the present report, a quite different analysis of the relationship of dose to response has been published (*8*).

DEWITT STETTEN, JR.
National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland

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28 June 1956

Activity of Cerebral Neurons in the Transition from Wakefulness to Sleep

The transition from wakefulness to sleep—whether natural or induced by barbiturates—is accompanied by a change in the electric activity of the brain, which has been classically described as a passage from a "desynchronized" to a "synchronized" state. Recent studies of this change in electric activity, by means of microelectrodes (*1*, *2*), have shown that it is related to the patterns of activity of cortical and thalamic neurons; synchronization is accompanied by a grouping, and desynchronization by a lack of grouping, of their action-potentials.

On the basis of the time, phase, and amplitude characteristics of the grouped action potentials, it has been inferred (*2*) that, in the synchronized state, some of the neurons of the diffuse thalamic projection system become active in a regular sequence, so that a wave of activity approaches, reaches, and goes beyond the tip of the recording microelectrode.

This report presents direct evidence, obtained by the use of paired microelectrodes, for the sequential character of the propagation of impulses during the synchronized state (*3*).

Experiments were performed in cats that had been anesthetized with Nembutal. Paired microelectrodes made of stainless steel were stereotaxically directed into the diffusely projecting nuclei of the thalamus, and the recording points were subsequently checked by histological control (*4*). Tracings were obtained through two identical amplification channels and a double-beam cathode-ray oscillograph (Fig. 1).

Figure 2*A–G* shows a series of groups of action potentials (from one complete spindle-burst *5*) recorded during the synchronized state from the center median of the thalamus, with a transversally directed pair of microelectrodes. In *A*, the activity reaches first the medial electrode and later the lateral electrode, indicating propagation in the lateral direction. In *B*, it reaches both electrodes at the same time, indicating propagation in a direction perpendicular to the plane of the electrodes. In *C*, it reaches first the lateral and later the medial electrode, indicating a reversal of propagation in the medial direction. In *D* and *E*, the amplitude of the action potentials increases considerably, indicating that the

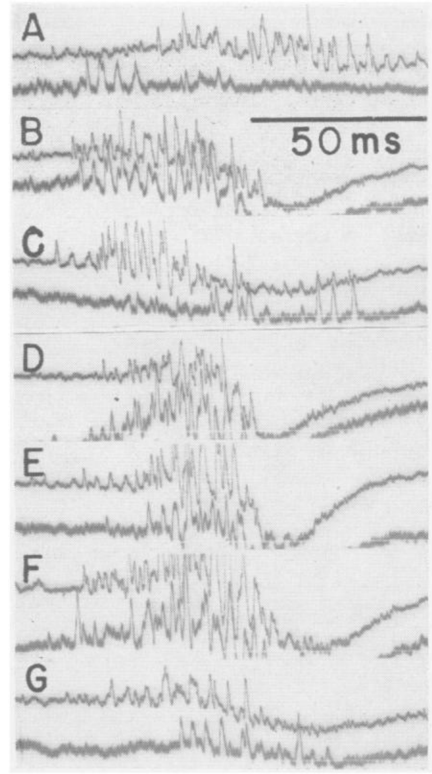

Fig. 2. Successive groups of action potentials (from a complete "spindle-burst" developing at 7 cy/sec) recorded from the center median, with one pair of microelectrodes, directed medio-laterally. Tips of microelectrodes 4 μ in diameter, 30 μ apart. Upper tracing in each strip is from the lateral electrode, lower tracing from the medial electrode. Amplifier time constant equals 0.2 sec. upward deflections are negative. Time between successive strips equals approximately 1/7 sec.

propagating wave of activity is now closer to the tips of the microelectrodes. In *F* and *G*, the wave of activity is again more distant and reverses its direction of propagation.

Recordings obtained from other diffusely projecting nuclei, in other experiments, with pairs of microelectrodes separated by 30 to 100 μ, directed either in the medio-lateral or the antero-posterior plane, show very similar patterns of propagation. The following conclusions can be drawn from these observations.

1) The transition of the electric activity of the brain from the desynchronized to the synchronized state is related to the appearance, in the diffuse thalamic projection system, of waves of activity propagated sequentially from neuron to neuron.

