominator in all our experiments with L.S.D. on normal subjects is a profound transformation and alteration of the psychic state of the individual, as it is a common factor in all psychotic states. The various mental phenomena that we have reported were brought about by mere traces (1:1,000,000g/kg. weight) of a chemical, d-lysergic acid diethylamide tartrate. The mental phenomena show similarities to symptoms that occur in actual psychoses. We noticed, predominantly, changes similar to those seen in schizophrenic patients. The subjects exhibited preeminently difficulties in thinking, which became retarded, blocked, autistic, and disconnected. The affect was shallow or there was clear-cut blunting. Feelings of indifference and unreality with suspiciousness, hostility, and resentment also approximated schizophrenic phenomena. Hallucinations and delusional disturbances though present were much less prominent or striking, but together with the manifestation

of depersonalization were most reminiscent of schizophrenic dissociation.

To a much lesser degree were there similarities to the confusional states. Gross clouding of consciousness was absent in our experiments, but illusional misinterpretations were not infrequently observed.

A few cases showed similarities to the manic-depressive states, with changes in mood of euphoria or depression. However, only in one cyclothymic-pyknic subject the intensity was of a hypomanic or manic state.

Delusions of grandiose or persecutory nature, familiar in the paranoic psychoses, were not seen.

We mention the similarities of the experimental phenomena to actual psychotic states in order to caution against fallacies that may occur in the interpretation of experimental psychotic disturbances. The same caution that is warranted in the application of an animal experiment to a pathological condition in man is needed in the application of the psychiatric experiment to natural psychosis. Our experiments have brought to light the fact that, in a short space of time, under the influence of a mere trace of a chemical agent in normal subjects, a variety of mental symptoms occur that are similar to natural psychoses, and that in psychotic patients an accentuation of existing, or elicitation of latent, schizophrenic phenomena takes place. It may be possible to assume that fundamentally the mechanism of origin of natural and experimental psychotic phenomena is a similar one: a chemical agent that pathologically stimulates selectively various higher, especially perceptive, brain centers with the result of hallucinatory and delusional experiences. H. J. DeShon, M. Rinkel, and H. C. Solomon(5) have already pointed out that the clinical effects of L.S.D. imply such an involvement of the higher and highest centers of the central nervous system, and perhaps of lower levels of the nervous system as well.

Many authors assume that chemical endogenous substances are the cause of schizophrenic psychosis. We must bear in mind that, in addition to d-lysergic acid, a great variety of seemingly unrelated chemical substances are capable of producing transitory psychotic-like symptoms. Although observations are still too few to allow the formulation of a well-founded scientific theory as to the chemical origination of psychotic symptoms, we strongly believe that this branch of experimental psychiatry is progressing in the right direction, and may some day provide an answer to the most perplexing problems in psychiatry.

SUMMARY

1. The effects of minute amounts of d-lysergic acid diethylamide tartrate (L.S.D.) on normal subjects, with an age range of 19-48 years, and some psychotic patients of the schizophrenic, depressive, and paranoic type are reported.

2. Psychotic phenomena and alterations of the autonomic nervous system were observed. The psychotic phenomena were predominantly schizophrenia-like symptoms that were manifested in disturbances of thought and speech; changes in affect and mood; perception; production of hallucinations and delusions; depersonalization and changes in behavior. The basic intelligence was not reduced.

3. Electroencephalographic examinations at the height of the L.S.D. reaction revealed only slight changes, principally increased alpha rhythm, except in one case where there occurred a slowing of about 2 cycles per second.

4. Rorschach tests showed abnormalities principally of the schizophrenic or paranoic type. Concrete-abstract thinking tests also, on the whole, showed responses similar to those obtained in schizophrenic patients.

5. No scientific theory for the origination of the natural psychotic phenomena or psychoses is being advanced, but the belief is expressed that experimental psychiatry progresses in the right direction.

Credits

Our preparation of L.S.D. was supplied, in ampules containing 1 mg. substance, by courtesy of Professor E. Rothlin, Director of the Pharmacological Laboratories of Sandoz Chemical Company, Inc., Basel, Switzerland.

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NEUROPHYSIOLOGY LABORATORY
HILLSIDE HOSPITAL
GLEN OAKS, N. Y.

CLINICAL EFFECTS OF A "STIMULANT" BARBITURATE

(Sodium 1:3-dimethylbutyl ethyl barbiturate) in Schizophrenics

By Harry H. Pennes, M.D.

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HARRY H. PENNES, M.D.*

Many barbiturates stimulate rather than depress the central nervous system in experimental animals but clinical evaluation of these drugs has been limited (15). Administration of a central-depressant barbiturate such as sodium amytal often produces transient amelioration of different symptoms in schizophrenics (6, 10, 3). These symptom changes are usually attended by a variable degree of hynotic (sleep-producing) effect which may proceed to actual sleep as the dosage is increased. In the drug therapy of schizophrenics the excessive narcosis produced by the central-depressant action of the barbiturates in common usage limits the total dosage which may be conveniently administered. It was considered possible that a central-stimulant barbiturate might possess the desirable therapeutic activity of the ordinary depressant barbiturates without the disadvantage of excessive narcosis.

