calcium there, makes the amount of calcium movement into the buds appear still more impressive. In most cases, on the specific activity basis, the 1-year-old buds have appreciably more calcium-45 in them than has the foliage on the tree shortly after injection.

These data, gathered from work during four different years and representing trees from four different areas, indicate that there was a substantial movement of previously deposited calcium into newly developed buds in this species.

The results indicate that calcium has considerably more mobility in western white pine than any previous reports would have led us to expect. We are conducting further investigations of this phenomenon.

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Relationship of Hormone Dosage to Physiological Response

A traditional method for the presentation of the relationship between the response to a hormone and dosage is to plot the logarithm of the dose against response. Whereas this choice of coordinates is convenient when a wide range of dosage has been studied, it appears to lack theoretical foundation. It is the purpose of the present paper to suggest an alternative system of coordinates, which may find usefulness in certain situations.

This analysis is based on the fact that, whereas the physiological response to many endocrine products at low dosage levels is roughly proportional to dosage, an apparent saturation may often be achieved at high dosage levels, the response becoming asymptotic with respect to dosage. By analogy to the Michaelis-Menten concept that the abundance of enzyme-substrate complex limits the velocity of an enzyme-catalyzed reaction (*1*), it is suggested that the magnitude of a hormone-provoked response is limited by the abundance of hormone bound to appropriate sites on the target organ. Direct evidence for such binding is already at hand, in the case of insulin (*2*), as is the strong indication of approximate proportionality between the quantity of insulin bound by muscle and the physiological response, in this case, synthesis of extra glycogen (*3*).

Let Q equal the total number of sites for physiologically responsive attachment of hormone to a target organ, $[HT]$ equal the number of such sites occupied by hormone, and $[T]$ equal the number of sites not so occupied. Whence

$$Q = [HT] + [T] \qquad (1)$$

Assume the occurrence of a reversible reaction between circulating hormone H and target-organ acceptor sites,

$$HT \rightleftharpoons H + T$$

with an equilibrium constant given by the expression,

$$K = \frac{[H]\quad[T]}{[HT]} \qquad (2)$$

If the physiological response observed is now assumed to be proportional to $[HT]$, the abundance of target-organ sites occupied by hormone, then the maximal response will be observed when all available sites are so occupied:

$$Q = [HT] \qquad (3)$$

and half of maximal response will be observed when one-half of the sites are occupied and one-half are not so occupied, under which circumstances

$$[T] = [HT] = \tfrac{1}{2}Q \qquad (4)$$

If $[H]_{\frac{1}{2}}$ is defined as that concentration of circulating hormone necessary to provoke one-half of maximal response, then, from Eqs. 2 and 4,

$$K = [H]_{\frac{1}{2}} \qquad (5)$$

an expression which formally resembles that of Michaelis and Menten. From Eq. 2,

$$[T] = K\,\frac{[HT]}{[H]} \qquad (6)$$

and from Eq. 1,

$$[T] + [HT] = Q = K\,\frac{[HT]}{[H]} + [HT] \qquad (7)$$

whence

$$\frac{[H]}{[HT]}\,Q = K + [H] \qquad (8)$$

and

$$\frac{[H]}{[HT]} = \frac{K}{Q} + \frac{[H]}{Q} \qquad (9)$$

This transformation is analogous to that of Lineweaver and Burk (*4*), and the same expression (Eq. 9) may be reached from considerations resembling those of the Langmuir sorption isotherm (*5*).

If it may now be assumed that the concentration of unbound hormone $[H]$ is proportional to the dose administered, Eq. 9 may be employed as a basis for plotting of data. If dose/response is plotted against dose, a straight line should be secured with slope $1/Q$ and intercept (dose = 0) K/Q. In Fig. 1 is shown a sample of data selected from the literature showing fairly good linearity when the foregoing coordinates are employed. The data are those of Riddle and Bates relating dose of prolactin to increase in weight of the pigeon crop-sac (*6*).

The possible usefulness of this method of plotting is that, from measurement of slope and intercept, numbers may be obtained indicating the capacity of target organ to bind hormone Q and the affinity of hormone for such binding sites K^{-1}. Such numbers, of little meaning by themselves, may prove of interest in the study of responses to families of related hormones and of the altered responses to a hormone in the presence of antagonists, disease, and so on. A decrease in response to a hormone, may, on these coordinates, appear as an increase in the slope of the line, reflecting a decrease in Q, the total number of tissue sites available for binding. Alternatively, such a decrease in response may appear, when plotted, as a line of unchanged slope but with a higher intercept, indicating an altered affinity of hormone to tissue-binding site.

