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3. Genetic and hematologic data as well as erythropoietin, ferrokinetic and oxygen dissociation studies in cases with Hb Rainier are in preparation for publication.
4. The columns used were 1.2 by 50 cm, with 0.05*M* phosphate buffer, *p*H 6.0, with linear increase in NaCl concentration from zero to 0.1*M* for the elution of hemoglobins A_3, $Rainier_3$, and A; 0.15*M* NaCl concentration for the elution of hemoglobins Rainier and A_2.
5. Hemoglobin denaturation by 0.06*N* NaOH was studied by following, in a Beckman DU spectophotometer, the rate of decrease in absorbance at 430 mμ at 28°C as a function of time for 15 minutes; the reaction was completed by warming the samples at 37°C for 30 minutes. The proportion of undenatured hemoglobin at a given time was calculated according to J. H. P. Jonxis and T. H. J. Huisman, *Blood* **11**, 1009 (1956).
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27 November 1967

Myotatic Reflex: Its Input-Output Relation

Abstract. *The dynamic properties of the myotatic reflex and of its components were determined by a systems-analysis approach. The gain and phase relations between an applied stretch, which initiates the reflex, and the output of the primary muscle spindles, which impinge upon α-motoneurons, are not further changed by the properties of the motoneurons. The dynamic relation between motoneuron activity and the resultant muscle tension balances these changes in gain and phase; the result is a flat gain and nearly zero phase difference between stretch and tension produced by the myotatic reflex. Moreover, the distribution of activity in multiple channels extends the range in which the overall reflex is linear.*

The myotatic reflex comprises at least the following events: (i) generation of impulse activity by the primary endings of muscle spindles as a consequence of the stretch applied to the muscle, (ii) excitation of α-motoneurons, and (iii) development of muscle tension resulting from α-motoneuron activation. The dynamic behavior of the systems responsible for these events is largely unknown, although some data are available (*1–3*). Once these systems are known, one can predict the behavior of the reflex under various conditions and can study the functional influence of supraspinal systems on spinal motoneurons.

Study of the myotatic reflex also enables one to inquire into the functional significance of neuronal systems composed of multiple channels having similar information content. Indeed, the primary endings of muscle spindles converge upon single motoneurons and they seem to behave rather uniformly in response to muscle stretch, since the rate of impulse activity generated in these endings is nearly the same for all amounts of sustained stretch (*4*). Moreover, their dynamic behavior is similar (*2*), and the unloading produced by the activation of even one, or of a few motor units, should affect all the spindles similarly, if one assumes that the muscle fibers belonging to each motor unit are not highly segregated within the muscle (*5*). By use of a preparation in which differences in spindle behavior due to γ-motoneurons are abolished by cutting of the ventral roots, one can examine the result of the convergence, upon single motoneurons, of information conveyed by parallel channels. Moreover, one can compare the behavior of single motoneurons with the behavior of the motoneuron population to see what properties may arise from handling of similar information by multiple units, on the assumption that the input distribution and the properties or the functional state (or both) of the individual motoneurons belonging to a uniform population are not the same.

The dynamic behavior of the overall myotatic reflex (stretch input and active-tension output) was measured in decerebrate cats (Fig. 1). The tendon was stretched as it would be for movements of the ankle joint as much as 15 deg about the steady-state position (foot at 90-deg angle from leg). The gain (*6*) of the dynamic length-tension relation was about flat (Fig. 2A, curve *b*), and only a small but constant phase difference was present between input and output (Fig. 2B, curve *b*), within the range of frequencies and amplitudes used. This behavior can be predicted from the dynamic characteristics of the systems responsible for the reflex.

Behavior of the primary endings of muscle spindles was measured in decerebrate cats (ventral roots cut or uncut) and in cats under barbiturate anesthesia (pentobarbital, 35 to 40 mg/kg). The modulation component of the impulse activity in a single primary ending, evoked by sinusoidal stretches of different amplitudes and frequencies, was determined by a reported technique (*7*). The results yielded by use of slightly different resting lengths and different average firing frequencies (between 18 and 30 impulses per second) can be fitted by a single curve (Fig. 2A, solid circles). The behavior ceased to be linear for displacements above 50 to 100 μ (Fig. 3B). Within these limits the percentage modulation increased linearly with increasing displacement amplitude, and the modulation component was sinusoidal. At the larger amplitudes the distribution of impulse activity was no longer sinusoidal, and saturation occurred at approximately 300 μ (Fig. 3A).