The stimulant barbiturate utilized to test this hypothesis was 1,3-dimethylbutyl ethyl barbiturate, sodium salt (15), (hereafter designated as DMBEB) which is similar structurally to sodium amytal (14). A small number of observations has also been included on another stimulant barbiturate, namely, 3,3-dimethyl allyl ethyl barbiturate, sodium salt, (supplied for research purposes by Eli Lilly and Company, Indianapolis) (16). According to reports, DMBEB produces a period of increased alertness and restlessnes in unanesthetized dogs, followed by convulsions; the seizures, which occur only in warm-blooded animals, are violently tonic in type and the locus is probably the spinal cord; no hypnotic or anesthetic effects are noted in sublethal doses (13, 14,). The reflex contraction of m. tibialis anticus is augmented in spinal and barbital-anesthetized dogs; in this regard it is 1/250th as active as strychnine, one-fourth as active as picrotoxin, and more active than caffeine, cocaine, or ephedrine (9). The crossed-extension reflex in m. gastrocnemicus and respiration are also augmented (8). The convulsant activity of DMBEB may be antagonized by administration of sodium amytal (14). The sodium salt of 3,3-dimethyl allyl ethyl barbiturate produces a restless, frightened, or boldly vicious animal in which con-

* From the Department of Experimental Psychiatry (Paul H. Hoch, M.D.), New York State Psychiatric Institute.

vulsions finally ensue; blood pressure and body temperature rise while respiration is stimulated (16).

Gottlieb has previously observed that DMBEB produces a euphoric effect in depressed patients after oral administration in subconvulsant doses (4). The drug was likewise maintained at a subconvulsant level in the present study in order to rule out the possible therapeutic effect of a generalized seizure.

Procedure

Patients.—DMBEB was administered to 20 hospitalized schizophrenics, 8 males and 12 females. Mean age was 32.5 years; mean duration of illness, 13.4 years; mean duration of hospitalization, 2.2 years. The diagnostic categories were as follows: pseudoneurotic, 6; catatonic, 2; hebephrenic, 1; mixed or unclassified schizophrenic, 11. The pseudoneurotics presented diffusely neurotic symptomatology in a basically schizophrenic setting and were diagnosed according to the criteria of Hoch and Polatin (7). The group of mixed and unclassified schizophrenics presented admixtures of catatonic, hebephrenic, and paranoid components as well as the primary features of the disease. Gross catatonic stupors or excitements and diagnostic categories other than schizophrenia were not included. Most of the patients were quite well preserved. Sixteen of the 20 cases had either no or slight deterioration (6 pseudoneurotics, 2 catatonics, 1 hebephrenic, and 7 mixed or unclassified schizophrenics); these patients were chiefly short-term, voluntary hospital admissions. The remaining 4 subjects displayed an advanced degree of schizophrenic deterioration and were long-term, state hospital patients. All but 2 patients had received at least one course of electric convulsive and/or insulin coma therapy at some time during the course of the illness.

Drugs.—DMBEB was dry-sterilized in an electric oven at 150-160° C. for one to two hours. Immediately prior to intravenous injection the drug was dissolved in 20.0 cc. of sterile distilled water at a concentration of 5.0 mg. per cc. A colorless solution was quickly formed. The average dose of DMBEB that was administered was 63.5 mg. in the 20 subjects. An injection rate of about 5.0 mg. per minute was used in all subjects. The same procedure was followed in the administration of 3,3-dimethyl allyl ethyl barbiturate, sodium salt, to 2 patients both of whom also received DMBEB on another occasion. Each patient also independently received intravenous injection of sodium amytal (Amobarbital sodium, Eli Lilly and Company, Indianapolis), 250-500 mg. dissolved in 10.0 cc. of sterile distilled water at a rate of about 50 mg. per minute, as well as 20.0 or 40.0 mg. of pervitin hydrochloride (Smith,

Kline and French Company, Philadelphia) in 2.0-4.0 cc. of solution in one minute. Six patients also received intravenous sodium amytal in the same dosage and rate of administration as that of DMBEB. The drugs were administered in random orders to the various subjects. Injections were performed between 8:00 A.M. and 4:00 P.M. without limitation of food or the subject's usual ward activities. Changes in the patient's base-line clinical status were recorded in protocol form for a period of at least 48 hours following injection.

Results

I. *Mental Reactions.*—DMBEB reduced clinical symptoms in 11 (55.0 per cent) of the series. Three patients (15.0 per cent) showed only increase of symptomatology and 6 (30.0 per cent) had no reactions except for side-effects to be described in section II.

A. *Symptom-reducing effect.*—The therapeutic action was most pronounced in the pseudoneurotic group. Four out of 6 patients in this group experienced complete or almost complete relief of anxiety and tension, phobic concerns, irritability and hostility, and depressive manifestations. All 3 obsessive-compulsive patients in this group experienced amelioration of the disabling symptomatology, slight in 1 and quite complete in 2. The usual duration of relief was two to eight hours, but in 2 subjects the improvement lasted 16 to 24 hours. The symptomatic improvement began during the injection, usually concurrently with cephalic sensations described variously as "light-headed" or a "subtle feeling of relaxation." In the 14 overt schizophrenics (hebephrenics, catatonic, mixed, and unclassified), 7 patients showed slight to moderate therapeutic responses which were in general less complete than those of the pseudoneurotics. The effects in the overt schoziphrenic group consisted principally of signs of personality reintegration with more normal emotional feeling and display, less self-concern and self-preoccupation, an increased tendency to contact the environment, and a somewhat higher verbal productivity. The most deteriorated cases responded least to the drug in a therapeutic sense; these patients also responded least to sodium amytal and pervitin.