The linearity here observed can be anticipated only if the magnitude of the response is limited by the amount of bound hormone, all other necessary reagents for the response being present in excess. In some situations, such as the increased accrual of glycogen in rat diaphragm in response to insulin, this condition does not appear to have been fulfilled.

The results of the foregoing development have previously been briefly presented (*7*). During the preparation of

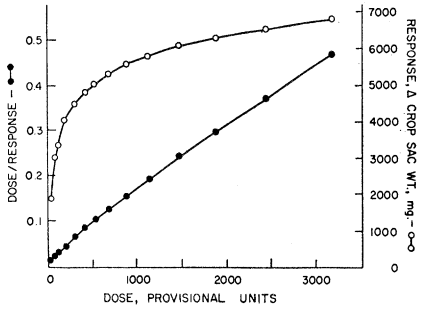

Fig. 1. Response, increase above control weight of crop-sac of a 450-g pigeon, plotted against dose of injected prolactin, in provisional units (open circles). The fraction, response/dose, plotted against dose (closed circles). Data are from Riddle and Bates (*6*).

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

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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 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.

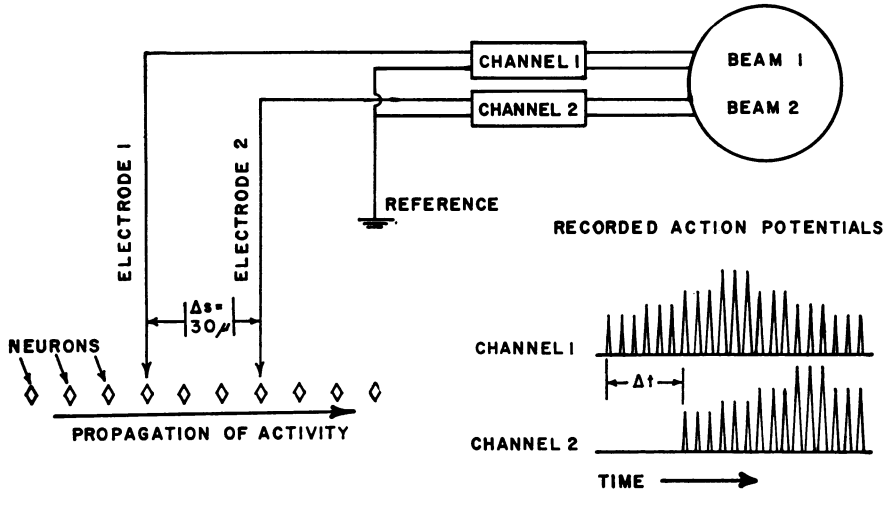

Fig. 1. Diagrammatic representation of the microelectrode, amplifier, and cathode-ray oscillograph arrangement and of the time relationships that should obtain between groups of action potentials recorded on two tracings, if activity is propagated in the direction of the arrow. ($\Delta s/\Delta t$ =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

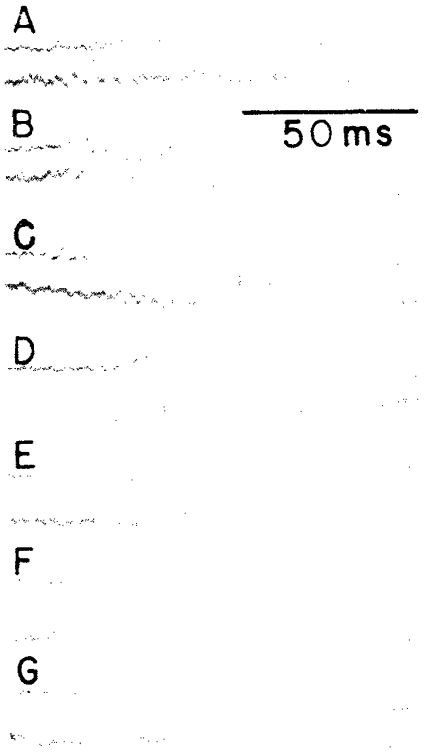

Fig. 2. Successive groups of action potentials (from a complete "spindle-burst" developing at 7 cy/sec) recorded from the center median, with one pair of microelectrodes, directed medio-laterally. Tips of microelectrodes 4 μ in diameter, 30 μ apart. Upper tracing in each strip is from the lateral electrode, 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.

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