The second step in the myotatic reflex, the processing of afferent information by α-motoneurons, involves at least two separate processes: demodulation of information carried by afferent impulses (synaptic processes), and re-

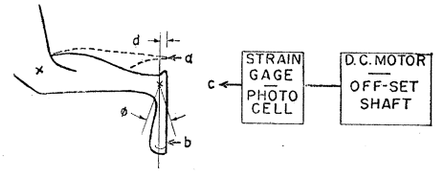

Fig. 1. Stimulator. The hind leg is fixed at the distal ends of the femur and tibia with pins. The steady-state value of muscle displacement was chosen to correspond to the limb position shown—foot approximately 90 deg from leg. The amplitude of sinusoidal displacement (*d*) of the extensor muscles is that due to displacement of the foot through angle φ (up to 15 deg). Stimulus applied at *a* displaces triceps surae only. Stimulus applied at *b* displaces both flexor and extensor muscles. Sinusoidal displacements were generated by a feedback-controlled, variable-speed d-c motor that turned a variable-offset shaft. Displacement was measured by a photocell, and tension was measured by a strain gage on the output shaft. The sinusoidal displacement at *c* was applied at *a* or *b*, appropriate adjustments in amplitude being made by variation in the amount of offset.

encoding of the information into impulse activity (motoneuron output).

For examination of the first process, gastrocnemius motoneurons of decerebrate cats, with ventral roots cut, were impaled with KCl-filled microelectrodes. Transmembrane potential changes, evoked by sinusoidal stretches applied to the triceps surae muscles, were measured. The impaled neurons were hyperpolarized through the microelectrode to prevent generation of impulse activity. There was no need to average the membrane potential changes (less than 10 mv in amplitude for the three cells included in the plot) for disclosure of the sinusoidal modulation. This finding is in sharp contrast with the demodulated output of stretch receptors (primary endings), with which a sample average was needed for recovery of the information. The gain and phase of the information, after demodulation by the synaptic processes, are essentially the same as those measured for the spindle output. This relation implies that, within the range of input frequencies used, (i) the frequency response of synaptic processes is flat, and (ii) virtually no time-integration takes place in the motoneuron. The membrane time constant of α-motoneurons and the decay time of the postsynaptic potentials are too short to provide for such time-integration within the range of frequency studied by us.

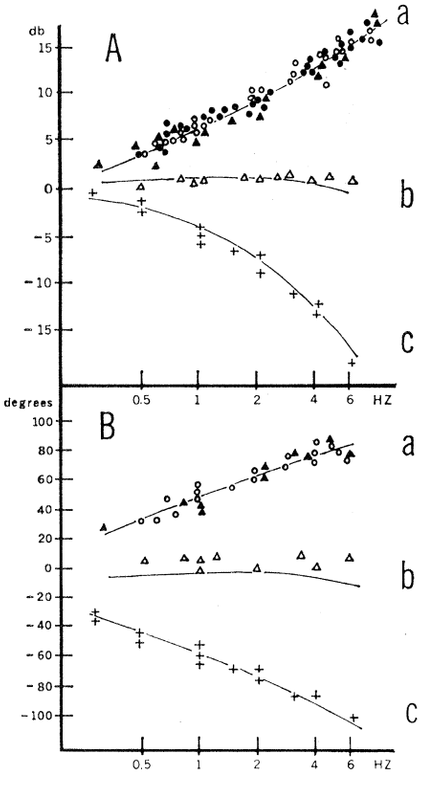

Fig. 2. Frequency-response characteristics. Bode plots of (A) relative gain (see text), and (B) phase of output with respect to input, as a function of stimulus frequency. Curve *a* is drawn through points representing the gain and phase of primary-spindle output (●), α-motoneuron transmembrane potential (○), and electromyogram (▲) in response to sinusoidal stretches of the triceps surae. Curve *c* is drawn through points (+) representing gain and phase of triceps surae tension in response to sinusoidally pulse-frequency-modulated stimuli to the gastrocnemius and soleus nerves. Curve *b* is the sum of curves *a* and *c* (note that this is equivalent to multiplication in (A), since this is a log-log plot). Experimental points (△) represent gain and phase of triceps surae tension in response to sinusoidal stretches.