These therapeutic responses to DMBEB were qualitatively identical with those often produced by central-depressant barbiturates. However, the therapeutic response to DMBEB was more complete than to sodium amytal administered in the same low dosage to 6 patients (30, 50, 65, 89, 100, and 100 mg.); this was particularly true in the pseudoneurotic group. Moreover, clinical signs of hypnosis with DMBEB occurred in only 4 patients in the series and consisted of transient drowsi-

ness and a sleepy expression; slurred speech, nystagmus, excessive euphoria, and other signs of acute barbiturate intoxication were not present. Some of the most completely relieved subjects reported no feelings of drowsiness and displayed no objective signs of such after DMBEB. In addition, DMBEB produced none of the signs of psychic "stimulation" that usually occurred after pervitin, a cephalotropic sympathomimetic amine. Administration of pervitin was almost invariably attended by a positive "stimulation" aspect consisting of increased alertness and energy, feelings of optimism, and heightened psychomotor activity. In patients responding therapeutically to DMBEB, the action may therefore be summarized as a symptom neutralization or elimination without concomitant "stimulation" and, as described above, with occasionally a minor degree of sedation.

B. *Symptom-increasing effects.*—Symptom intensification occurred in 3 patients as follows: one subject wept copiously, felt sorry for himself, and complained bitterly of mistreatment by doctors; a second subject had a brief, opisthotonic seizure of hysterical origin identical with the type occurring in the drug-free state; the third subject felt more perplexed, confused, and depressed. These reactions were all exacerbations of pre-existent manifestations which had also previously increased spontaneously or in response to amytal and/or pervitin. These excessive reactions appeared to be precipitated "psychologically" as a secondary reaction to the unusual side effects produced by DMBEB (see Section II). None of these subjects showed signs of acute barbiturate subnarcosis. In addition, the reactions did not entirely resemble the exaggerated emotional discharges so often produced after pervitin, since none of the primary "stimulation" effects of pervitin on psychomotor processes was present.

C. *Absent mental reactions.*—Six patients (30.0 per cent) had no reactions to the drug in terms of pre-existent symptomatology. In 3 of these, the side-reactions to the drug were so intense that the patients were preoccupied with little else. In the 3 other subjects, there were no mental changes of significance despite the absence of considerable side-effects.

II. *Side Reactions.*—Practically all (18 out of 20) patients experienced side-reactions. The toxic effects appeared during the injection and the sequence of events was approximately the same in the majority of subjects. Tingling sensations or other paresthesias began in any part of the body, and rapidly became pruritic in nature; this was followed by or associated with hot and cold sensations and a mottled erythema in face, chest, and trunk. Pilomotor reactions often appeared on arms

and back; less frequently there were feelings of vague abdominal discomfort or slight nausea; repeated, forceful sneezing; and occasionally burning of the eyes. Cephalic sensations previously referred to (Section IA) usually began early in the injection in a small minority of subjects; on assuming the erect position some patients complained of a vague vertigo of nonspecific nature and minimal degrees of ataxia were observed.

The maximum dosage of DMBEB that could be comfortably tolerated by the subjects was limited by the pruritis, which was the most frequent side-reaction (18 out of 20 patients). The itching usually began in scalp, face, eyes, soles of feet, or genital areas. Spread was rapid and in some cases the pruritis became generalized; some subjects rubbed and scratched vigorously and became extremely distressed, tending to disregard the other actions. All the side-reactions enumerated above were of relatively short duration, usually subsiding in 10 to 30 minutes. In some cases, the pruritis persisted for several hours, although distress was always minimal after the first 10 to 30 minutes.

In 17 cases, the injection was discontinued when the above reaction definitely appeared, particularly the pruritis. The average dosage administered to these subjects was 64.4 mg. total or 1.01 mg. per Kg. of body weight. The threshold dosage for the appearance of any effect, mental or toxic, was in the neighborhood of 30.0 mg. The range of effective therapeutic dosage without toxicity was therefore quite narrow. Two patients received full dosage of 97.0 and 101.0 mg. total without side-effects and a marked symptomatic improvement in one.

Two subjects displayed seizures at dosages of 59.0 mg. (0.65 mg. per Kg.) and 68.0 mg. (1.04 mg. per Kg.), although other subjects receiving equal or larger dosages did not display seizures. The involuntary movements were of a jerky, nonrhythmic myoclonic type; in one subject the movements were more or less generalized and in the other limited to the right arm. The movements occurred in cycles of about 15-20 seconds duration for a period of about 10 minutes. Consciousness was not impaired during the seizures; deep reflexes were normal in the inter-seizure phases; there were no facial weakness, pupillary changes, nystagmus, Hoffman or Babinski reflexes. The seizures appeared in these two subjects after the itching had become severe and generalized. Continued experience with the drug showed that no patient developed a seizure if the injection was discontinued at or shortly after the appearance of the pruritis.

None of the side-effects of DMBEB occurred after sodium amytal with the exception of its quite minor hypnotic action. Pervitin side-effects were totally distinct, consisting usually of mouth and throat

dryness, peripheral numbness and lightness, chest pressure, and cephalic tightness or aching.