2) The changes and reversals in the direction of propagation of the wave of activity (that is, from medio-lateral, to antero-posterior then to latero-medial, and so on) indicate that the latter goes

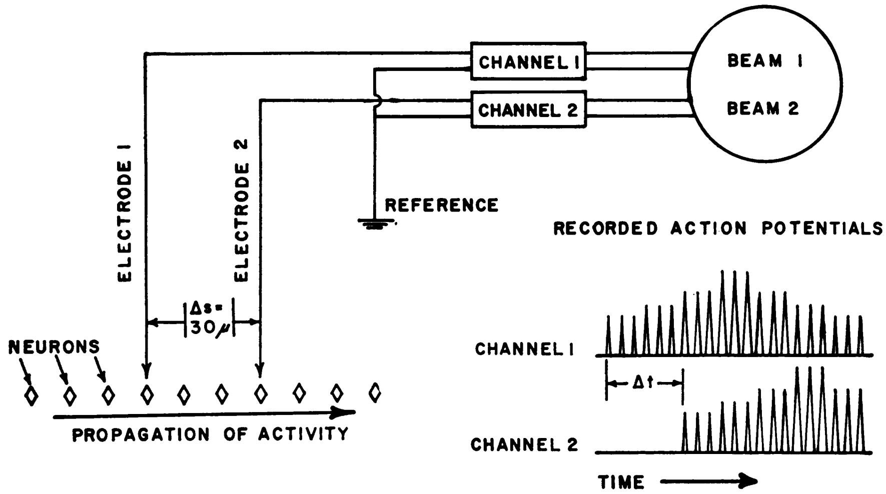

Fig. 1. Diagrammatic representation of the microelectrode, amplifier, and cathode-ray oscillograph arrangement and of the time relationships that should obtain between groups of action potentials recorded on two tracings, if activity is propagated in the direction of the arrow. ($\Delta s/\Delta t$ = velocity of propagation.)

back and forth, through, and around the recording site, which suggests some kind of "reverberation," although the exact geometric pattern of the pathway and its dimensions could not be determined at this stage of the investigation.

3) Since the distance between the tips of the microelectrodes is known, the velocity of propagation can be estimated by measuring the time that the "wave-front" takes to travel from one tip to the other. It has been found in these experiments that the order of magnitude of the velocity of propagation is 0.5 to 5 mm/sec.

M. VERZEANO
Department of Biophysics, University of California, Los Angeles

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3. Aided by grant B-649, National Institute of Neurological Diseases and Blindness, U.S. Public Health Service.
4. It is a pleasure to acknowledge the assistance of Cora Rucker, department of anatomy, University of California, Los Angeles, in the preparation of the anatomical material.
5. *Spindle-bursts* is a term used in electroencephalography to designate the wave-trains of progressively increasing and decreasing amplitudes that characterize the appearance of the "synchronized" state.

4 June 1956

Selective Action of Pentobarbital on Component Behaviors of a Reinforcement Schedule

Dews (*1*) has shown that the effects of sodium pentobarbital on a learned response in pigeons depend critically on the schedule of reinforcement used to maintain the response. Behavior under a fixed-interval reinforcement schedule (that is, after a fixed period of time, the first occurrence of some arbitrarily selected response makes food accessible to the subject for a brief period) shows great sensitivity to sodium pentobarbital. Different subanesthetic dosages produce a variety of changes, including both a depressive and an excitatory effect. On the other hand, behavior under a fixed-ratio reinforcement schedule (that is, food is presented after every *n*th occurrence of the response) is resistant to the drug. With this schedule of reinforcement, dosages approaching the anesthetic level are required to produce any change in the rate of emission of the response under observation.

The differential reaction of differently maintained behavior to sodium pentobarbital is here further investigated (*2*).