The output from the motoneuron population, which in each of the cells results from the reencoding of information contained in the synaptically induced membrane potential changes, was examined in decerebrate cats by recording of the gastrocnemius electromyogram with four large disk electrodes. The activity was demodulated by a filter having characteristics such that signals with frequency content below 6 hz were unaffected.

The data points (Fig. 2, open circles) fall along the line (curve *a*) that describes the muscle-spindle behavior; thus the reencoding of information by the participating motoneuron population has no appreciable dynamic effect on transfer of information in the range of frequencies considered.

Curve *c* (Fig. 2) describes the dynamic relation between impulse activity in the motor nerve and muscle tension in the triceps surae, which is the last event occurring in the myotatic reflex. Our results do not differ from those of Partridge (*3*), who showed an increasing phase lag and a decrease in tension amplitude as the modulation rate of the electrical stimuli applied to the motor nerve was increased. In our experiments modulation depths up to 15 percent of the carrier frequencies (20 to 35/second) were used; within these limits there was no deviation from linear behavior.

Comparison of curves *a* and *c* (Fig. 2) shows that the increases in gain and phase lead with frequency that are observed at the output of the primary endings, and which are found unaltered at the motoneuron output, are absorbed by the loss of gain and by the phase lag that characterize the relation between motoneuron activities and muscle tension [curve *b* is the sum of curves *a* and *c* (Fig. 2)]. Thus the dynamic behavior of primary endings offers a frequency compensation for the tension-producing mechanisms; this factor contributes to stabilization of the myotatic reflex when this is viewed as a feedback-control system (*8*).

Concerning the effect of multiple channels, our findings are:

1) The transmembrane potential changes that result from the synaptic excitatory actions exerted by the information converging upon the single cell, through the primary-spindle afferences, follow more closely the sinusoidal input, or information, than does the modulation of impulse activity in individual afferent channels. This fact suggests that the convergence of similar information upon a single motoneuron allows this cell to perform a sample average; consequently information applied at the input (displacement) is present in the motoneuron without the need of averaging the incoming information over repeated trials.

2) Although the output from pri-

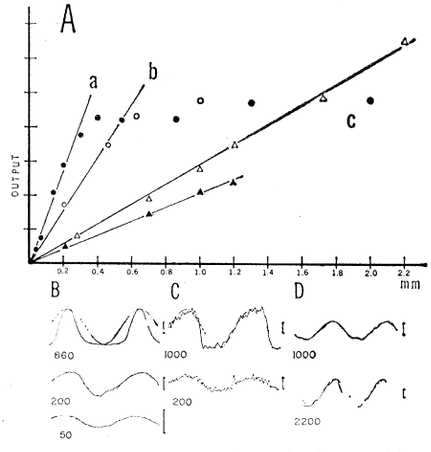

Fig. 3. Responses to sinusoidal stretching. (A) Peak-to-peak output amplitude (impulses per second or millivolts) plotted in arbitrary units as a function of peak-to-peak amplitude at sinusoidal muscle stretch (millimeters) at 1 hz. *a*, Primary spindle from gastrocnemius muscle (●). *b*, Gastrocnemius motoneuron transmembrane potential (○). *c*, Gastrocnemius electromyogram; two preparations (△, ▲). (B–D). Heavy curves are the averaged responses of primary spindles (B), motoneuron transmembrane potential (C), and electromyogram activity (D). Light curves are reference sinusoids added for comparison; they do not represent the input function. Numbers indicate the peak-to-peak input stretch amplitudes in microns. All records were taken with input frequency at 1 hz. The vertical bars to the right of each group represent equal amplitudes. See text.