Sodium 1,3-Dimethyl Allyl Ethyl Barbiturate.—This stimulant barbiturate was administered in doses of 1.26 and 1.37 mg. per Kg. to 2 subjects. The same side-effects were produced as with DMBEB and with the same apparent intensity. One subject experienced generalized myoclonic-like twitchings. No therapeutic effect on mental symptomatology was observed.

Discussion

DMBEB has been classified as a "stimulant" barbiturate in animals in the experimental pharmacologic literature because of its convulsion-producing property and augmentation of spinal reflexes (13, 14, 8). The epileptogenic action was confirmed in this clinical assay of the drug inasmuch as 2 subjects had seizures under the drug, the dosage being maintained at the subconvulsant level in the other patients. The seizures occurring in these 2 subjects were of myoclonic type, whereas Swanson and Chen reported that the drug produced severe convulsions of tonic type in laboratory animals (14). This difference as to type of convulsion may be a species difference or reflect the limitation of dosage in man. The median convulsant dosage after intravenous administration to guinea pigs, rabbits, cats, dogs, and monkeys ranged from 2.0-3.0 mg. per Kg. body weight (14), whereas the brief myoclonic episodes with DMBEB in this series occurred with dosages of 0.65 and 1.04 mg. per Kg.

The numerous side-reactions observed in man have not been reported in animals; some of these side-reactions are purely subjective and therefore not observable in animals. Knoefel found that DMBEB produced a stage of increased alertness and restlessness prior to the seizures (8); dogs under sodium 1,3-dimethyl allyl ethyl barbiturate became restless and also appeared frightened or boldly vicious prior to the onset of convulsions (16). These apparent changes in emotion and behavior in animals could have been secondary to a highly distressing action such as occurred in man, mainly the severe paresthetic and pruritic response. Either a peripheral or central locus of action might underlie the typical constellation of tingling, burning or cold, pruritis, pilomotor contractions, erythema and sneezing. The sneezing in man may be analogous to the respiratory augmentation observed in animals (16). Gottlieb noted that the toxic reactions to DMBEB in man were not significantly affected by administration of antihistaminic drugs (4).

Despite the motor stimulation caused by DMBEB in man and reported in animals, there was little or no evidence that the drug acted

as a "psychic stimulant" in patients. The term "psychic stimulation" in man is generally applied to the exaggerated emotional and behavioral phenomena of subnarcosis as with intravenous sodium amytal, or to the "primary" heightening of mood or psychomotor processes, as with the cephalotropic sympathomimetic amines. Neither of these types of reactions occurred after DMBEB. In this respect the drug may be grouped with such agents as metrazol and strychnine which are potent convulsants but relatively weak "psychic stimulants." The absence of obvious signs of "psychic stimulation" with DMBEB in man may be associated with the fact that the seizure locus in animals is apparently the spinal cord (14).

Although DMBEB has been reported to have no hypnotic or anesthetic effects in animals (14), a weak hypnotic effect was observed in the minority of the patients of the present series. This difference may reflect species variation or technical limitations in animal experimentation inasmuch as a slight degree of narcosis is often purely subjective.

From the therapeutic point of view, DMBEB produced symptom amelioration in 11 out of 20 or 55.0 per cent of the series; the effects were most complete in pseudoneurotic schizophrenics. Gottlieb obtained almost the same results in different patient material, i.e., 60.0 per cent improvement, after oral administration in a series of 10 severely depressed patients, only one of whom was diagnosed as a schizophrenic (4). It has not been deemed advisable to establish therapeutic value on more than the present preliminary tentative basis because of the high toxicity of the drug which would preclude therapeutic application. The same conclusion was reached by Gottlieb (4).

The observed therapeutic activity of DMBEB cannot be explained in terms of its weak hypnotic-narcotic action because symptom alleviation (particularly in pseudoneurotic schizophrenics) occurred without appreciable such action. In view of this fact and the absence of obvious "psychic stimulation," it is apparent that the therapeutic action of the drug requires another explanation. Two hypothetical explanations are the following:

1. DMBEB really does possess "psychic stimulation" properties and in addition the hypnotic action of the ordinary barbiturates; the balance between these two actions is such that a net weak hypnosis is occasionally the resultant in man. In this case it would have to be assumed that the therapeutic action is retained despite the theoretically almost complete cancelling-out of narcotic and stimulant effects in so far as level of consciousness is concerned. In support of such a possibility is the clinical observation that in simultaneous administration of amytal and benzedrine to mental patients, considerable therapeutic activity may ensue

despite a fairly complete mutual neutralization of the narcotic and stimulant actions of the two drugs (11). In this connection it may be observed that Gottlieb interpreted the euphorizing action of DMBEB in mental depression as a consequence of its "stimulant" properties and from this concluded that amytal may exert its euphorizing action in the same condition by a stimulant rather than a narcotic action (4). Gottlieb did not report any hypnotic action of DMBEB in his series such as was observed in the present study; the difference may possibly be a function of the oral route of administration in his study as compared with the intravenous route in this report. His data could also be interpreted in terms of a narcotic rather than a stimulant action of DMBEB and the beneficial effect of amytal in depression still explained in terms of a narcotic action rather than a stimulant one.

