giving in % the probability of response. This was plotted versus intensity of stimulus given in % of threshold. The points fit an S-shaped curve (Figure D and E). When the ordinates are subjected to the Probit[13] transformation, a straight line is obtained which shows the S-shaped curve to be the integral of a Gaussian distribution[2]. The sigmoid obtained for the longer current pulses (Figure E) is steeper than the one for the shorter pulses (D) in the same fibre. The amplitude of the excitability fluctuation is thus smaller when longer pulses are used. This result has been consistently observed in 11 nerve fibres in which the effect of square pulses of 0.1 and 10 msec has been systematically compared. Indeed, by applying Student's test by pairs to the experimental results, the difference proved significant at the level of 0.001.

Whatever the intrinsic processes governing the uncertainty of response near threshold, some conclusions about the frequency spectrum of the resultant fluctuation might be drawn from the experimental data. Of course, the really effective duration as a stimulus of the longer current pulses will be limited by accommodation. If the random changes in excitability were rather slow compared to the time scale of the electrical stimuli used, the duration of the latter would not affect their ability to trigger a spike and the probability of response would depend only on the level of depolarization produced at the membrane of the node (within the limits allowed by 'accommodation'). On the contrary, if the mean period of the random fluctuation in excitability was of the same order as the duration of the current pulses used, the probability for a stimulus inducing a given depolarization to trigger a spike would increase with its duration, because the longer depolarization has more chance to benefit from any random intermittent change in the membrane which facilitates the firing off. In other words, when the voltage of the stimuli is increased close to the region of uncer-

tainty, a point is reached where the depolarization produced by either the longer or the shorter pulses triggers a response in only a few of the trials; further increase in depolarization will augment the probability of response more rapidly in the case of the longer pulse, hence the steeper S-shaped relation seen in E. Along this line, it can be suggested that the duration of the current pulses used is of the same order as the mean period of the fluctuation process.

No specific hypothesis can be elaborated from the data but it can be pointed out that such rather rapid random changes in excitability might be related to thermal agitation at molecular level[14].

Résumé. Il est possible de montrer des fluctuations aléatoires de l'excitabilité électrique de fibres nerveuses myélinisées isolées excitées au moyen de chocs proches du seuil. L'amplitude de cette fluctuation a été comparée pour des excitants rectangulaires de deux durées (0,1 et 10 msec); elle est plus grande quand on utilise des chocs brefs. Ces résultats suggèrent que les composantes de relativement haute fréquence du spectre de la fluctuation sont importantes.

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Reduction of Dynamic Sensitivity of Primary Muscle Spindle Endings in Experimental Tremor

The main sensing elements of the proprioceptive feedback system, primary muscle spindle endings, respond statically to amount, as well as dynamically to rate, of muscle length changes[1-3]. In a servomechanism of this type, the derivative component improves the stability of the whole system and counteracts inherent oscillatory tendencies[4-7]. Supraspinal muscle spindle activation modulates the dynamic properties of the spindle endings[8]. Furthermore, relatively independent fusimotor controls of their static and dynamic responses, respectively, seem to exist[7,9]. Hence, if some differential fusimotor action would predominantly reduce the dynamic sensitivity of primary spindle endings, this would, by analogy with technical feedback systems, favour oscillations in the proprioceptive feedback loop and could thus be one possible cause for tremor motor phenomena.

We have induced, in cats under steroid anaesthesia with 'Presuren'[10], a state of experimental tremor by perfusing the cerebral ventricular system with a solution of *d*-tubocurarine chloride[10] in artificial cerebrospinal fluid (5–100 μg/min)[11,12]. Methods and results of a detailed analysis of the mechanical and electrophysiological aspects of this type of tremor will be published elsewhere[13].

Here we wish to report on the responses of innervated muscle spindles from ankle extensors and flexors, recorded from filaments of centrally cut dorsal roots. Impulses conducted at velocities exceeding 72 m/sec were considered to originate from primary spindle endings. A

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pneumatic device provided muscle stretches which increased linearly at a rate of 5–25 mm/sec to a maintained amount of 10 mm, starting from near-zero initial muscle tensions. The 'dynamic response' of the spindle ending was evaluated[7] as the difference between mean impulse frequency during the last 0.1 sec of the rising phase of the stretch and mean adapted frequency 0.5 sec after the end of this phase (='static response').

Results. Generalized tremor with preferred frequencies of about 10–20 cps developed 3–15 min after the onset of curare perfusion. At the same time, some spindle units which were originally silent at the stretch-free intervals started with irregular low-frequency discharges. All units identified as primary endings showed unexceptionally, though after different latencies, a more or less pronounced reduction of their dynamic response. The discharge frequency curves of Figure 1 are representative. The peak frequency is clearly lower after curare action, while the adapted static frequency is almost unchanged. Figure 2 summarizes the dynamic response changes of 11 primary and 4 secondary spindle endings. The secondary endings exhibit moderately increased dynamic responses. Conversely, the dynamic responses of primary endings are decreased, the strongest effects being found among faster conducting units. Static responses of both primary and secondary endings (not illustrated) were mostly increased but also slightly decreased or not changed in some cases.