mary endings is linear in our experiment only for displacement amplitudes of 50 to 100 μ, in the range of frequencies used, the motoneuron output (electromyogram) is still linear for stretches of up to about 2 mm. This averaged output from the motoneuron population is sinusoidal for input amplitudes greatly exceeding those at which linear behavior ceases for primary endings and single motoneurons (Fig. 3). Although the contribution by individual motoneurons to this linearization process is still to be assessed, there can be no doubt that the distribution of activity in parallel output channels is the factor mainly responsible for extension of the linear range of the overall reflex; the distribution of thresholds in the participating motoneuron population could largely account for this result. However, the effects of nonmonosynaptic excitatory actions upon α-motoneurons, which may depend on either primary-spindle ending or other receptors, cannot be excluded. We have excluded only the possibility that the presence of inhibitory actions from antagonistic muscles may favor linearization. In a series of experiments in which the innervation of muscle antagonistic to the triceps surae was initially intact, the stimulus being applied to the foot so that the activities of flexor and extensor muscles were interacting normally, removal of the influence from antagonistic muscles caused no apparently significant difference; the gain was reduced by only 5 to 10 percent, the suggestion being that inhibition from antagonistic flexor muscles has no great effect on the output of extensor motoneurons under the stated conditions.

Preliminary data indicate that Renshaw negative feedback may have a measurable effect on higher input frequencies than those encompassed here (above 8 hz), at which the feedback seems to synchronize the activity of motoneurons. This synchronization provides the possibility of increase in peak tension after recruitment of motoneurons ceases to contribute. However, there is no indication of a detectable contribution by Renshaw inhibition to extension of the linearity.

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Paradoxical Sleep: Effect of Low Partial Pressures of Atmospheric Oxygen

Abstract. *When cats are subjected to an atmosphere of 100 percent oxygen at a sufficiently low pressure, their sleeping patterns are changed: paradoxical sleep disappears and drowsiness increases. This change appears when the pressure decreases to a level close to that at which the hemoglobin begins to dissociate. Return of a cat to a normal atmosphere produces a rebound: the cat spends more time in paradoxical sleep than it did during the base-line period. This finding suggests that a mechanism, closely related to the metabolism of oxygen in the brain, must play an important role in the production of paradoxical sleep. Yet the increase in paradoxical sleep after decompression indicates that still other mechanisms must merge to produce paradoxical sleep.*

While seeking the effects of different tensions of atmospheric oxygen on the spinal reflexes of monkeys and cats, we noticed alterations in sleep patterns in the experimental animals (*1*). The most striking change was disappearance of the paradoxical phase of sleep when atmospheric pO_2 reached a certain low. Recent studies of animals indicate correlation between changes in behavior, metabolism, and circulation and the onset of paradoxical or REM (rapid eye movement) sleep (*2*). These studies suggest directly or indirectly changes in the metabolic patterns of neurons, which seem to reach a particular state of increased metabolic activity during REM sleep (*3*), but the mechanism by which REM is released or provoked remains unknown. Most reported measurements are concerned with changes in a physiological process: for example, change in brain-tissue impedence indirectly implies changes in activity within the brain (*4*). The electroencephalogram (EEG) changes (*5*), temperature changes (*6*), and alterations in cerebral blood flow (*7*) imply the same. One result suggests that the changes in temperature are achieved by peripheral diversion of blood rather than by brain metabolism (*8*); other reports are of concomitant changes in hormonal levels in the blood and the urine during paradoxical sleep (*9*); but none of these findings can be manipulated for induction or deprivation of paradoxical sleep in an animal. Some ingenious methods have been designed to prevent REM, but they are mainly concerned with waking or manipulating the animal as soon as it enters paradoxical sleep (*10*). Ability to deprive an animal of a phase of sleep, particularly paradoxical sleep, without having to wake it, offers a new approach toward understanding of the significance of as well as the mechanisms involved in sleep. Our experiments show how a low partial pressure of oxygen can deprive cats of paradoxical sleep.

We used five cats in which surgical stainless steel electrodes were implanted in the roof of each orbit to monitor ocular movements. Stainless steel screw electrodes were placed bilaterally on the occipital and frontal cranium to ob-