2. The second hypothetical mechanism for the therapeutic action of DMBEB would be that the drug exerts this effect by a mechanism other than central depression or stimulation. Direct evidence for this interpretation is lacking. However, there are several sets of data which suggest that the ordinary central-depressant barbiturates exert their therapeutic action on mental symptomatology independently of their hypnotic-narcotic actions. These data are the following: (a) a few subjects display almost complete relief of symptomatology after intravenous injection of small amounts of sodium amytal before any or much intoxication is apparent in the form of drowsiness, slurred speech, or nystagmus. Conversely, a few subjects show little change in the mental status even though the central-depressant action may be carried to the point of sleep (10, 5). (b) The first effect of the barbiturates on the human electroencephalogram is the appearance of relatively rapid (20-25 sec.), medium-high voltage activity, particularly in the frontal leads (11, 1, 12). The appearance of this activity coincides temporally with reduction of anxiety and tension in some patients and the appearance of a more or less euphoric state (11, 12). The physiologic significance of this rapid activity has not been fully determined as yet but in any event it is distinct from the EEG charges which are usually accepted as manifestations of depressed consciousness, i.e., high voltage, slow activity (2).

In view of these considerations, it is possible that both DMBEB and the ordinary barbiturates owe their therapeutic effect on mental symptomatology to some hitherto undisclosed feature of their action. The pharmacologic literature contains reference to a large number of motor stimulant barbiturates which have never received clinical assay. These compounds show no underlying uniformity of chemical structure and many are in the thiobarbiturate series. The possibility exists that

therapeutic action may be obtainable with some of these drugs without the excessive toxicity of DMBEB.

Summary

The "stimulant" barbiturate, sodium 1,3-dimethylbutyl ethyl barbiturate, was administered intravenously to 20 patients with various forms of schizophrenia in a preliminary assay of its therapeutic value.

1. The drug exerted an irregularly occurring therapeutic effect (55.0 per cent) which was of most complete degree in pseudoneurotic schizophrenics. It has not been deemed advisable to establish further the therapeutic efficacy because of the relatively high toxicity which would preclude therapeutic application.

2. In accord with the literature that the drug is a convulsant in animals, 2 patients in this series had myoclonic seizures; in the remaining subjects the dosage was maintained at a subconvulsant level. A small minority of subjects showed weak signs of central nervous system depression in the form of slight drowsiness; the central-depressant action has not been reported in animals.

3. The therapeutic effect of the drug usually occurred independently of its weak and infrequent central-depressant action. No evidence was obtained that the drug acted as a "psychic stimulant" in the sense of heightening of mood and psychomotor processes.

4. Several explanations of the mechanism of the therapeutic action were offered and the desirability of further investigation of the stimulant barbiturate series indicated.

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EFFECT OF ATARACTICS ON SOME CONVULSANT AND DEPRESSANT AGENTS IN MICE.*

by

P. Shore and J. D. McColl

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Proofs to: Dr.J.D.McColl
Frank W. Horner Ltd.
Box 959
Montreal, Que.
Canada

Among the varied activities of the ataractics (chlorpromazine, reserpine, benactyzine, etc.), the alteration of the action of convulsant and depressant agents appears to be one of their common properties. There is ample evidence of either facilitation with, or antagonism to, one or another chemical convulsant. However, a detailed comparison of the effects of ataractics on several convulsants has not been reported. Their action in enhancing the depressants, such as alcohol and barbiturates, is also well known (Courvoisier et al, 1953; Berger, 1955, 1957; Bianchi 1955, 1956; Chen & Bohmer, 1956).

From these reports it is clear that the ataractics must act on specific and perhaps different portions of the cerebrospinal axis. It was anticipated that the comparison of their effect on a variety of convulsant and depressant drugs would suggest, in an approximate way, a similarity or difference in this site of action.

The results to be reported here were obtained following the administration of several clinically useful ataractics and some congeners, in the presence of pentylenetetrazole, picrotoxin, strychnine, nicotine and phenobarbital, to intact mice.

Experimental Methods

CFW mice weighing between 18 and 20 grams were used; all compounds were injected intraperitoneally in a volume of 0.2 ml. The experiments were carried out at a room temperature of 80 - 82°F.

The clonic convulsion (produced by nicotine, pentylenetetrazole, strychnine or picrotoxin*) was taken as the end point and the CD_{50} in terms of mgm./kgm. was calculated from the observed data. (LITCHFIELD & WILCOXON 1949).

The increase in the normal duration of phenobarbital hypnosis (measured by the loss of righting reflex) produced by these compounds was investigated. The intensity of the potentiation of phenobarbital by these agents was compared in the mouse by a series of dose-response curves obtained by varying the dose in the presence of a constant dose of phenobarbital (30 mgm./kgm.)

Preliminary experiments were carried out to establish the latent period of the phenobarbital and to ensure that the doses of the ataractics used were subconvulsant. The latter were injected 15 minutes before the administration of either the convulsant or the barbiturate. Reserpine, being slower acting than the other agents, was given 4 hours before.

Twelve compounds, including chlorpromazine, reserpine and meprobamate were tested. Five of these were clinically useful ataractics while others were selected because of their structural relationship to benactyzine (Table I).

* Pentylenetetrazole and picrotoxin were obtained from Mann Research Laboratories; nicotine 95% from Eastman Organic Chemicals; strychnine sulfate from T. & H. Smith, Ltd.

Results

The alteration of the CD_{50} of the four convulsants by the various compounds tested are summarised in Table II. All compounds modified the convulsant dose of one or more convulsants; however, only three (benactyzine, pipradol and SKF 525A) affected that of all convulsants.