Our findings suggest that under curare perfusion the tonic activity of predominantly γ_2-fusimotor fibres was enhanced, leading to contraction of the nuclear-chain intrafusal fibres[14]. Nuclear-bag fibres, lying in parallel with the chain fibres, will thus be unloaded and partially lose the dynamic properties of their bag regions, where only primary sensory endings are located[7,9]. Dynamic properties are poor, but not completely absent, in the nuclear-chain fibres which carry the majority of secondary endings. Their contraction will therefore enhance, within limits, the dynamic responses of the secondary endings. The static responses of both primary and secondary endings depend upon the static properties of both types of intrafusal fibres. The actual static response of the individual sensory unit will thus be an unpredictable compromise between counteracting influences.

In conclusion, cerebral curare perfusion reduces the dynamic sensitivity of the primary spindle endings, thus favouring oscillations within the proprioceptive feedback loop. This provides a possible formal explanation for the resulting tremor, although it does not describe in detail the actual processes forcing the motoneurones into grouped rhythmic activity bursts. Other factors might be involved as well, and might dominate in other tremor states[15]. However, it seems worthwhile to check whether the same basic deviation from normal muscle spindle behaviour would also occur, for instance, in shivering, extrapyramidal, or cerebellar tremor[16].

Fig. 2. Dynamic response changes of muscle spindle endings induced by curare perfusion. Dynamic response values before perfusion (average of 3–5 tests) were set as 100%. For each ending, a bar represents, in plus or minus % values, either increase (upward) or decrease (downward) of the dynamic response. Total bar length: maximum effect irrespective of observation time. Black part of bar: average value of all observations during curare. The bars are arranged in ascending order of fibre conduction velocity (velocity scale on abscissa).

Zusammenfassung. Curareperfusion der Hirnventrikel setzt die dynamische Empfindlichkeit primärer Muskelspindelendigungen herab, wahrscheinlich durch bevorzugte Aktivierung der γ_2-Fusimotoneurone. Dies begünstigt Oscillationen im proprioceptiven Regelkreis, worin eine mögliche Ursache des induzierten Tremors zu suchen ist.

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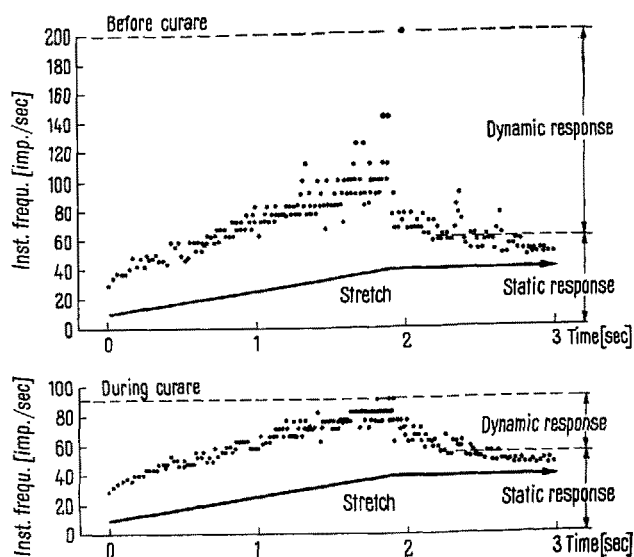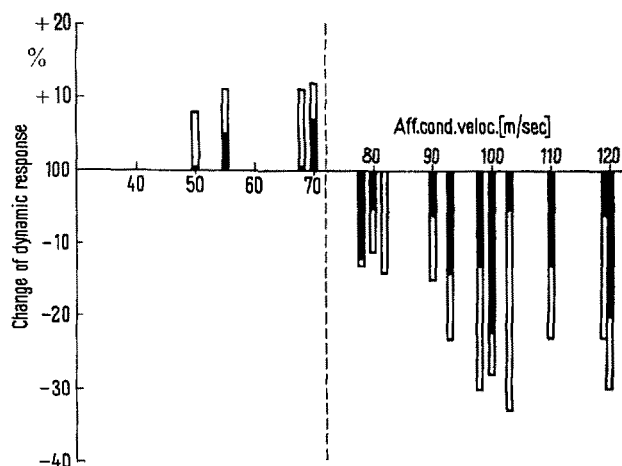*Physiologisches Institut der Universität Göttingen (Germany), April 29, 1964.*

Fig. 1. Response of primary muscle spindle ending to linearly increasing stretch of soleus muscle. Instantaneous discharge frequencies (reciprocal spike intervals) plotted against time in sec. Upper curve before, lower curve 9 min after onset of ventricular curare perfusion. Same stretch rate (5.25 mm/sec) and amount (10 mm) in both tests. Note that the dynamic responses, as marked in this graph, are derived from instantaneous peak frequency rather than from the mean frequency during the last part of stretch rise, as calculated for Figure 2.

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