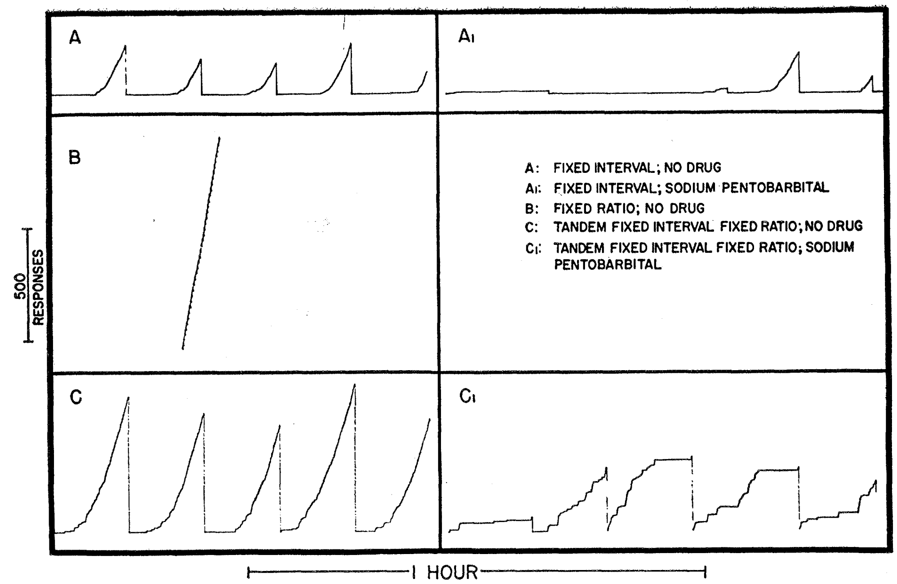

Fig. 1. Cumulative response curves showing the effects of sodium pentobarbital on behavior maintained by fixed-interval and tandem schedules of reinforcement.

Two food-deprived pigeons were used, and the response was pecking an illuminated disk. The reinforcement was brief access to food. The experimental apparatus has been described by Ferster (*3*).

The schedule of reinforcement used in this experiment is one that combines certain features of both fixed-interval and fixed-ratio schedules. The pigeon is reinforced after 10 min, but for the 13th response after 10 min, instead of the 1st response after 10 min (as in an ordinary 10-min fixed interval). This schedule is designated as a *tandem*: fixed interval of 10 min, fixed ratio of 12 responses (*4*).

The behavior resulting from the tandem schedule is similar to behavior under fixed-interval reinforcement, in that the animal's response rate increases as the end of the 10-min period approaches. The behavior shows the effect of the fixed-ratio component in the relatively high rates of response that occur.

Figure 1 shows sample cumulative records for fixed-interval, fixed-ratio, and tandem schedules of reinforcement, in *A, B,* and *C,* respectively. Cumulated number of responses is along the ordinate; time is along the abscissa. *A* shows a record for a 10-min fixed interval. Five successive 10-min intervals are shown. The pen is reset to the bottom of the record after each reinforcement. The typical characteristics of each fixed-interval performance are the initial period of no responding and the subsequent positive acceleration in the curve up to a terminal rate of about two responses per second. *B* shows records for a fixed ratio of 25 responses. The short diagonal strokes to the right of the record indicate reinforcements. The rate here is four to five responses per second and there are no pauses. In *C,* a sample record for a tandem (fixed interval of 10 min, fixed ratio of 12 responses) is shown. There are again five successive intervals, the pen being reset after each reinforcement. Although the performance here retains the positive curvature of the ordinary fixed interval, it can be seen that the over-all rate of response is much higher than in the ordinary fixed interval and that there is some tendency for short groups of responses at high rates to occur. Both of these differences from ordinary fixed-interval performance can be attributed to the presence in the tandem schedule of the small fixed-ratio component.

The effect on the fixed-interval performance of 2 mg of sodium pentobarbital, injected intramuscularly 5 min before the start of the record, is shown in *A*1. The effect is clearly one of depression, even though casual observation of the pigeon's general activity would not reveal any disturbance. The second interval in *A*1 contained only one response, the reset of the pen is therefore absent for this interval. The first and third intervals exemplify another frequently observed effect of pentobarbital, in addition to the depression. In these two intervals, the response curve did not show the positive acceleration that is typical of normal fixed-interval performance.

*C*1 shows the tandem performance 5 min after the intramuscular injection of 4 mg of sodium pentobarbital. The drug has again resulted in an over-all depression of responding. There is, in addition, no evidence of positive curvature in each interval and almost all low or intermediate rates of response have disappeared.