In general, the main action was facilitation of the CD_{50}. The exceptions to this were the antagonism of pentylenetetrazole and strychnine convulsions by meprobamate and of nicotine convulsions by chlorpromazine, benactyzine, adiphenine and Histol.

With pentylenetetrazole, the degree of facilitation of the CD_{50} produced by the ataractics, was remarkably similar at the different dose levels employed. The tonic phase of the convulsive seizures was abolished by all the diphenylmethane derivatives, and the duration of the clonic seizures was increased by benactyzine.

All the compounds tested either facilitated the convulsive doses of picrotoxin or were inactive. The tonic phase of the convulsions was abolished by pipradol, diphenhydramine, Histol and SKF 525A.

Comparatively few of the compounds tested facilitated the CD_{50} of strychnine and that, to a lesser extent than with the other convulsants. Meprobamate produced antagonism and, with this exception, in these cases where the compound affected the convulsant dose, the action was of the same order. Reserpine, pipradol, Histol and SKF 525A abolished the tonic seizure phase. Reserpine prolonged the duration of the convulsions by 50%.

With nicotine, a greater range of effect of these compounds on the CD_{50} was observed. Chlorpromazine, benactyzine and Histol

antagonized the convulsions as did adiphenine. Azacyclonol, pipradol and SKF 525A abolished the tonic phase.

The effect of some of the ataractics on the hypnotic action of phenobarbital is shown in Table III. The time of onset was significantly shortened with each compound used while the duration of action was significantly prolonged .

Further indication of the intensity of this enhancement of phenobarbital action can be seen in Figure 1. These dose-response curves demonstrate the relative effectiveness milligram for milligram of these compounds. Chlorpromazine was the most potent, while benactyzine and Histol appeared somewhat similar to each other. Azacyclonol and meprobamate were the least effective. The slope of the dose-response curve for meprobamate was considerably different from those of the other compounds.

Discussion

Interpretation of these results as to the similarity or difference of the site of action on the central nervous system is dependent upon our knowledge of the focus of action of the convulsant agents. While this localization of central convulsant action is not definitely known, it is generally acknowledged that pentylenetetrazole acts predominantly on the cerebral cortex, while the medullary and pontine regions are less sensitive. Picrotoxin has its predominant action on bulbar structures while strychnine acts at a lower level of the cerebrospinal axis. Nicotine is believed to produce its central convulsant action at the level of the diencephalon.

It must be acknowledged that the convulsants act simultaneously at different levels of the central nervous system. Our results suggest

that the compounds which influence the clonic convulsant pattern of one or more of these agents may also affect several regions of the central nervous system.

Comparison of ataractics by means of their effect on convulsants does not necessarily imply that those drugs which modify convulsive seizures are ataractics, or even specific for central nervous system effects.

SKF 525A and adiphenine are examples of compounds which modify the convulsants and yet possess little or no specific action on the central nervous system.

BRODIE ET AL (1955) have described the action of SKF 525A as inhibiting metabolic biotransformations. They have pointed out an essential difference between compounds such as SKF 525A and chlorpromazine. If a mouse just awakening from hexobarbital anesthesia is injected with chlorpromazine, a recurence of hypnosis results; if SKF 525A is injected no such effect is observed. The compounds in Table III were tested by this criteria and in no case did hypnosis recur. This indicates that these compounds must have a predominant effect of sensitising portions of the central nervous system rather than of altering the rate of metabolism of the convulsant and depressant agents.

Adiphenine, a potent antispasmodic, may also be differentiated from these other agents by its inability to enhance the action of barbiturates (HOLTEN AND LARSEN 1956). HOLTEN AND SOENE (1955) also observed adiphenine was inactive in normalizing stress induced behaviour in the rat.

Benactyzine is also a potent antispasmodic agent(HOLTEN AND LARSEN 1956). This property possibly contributes to the alteration of the action of the convulsant agents. However, the enhancement of

barbiturate activity, together with its effect on all four convulsants, emphasizes its predominant action on the central nervous system.

With these reservations in mind as to mixed pharmacological action of the compounds it is nevertheless interesting to speculate on the implications of the results observed with chlorpromazine, benactyzine, and Histol on nicotine-induced convulsions.

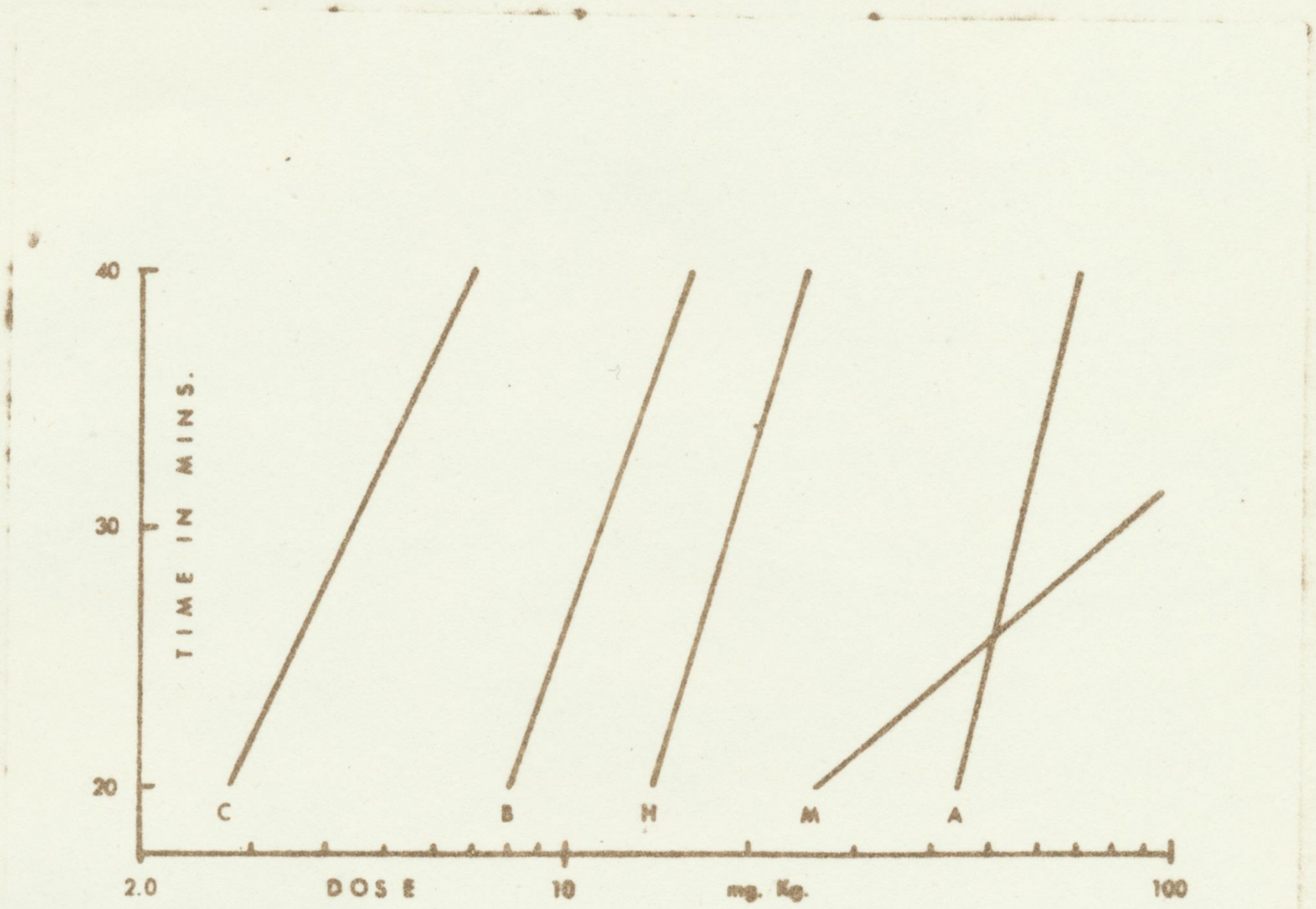
Further evidence of the nicotinolytic action of chlorpromazine, benactyzine and Histol has been observed by McCOLL AND SACRA (1957). In mice, the simultaneous administration of the histamine releaser 48/80 reversed the antagonism of these compounds to nicotine. Pentylenetetrazole-induced convulsions were unaltered in the presence of these compounds and 48/80.

Meprobamate was also unaffected by this treatment. The implication of these findings must await further study presently under way.

[redacted] (1957) has recently classified ataractics as either "autonomic suppressants" (chlorpromazine, benactyzine, etc.) or as "central relaxants" (meprobamate, nephanetin) on the basis of their varied actions. Our results confirm the logic of differentiating the mode of action of meprobamate from that of chlorpromazine and of benactyzine, but they also demonstrate the desirability of division of "autonomic suppressants".

On the basis of the similarity of the pharmacological action of benactyzine and Histol, this latter compound was tested clinically for ataractic potency in patients with neurosis. Preliminary results confirm these laboratory observations as to ataractic action. Like benactyzine, Histol has been observed to "normalize" stress induced behaviour in the cat (SACRA, [redacted] AND McCOLL, 1957).

Figure 1



Dose response curves for effect of chlorpromazine (C), benactyzine (B) Histol (H), meprobamate (M) and azacyclonol (A) on duration of hypnosis in mice produced by 30 mgm./kgm. phenobarbital.

Summary

1. Chlorpromazine, reserpine, meprobamate, asacyclonol, benactyzine and several diphenylmethane derivatives produce either facilitation with or antagonism to the clonic convulsive dose of pentylenetetrazole, picrotoxin, strychnine or nicotine when tested in mice.

2. Chlorpromazine, benactyzine, Histel, asacyclonol and meprobamate augmented the onset, duration and intensity of action of phenobarbital in mice in that order of decreasing activity.

3. On the basis of their action on convulsant agents the results of this study indicate that the compounds studied appear to act at several and, in some cases, different, regions of the central nervous system.

4. On the basis of the similarity to benactyzine in relation to its actions on convulsants and depressants, Histel was predicted to possess ataractic activity. Clinical studies subsequently confirmed this prediction.

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Kolton	.....	Chemische Fabrik Promonta Hamburg, Germany
Meprobamate	.....	Wallace Laboratories New Brunswick, N.J.
SKF 525A	.....	Smith, Kline & French Philadelphia, Penn.
Pipradol and Azacyclonol	.....	Wm. S. Merrell & Co. Cincinnati, Ohio.
Chlorpromazine	.....	Poulenc, Ltd. Montreal, Quebec.

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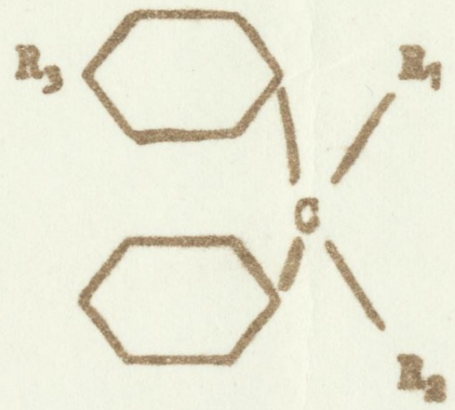
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Legend for Figure 1.

Dose-response curves for various ataractic agents in enhancing the duration of action of phenobarbital in mice. All compounds given intraperitoneally together with 30 mgm./kgm. phenobarbital.
(C - Chlorpromazine, B - Benactyzine, H - Histol, M - Meprobamate, A - Azacyclonol)

Table I

STRUCTURAL FORMULAE OF DIPHENYLMETHANE DERIVATIVES TESTED



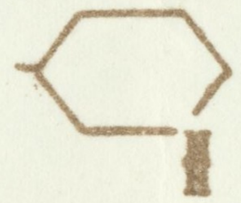
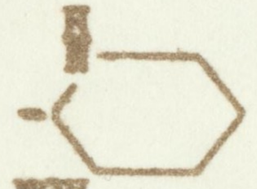
Compound	R_1	R_2	R_3
Benactyzine	OH	$COO\ CH_2\ CH_2\ N.(C_2H_5)_2$	H
D.M.A.	OH	$COO\ CH_2\ CH_2\ N\ (CH_3)_2$	H
Adiphenine	H	$COO\ CH_2\ CH_2\ N\ (C_2H_5)_2$	H
SKF. 525A	C_3H_7	$COO\ CH_2\ CH_2\ N\ (\ C_2H_5)_2$	H
Histol	CH_3	$OCH_2\ CH_2\ N\ (CH_3)_2$	Cl
Diphenhydramine	H	$OCH_2\ CH_2\ N(CH_3)_2$	H
Azacyclanol	OH		H
Pipradol	OH		H
Kolton	H	$OCH\ (CH_2CH_2)_2\ NCH_3$	H

Table II

THE EFFECT ON CD_{50} OF CONVULSANT AGENTS BY THE COMPOUNDS TESTED IN MICE

Compound	Dose mgm./kgm.	Pentylenetetrazole CD_{50} mgm./kgm.	Pentylenetetrazole C/T (1)	Picrotoxin CD_{50} mgm./kgm.	Picrotoxin C/T	Nicotine CD_{50} mgm./kgm.	Nicotine C/T	Strychnine CD_{50} mgm/kgm	Strychnine C/T
Control	-	56 (52-60)	-	4.5 (4.2-4.8)	-	2.2 (1.3-3.1)	-	1.3 (1.2-1.4)	-
Reserpine	10	36 (28-44)	1.6	3.1 (3.0-3.2)	1.5	0	-	0	-
Chlorpromazine	10	0 (3)	-	0	-	3.9 (3.4-4.7)	0.6	0	-
Meprobamate	100	98 (91-140)	0.6	0	-	0	-	1.8 (1.6-2.0)	0.7
Benactyzine	50	35 (31-38)	1.6	0.8 (0.7-0.9)	5.6	4.5 (3.7-5.3)	0.5	0.7 (0.6-0.8)	1.9
D.M.A. (2)	50	35 (30-37)	1.6	3.5 (3.2-3.8)	1.3	0	-	0	-
Adiphenine	100	0	-	0	-	9.0 (8.4-9.6)	0.3	0	-
S.K.F. 525A	50	34 (28 - 37)	1.6	1.0 (0.9-1.1)	4.5	1.2 (1.0-1.4)	1.8	0.9(0.8-1.0)	1.4
Histol	50	34 (30-38)	1.6	1.3 (1.1-1.5)	3.5	3.5 (2.5-4.7)	0.6	0	-
Diphenhydramine	25	0	-	0	-	0	-	0.9 (0.8-1.0)	1.4
Azacyclonol	100	0	-	0	-	0.9 (0.8-1.0)	2.5	0.5 (0.4-0.6)	2.6
Pipradol	25	23 (20-26)	2.4	1.4 (1.0-2.0)	3.2	0.9 (0.8-1.0)	2.5	0.8 (0.7-0.9)	1.6
Kolton	25	0	-	0	-	0	-	0	-

(1) Ratio of CD_{50} of Control to CD_{50} of Treated

(2) Dimethyl analogue of Benactyzine

(3) 0 - no effect

~~12-12-12~~

Table III

EFFECT OF SOME ATARACTICS ON THE TIME OF ONSET AND DURATION OF ACTION OF PHENOBARBITAL IN MICE.

Compound	Dose I.P. mgm./kgm.	Time of Onset (Min. ± S.E.M.)	Duration of Action (Min. ± S.E.M.)
Phenobarbital	30	15 ± 1.7	12 ± 2.5
+ Histol	50	7 ± 2.2	82 ± 5.1
+ Chlorpromazine	5	3 ± 0.7	42 ± 2.6
+ Benactyzine	10	5 ± 1.5	33 ± 5.3
+ Meprobamate	50	5 ± 0.3	25 ± 1.7
+ Amacyclonol	50	10 ± 1.3	26 ± 3.9